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1 **β -cell specific *E2f1* deficiency impairs glucose**
2 **homeostasis, β -cell identity and insulin secretion**

3
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38 Running title: E2F1 and beta-cell identity

39 **Abstract**

40 The loss of pancreatic β -cell identity emerges as an important feature of type 2 diabetes
41 development, but the molecular mechanisms are still elusive. Here, we explore the cell-
42 autonomous role of the cell cycle regulator and transcription factor E2F1 in the maintenance
43 of β -cell identity, insulin secretion and glucose homeostasis. We show that the β -cell-specific
44 loss of *E2f1* function in mice triggers glucose intolerance associated with defective insulin
45 secretion, an altered endocrine cell mass, a downregulation of many β -cell genes and a
46 concomitant increase of non- β -cell markers. Mechanistically, the epigenomic profiling of
47 promoters of these non- β -cell upregulated genes identified an enrichment of bivalent
48 H3K4me3/H3K27me3 or H3K27me3 marks. Conversely, promoters of downregulated
49 genes were enriched in active chromatin H3K4me3 and H3K27ac histone marks. We find
50 that specific E2f1 transcriptional, cistromic and epigenomic signatures are associated with
51 these β -cell dysfunctions, with E2F1 directly regulating several β -cell genes at the chromatin
52 level. Finally, the pharmacological inhibition of E2F transcriptional activity in human islets
53 also impairs insulin secretion and the expression of β -cell identity genes. Our data suggest
54 that E2F1 is critical for maintaining β -cell identity and function through a sustained control
55 of β -cell and non β -cell transcriptional programs.

56
57 **Article Highlights**

- 58 • β -cell specific *E2f1* deficiency in mice impairs glucose tolerance.
- 59 • Loss of *E2f1* function alters α -to- β -cell ratio but do not trigger β -cell conversion into
60 α cells.
- 61 • Pharmacological inhibition of E2F activity inhibits glucose-stimulated insulin secretion
62 and alters β - and α -cell gene expression in human islets.
- 63 • E2F1 maintains β -cell function and identity through the control of transcriptomic and
64 epigenetic programs.

65

66 Introduction

67

68 Type 2 Diabetes (T2D) is a progressive metabolic disorder characterized by chronic
69 hyperglycemia due to inadequate pancreatic β -cell response to peripheral insulin resistance.
70 Usually, β -cells respond to obesity and aging-associated loss of insulin sensitivity by
71 increasing insulin secretion to compensate for rising glycemia. However, when insulin
72 secretion and action are imbalanced, the emerging chronic hyperglycemic state
73 progressively leads to massive β -cell dysfunction and decreased mass (1). Importantly,
74 single cell transcriptomic analysis of human pancreatic islet cells from T2D and healthy
75 individuals revealed the complex identity of endocrine cells associated with the
76 pathophysiology (2-4). In addition, recent studies demonstrated a loss of transcriptional
77 maturity (5) and cell-type-specific regulatory profiles underlying T2D pathogenesis (6).
78 Moreover, histology studies of human diabetic pancreata found a significant increase in bi-
79 hormonal Insulin+ (Ins+)/Glucagon+ (Glu+) cells suggesting an altered β -cell identity (7; 8).
80 Accordingly, recent studies using β -cell lineage tracing murine models have demonstrated
81 that islet cells can trans-differentiate directly toward another islet cell fate and/or de-
82 differentiate toward a progenitor-like cell (9). In this context, both genetic and epigenetic
83 mechanisms are important to maintain adult β -cell fate and function in mouse and human
84 (10-13). Yet, the molecular actors controlling β -cell mass, identity maintenance and cellular
85 plasticity still need to be identified.

86 Gene transcription and chromatin states are tightly regulated to ensure the
87 appropriate transcriptome for a specific cell type. Many transcription factors have been
88 identified as key regulators of β -cell identity and function, including Pdx1 (14), Pax6 (15),
89 Nkx6.1 (16) and Nkx2.2 (17). Interestingly, pleiotropic transcription factors are also involved
90 in the control of β -cell functions and glucose homeostasis, suggesting their important roles
91 in activating or repressing gene transcription. Amongst those, members of E2F transcription

92 factor (E2F1 to E2F8) family play critical roles in cell survival and proliferation, by regulating
93 the expression of genes involved in cell-cycle progression (18). The transcriptional activity
94 of E2F1, the founder member of the family, is regulated by several protein complexes
95 including the retinoblastoma tumor suppressor family (pRB, p107, p130), cyclin-dependent
96 kinases (such as CDK4) and their regulatory partner cyclins (Ccn), as well as the family of
97 the cdk inhibitors (CDKi, such as p16^{Ink4A} encoded by the *Cdkn2a* locus). Interestingly, the
98 role of the cell cycle machinery goes beyond the unique regulation of cell proliferation.
99 Indeed, modulating the expression levels of these cell cycle regulators revealed an
100 important role for these proteins in glucose homeostasis (19) and diabetes development
101 through the control of β -cell mass and function (20; 21). We and others have recently
102 identified a molecular crosstalk between E2f1/pRb and Glucagon-like peptide-1 (Glp-1)
103 pathways (22; 23). Although *E2F1* gene expression is decreased in human T2D islets (24),
104 the causal effect of *E2F1* deficiency on impaired β -cell mass, function and T2D development
105 is not elucidated. In particular, the cellular and molecular mechanisms underlying the
106 contribution of E2F1 as a transcription factor to β -cell identity and/or plasticity in mice and
107 humans remain unknown. We recently demonstrated that the germline deletion of *E2f1* in
108 the obese and diabetic *db/db* mouse model, despite lowering liver steatosis, does not protect
109 against diabetes or obesity (25). Interestingly, we observed decreased plasma insulin levels,
110 increased plasma glucose and glucose intolerance in *db/db::E2f1^{-/-}* mice compared to
111 *db/db::E2f1^{+/+}* controls (25). These metabolic alterations in a diabetic background raises the
112 possibility that *E2f1* may contribute to islet morphology, cell identity and function in a cell-
113 autonomous manner. To test this hypothesis, we generated mice lacking *E2f1* in β -cells and
114 identified that *E2f1* is mandatory to maintain β -cell identity gene expression in both mouse
115 models and human islets. By combining cellular and mouse models to pharmacological
116 approaches, we identify *E2f1* as a critical transcription factor necessary to maintain proper
117 β -cell gene expression and function, while repressing non β -cell transcriptional programs.

118 **Research design and methods**

119

120 A detailed description of the following procedures can be found in the Supplemental Material
121 section.

122 **Animal Experiments.** *In vivo* experiments were performed in compliance with the French
123 ethical guidelines for studies on experimental animals (animal house agreement no. A 59-
124 35015, Authorization for Animal Experimentation no.59-350294, project approval by our
125 local ethical committee no. CEEA 482012, APAFIS#2915-201511300923025v4). All
126 experiments were performed with male mice. *E2f1*^{-/-} (Jax Lab, stock number #002785),
127 *CMV-CDK4^{R24C}* (26), *Cdkn2a*^{-/-} (27), *db/db::E2f1*^{-/-} (25), *E2f1* floxed (*E2f1^{flox/flox}*, Taconic
128 Biosciences, NY, USA) and RIP-Cre^{+/+} mice were previously described (25; 28). MIP-CreERT
129 mice were obtained from Jax Lab (stock number #024709, (29)). For lineage tracing
130 experiments, Rosa26R-td-tomato (Jax Lab, stock number #007914) and Rosa26R-ECFP
131 (Gt(ROSA)26Sortm2(ECFP)Cos, (30)) mice were used. Intraperitoneal glucose and insulin
132 tolerance tests (ipGTT and ITT, respectively) were performed on 6, 8 and 12-week-old male
133 (*E2f1^{fl/fl}* and *E2f1^{β-/-}*) or 5-month-old (*E2f1^{fl/fl}* and *E2f1^{MIP-CreERT β-/-}*) littermates as previously
134 described (31) on 16-hr-fasted animals for ipGTT and 5-hr-fasted animals for ITT. Glycemia
135 was measured using the Accu-Check Performa (Roche Diagnostics). Circulating insulin
136 levels were measured using the mouse Insulin ELISA kit (Merckodia).

137

138 **Immunofluorescence, Immunohistochemistry and Morphometry.** Immunofluorescence
139 and immunohistochemistry were performed exactly as described previously (31). Briefly,
140 pancreatic tissues were fixed in 10% formalin, embedded in paraffin and sectioned at 5 μm.
141 For immunofluorescence microscopy analyses, after antigen retrieval using citrate buffer, 5-
142 μm formalin-fixed paraffin-embedded (FFPE) pancreatic sections were incubated with

143 primary antibodies as indicated. Immunofluorescence staining was revealed by using a
144 fluorescein-isothiocyanate-conjugated anti-rabbit (for cleaved caspase-3, Alexa-conjugated
145 anti-mouse (for glucagon), anti-rabbit (for Glut-2) or anti-guinea pig (for insulin) secondary
146 antibodies were used to identify specifically primary antibodies. Nuclei were stained with
147 Dapi (Sigma-Aldrich, D9542). For morphometric analysis, three to ten animals from each
148 genotype were analyzed, and images were processed and quantified using ImageJ software
149 by an observer blinded to experimental groups. Morphometric analysis including islet
150 density, β -cell fraction and mass was performed as previously described (32). β -cell size
151 was measured using immunofluorescent staining of pancreatic sections using an anti-Glut-
152 2 antibody (Merck, #07-1402-1) on 5 mice from each genotype and acquisition was done on
153 a Spinning disk confocal microscope (Zeiss). 20 islets per mice were analyzed, and 5 mice
154 from each genotype were used to analyze β -cell size. Quantification was then performed
155 using a custom-made script with ImageJ software (available upon request). β -cell
156 proliferation was measured using BrdU staining on FFPE pancreatic sections. Apoptosis
157 was quantified using an immunofluorescent staining using an anti-cleaved caspase 3.

158

159 **Cell Culture, Pancreatic Islet Studies and Pharmacological Treatments.** For mouse islet
160 studies, pancreata were digested by type V collagenase (Sigma-Aldrich, C9263; 1.5 mg/ml)
161 for 10 min at 37°C as described previously (31). Briefly, after digestion and separation in a
162 density gradient medium, islets were purified by handpicking under a microscope and
163 cultured during 16 hours before subsequent analysis. For expression studies, mouse
164 isolated islets were snap-frozen in liquid nitrogen before RNA extraction. Human pancreatic
165 tissues were harvested from brain-dead, non-diabetic adult human donors (see
166 Supplementary Table S1 for donor information). Isolation and islets culture were performed
167 as described (33). Human islets were treated for 48 hours with DMSO 0.1% or HLM006474
168 (34; 35) at 10 μ M. Data are expressed as a ratio of total insulin content. For mRNA and

169 protein quantification, human islets were isolated as described above and snap-frozen for
170 further processing. Min6 cells (AddexBio) were cultured in DMEM (Gibco) with 15% fetal
171 bovine serum, 100 mg/mL penicillin-streptomycin, and 55 mM beta-mercaptoethanol. Min6
172 cells were treated with HLM006474 (10 μ M) or DMSO 0.1% (35) for 48 hours before GSIS
173 assay or RNA extraction.

174

175 **RNA extraction, qPCR and RNA-Sequencing.** Total RNA was extracted from cells and
176 tissues using TRIzol reagent (Life Technologies) as described previously (22). mRNA
177 expression was measured after reverse transcription by quantitative real-time PCR (qRT-
178 PCR) with FastStart SYBR Green master mix (Roche) using a LightCycler Nano or LC480
179 instruments (Roche). qRT-PCR results were normalized to endogenous cyclophilin
180 reference mRNA levels. The results are expressed as the relative mRNA level of a specific
181 gene expression using the formula $2^{-\Delta Ct}$. The complete list of primers is presented in
182 Supplementary Table S2. For RNA sequencing, total RNA was extracted from Min6 cells or
183 pancreatic islets using the RNeasy Plus Microkit (Qiagen) following manufacturer's
184 instructions. Using a $P < 0.05$ adjusted for multiple comparisons as threshold for differential
185 gene expression analyses, we then performed pathway analysis using Ingenuity Pathway
186 Analysis (Ingenuity Systems, Qiagen), Metascape (36) and Gene Set Enrichment Analysis
187 (GSEA; <http://software.broadinstitute.org/gsea/>).

188

189 **Chromatin immunoprecipitation and ChIP-Sequencing.** ChIP experiments were
190 performed on formaldehyde-fixed Min6 cells. Briefly, 20×10^6 Min6 cells or 100×10^6 Min6
191 cells (for E2f1 ChIP-seq) were treated with formaldehyde at a final concentration of 1% to
192 crosslink DNA and protein complexes during 10 min. The reaction was stopped by the
193 addition of glycine (0.125 M) during 5 min. Cells were lysed and DNA-protein complexes
194 were sheared using the Bioruptor Pico (Diagenode, ref B01060010) for 8 minutes. The

195 sheared chromatin was immunoprecipitated with either the non-specific antibody IgG (Santa
196 Cruz, sc2025), H3K4me3 (Active motif, #61379), H3K27me3 (Active motif, #61017),
197 H3K27ac (Active motif, #39685) or anti-flag (Clone M2, Sigma-Aldrich). Further
198 bioinformatic analyses of the public data sets and those of this study were performed using
199 the open web-based platform Galaxy Europe (<https://usegalaxy.eu>). A list of ChIP-seq and
200 RNA-seq data sets used in this study can be found in Supplementary Table S3. A detailed
201 description of RNA-seq and ChIP-seq procedures can be found in the Supplemental
202 Material.

203

204 **Statistical Analysis.** Data are presented as mean \pm s.e.m. Data are derived from multiple
205 experiments unless stated otherwise. Statistical analysis was performed using a two-tailed
206 unpaired *t*-test or one-way or two-way ANOVA with Tukey's post hoc test comparing all
207 groups to each other, using GraphPad Prism 9.0 software. Differences were considered
208 statistically significant at $p < 0.05$ (* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$).

209

210 **Data and Resource Availability.** The datasets and resource generated during and/or
211 analyzed during the current study are available from the corresponding author upon
212 reasonable request.

213 **Results**

214

215 **β -cell specific *E2f1* deficiency impairs glucose tolerance due to defective *in vivo***
216 **glucose-stimulated insulin secretion.**

217

218 To determine whether *E2f1* regulates insulin-producing β -cell fate and function in a cell-
219 autonomous manner, we generated β -cell specific *E2f1*-deficient mice by crossing *E2f1*
220 floxed (*E2f1^{fl/fl}*) with RIP-Cre (Rip-Cre⁺) mice (28). Quantitative RT-PCR showed a 91 %
221 tissue-specific reduction in *E2f1* expression in pancreatic islets isolated from *E2f1 ^{β -/-}* mice
222 (Supplementary figure S1A). 12-week-old *E2f1 ^{β -/-}* mice displayed normal body weight
223 (Supplementary figure S1B) and fasting glycemia when fed a chow diet (Supplementary
224 figure S1C) when compared to age-matched control *E2f1* floxed (*E2f1^{fl/fl}*) and Rip-Cre (Rip-
225 Cre⁺) male littermates. No significant difference was observed between *E2f1 ^{β -/-}* mice and
226 *E2f1^{fl/fl}* control littermates for body weight, fasting glycemia, glucose tolerance or insulinemia
227 in 6-week-old (Supplementary figures S2A to S2E) and 8-week-old animals (Supplementary
228 figures S2F to S2J). However, when challenged with a bolus of glucose, 12-week-old *E2f1 ^{β -/-}*
229 ^{-/-} mice exhibited glucose intolerance (Figures 1A-B), primarily due to decreased insulin
230 secretion in response to *in vivo* glucose injection (Figure 1C) rather than defective insulin
231 sensitivity (Supplementary figure S2K).

232 We next sought to evaluate the metabolic consequences of modulating *E2f1* expression in
233 adult β cells. To this end, we generated β -cell specific *E2f1* deficient mice (*E2f1^{MIP-CreERT β -/-}*
234) by crossing *E2f1^{fl/fl}* with the tamoxifen-inducible model MIP-Cre-ERT (MIP-CreERT⁺) mice
235 (29). We first confirmed efficient recombination upon tamoxifen treatment in pancreatic islets
236 isolated from *E2f1^{fl/fl}* and *E2f1^{MIP-CreERT β -/-}* (Supplementary figure S2L). Like *E2f1 ^{β -/-}* mice,
237 the genetic deletion of *E2f1* in adult β cells revealed glucose intolerance 1 month after
238 tamoxifen administration (Supplementary figures S2M and S2N), a phenotype that was

239 aggravated 3 months post-tamoxifen gavage (Figures 1D-E). Interestingly, insulinemia
240 during ipGTT was also impaired in *E2f1^{MIP-CreERT} β^{-/-}* mice 20 minutes after glucose injection
241 (Figure 1F). Altogether, these data suggest that the β-cell specific *E2f1* deficiency, either
242 triggered early during development or in fully mature adult β cells, impairs glucose tolerance
243 and insulin secretion in response to glucose.

244

245 **Increased alpha-to-beta-cell ratio in the pancreas of *E2f1*-deficient mice.**

246

247 As *E2f1^{β^{-/-}}* mice displayed impaired insulin secretion in response to glucose, we investigated
248 the contribution of *E2f1* to islet morphology. We observed that islet density (Figure 2A), islet
249 size (Figure 2B), β-cell fraction (Figure 2C), β-cell mass (Figure 2D) and β-cell size (Figure
250 2E and Supplementary figure S3A) were comparable between 3-month-old *E2f1^{β^{-/-}}* and
251 *E2f1^{fl/fl}* pancreata. We then analyzed proliferation and apoptosis in *E2f1^{β^{-/-}}* and *E2f1^{fl/fl}*
252 pancreas. Apoptotic cells were not detected in the pancreas from control and β-cell specific
253 *E2f1*-deficient mice, as shown by cleaved caspase 3 immunofluorescent staining
254 (Supplementary figures S3B-C). BrdU staining of *E2f1^{β^{-/-}}* and *E2f1^{fl/fl}* pancreatic sections
255 revealed that the number of proliferative cells was decreased in *E2f1^{β^{-/-}}* islets (Figure 2F and
256 Supplementary figures S3D). Remarkably, an immunofluorescence analysis of sections
257 from control and *E2f1^{β^{-/-}}* pancreas demonstrated a significant increase of glucagon-positive
258 cells (Figures 2G-H), whereas the number of somatostatin-positive cells was not modified
259 in *E2f1^{β^{-/-}}* islets (Figures 2I-J). These results suggest that the loss of *E2f1* expression could
260 induce an α-cell hyperplasia associated with lower endocrine cell proliferation.

261 To confirm the role of *E2f1* in maintaining physiological α-to-β-cell ratio, we performed
262 immunofluorescence staining of insulin and glucagon in the pancreas of wild-type and global
263 *E2f1* knock-out mice (*E2f1^{-/-}*). The detailed analysis of *E2f1^{-/-}* pancreas revealed a
264 decreased proportion of ins⁺ β-cell and a concomitant expansion of the glu⁺ α-cell

265 percentage per islet in chow-fed 16-week-old animals, as demonstrated by the quantification
266 of insulin and glucagon positive cells in *E2f1*^{+/+} and *E2f1*^{-/-} pancreas (Supplementary
267 figures S4A, S4B and S4C). To test whether *bona fide* regulators of E2F1 activity could
268 rescue the altered α -to- β -cell ratio observed in *E2f1*^{-/-} mice, we used 2 different genetically-
269 engineered mouse models (Supplementary figures S4D). We first used the R24C mouse
270 model of CDK4 hyperactivation (CMV-CDK4^{R24C}) that constitutively expresses a CDK4
271 mutant protein that restores β -cell mass and function during diabetes development (37; 38).
272 As previously observed (38), α -to- β -cell ratio was decreased in *CMV-Cdk4*^{R24C} pancreas
273 (Supplementary figures S4C and S4E). We then generated compound mutant mouse
274 models with both *E2f1* deficiency and overactive CDK4 (*E2f1*^{-/-}::*CMV-Cdk4*^{R24C}).
275 Interestingly, the decreased α -to- β -cell ratio ~~β -cell number~~ observed in *CMV-Cdk4*^{R24C}
276 pancreas was blunted in *E2f1*^{-/-}::*CMV-Cdk4*^{R24C} mice, with a concomitant increase of
277 glucagon immunofluorescent staining (Supplementary figures S4C and S4F). To sustain
278 such findings, we then replicated these observations in an alternative model using *Cdkn2a*-
279 deficient mice (*Cdkn2a*^{-/-}; (27)), an upstream regulator of the E2F1-CDK4-pRb signaling
280 pathway involved in β -cell function (39-41). Although Glu⁺ and Ins⁺ immunofluorescent
281 positive cell staining was similar between *Cdkn2a*^{+/+} and *Cdkn2a*^{-/-} pancreas
282 (Supplementary figures S4C and S4G), *E2f1*^{-/-}::*Cdkn2a*^{-/-} compound mutant mice
283 displayed an altered α -to- β -cell ratio with a decrease of Ins⁺ and an increase Glu⁺ cell
284 numbers (Supplementary figures S4C and S4H). In addition, our recent observation of
285 decreased plasma insulin levels, increased plasma glucose and glucose intolerance in
286 *db/db*::*E2f1*^{-/-} mice compared to *db/db*::*E2f1*^{+/+} controls (25) prompted us to evaluate islet
287 morphology in these diabetic mouse models. Accordingly, in the *db/db* background, *E2f1*
288 deficient mice displayed a further increase of the α -cell number per islet, while exhibiting a
289 lower β -cell count compared to *db/db*::*E2f1*^{+/+} controls (Supplementary figures S5A-B).
290 Altogether, these results suggest a specific role of E2f1 in maintaining pancreatic β -cell

291 numbers under normal conditions but also in a diabetic environment associated to glucose
292 intolerance, insulin resistance and obesity. We may then hypothesize that *E2f1* expression
293 in β cell may be necessary to maintain insulin secretion and glucose homeostasis
294 associated to normal α -to- β -cell ratio.

295

296 ***E2f1*-deficiency in β cells does not induce their conversion into α cells.**

297

298 To evaluate the fate of *E2f1*-deficient β cells and the potential origin of the increased number
299 of α -cells in *E2f1* ^{β -/-} mice, we performed lineage-tracing experiments. To track the destiny of
300 β -cells, the expression of the tomato tracer was monitored in Rip-Cre^{+/+}::tdTomato and *E2f1* ^{β -/-}
301 ^{+/+}::tdTomato. As expected, tomato positive (Tom+) cells were colocalized with ins⁺ cells in
302 controls and *E2f1* ^{β -/-}::tdTomato pancreata (Figure 3A). Interestingly, we could not detect any
303 colocalization of Tom+ and glu+ cells in controls, nor in β -cell specific *E2f1* deficient
304 pancreata (Figure 3B). β -cell lineage tracing results were further confirmed in *E2f1* ^{β -/-} mice
305 by using the ECFP reporter mouse strain model (30) (Figure 3C-D). These data suggest
306 that, although the number of α cells is increased upon *E2f1* deficiency, loss of *E2f1*
307 expression in β cells does not trigger their conversion into α cells.

308

309 **Loss of β -cell identity markers in *E2f1* deficient pancreatic islets.**

310

311 E2F1 is a transcription factor that controls gene expression in several cellular systems. In
312 order to get a global view of the transcriptional mechanisms associated with the loss of *E2f1*
313 expression in the β -cell, we performed RNA sequencing (RNA-seq) in control (*E2f1*^{fl/fl}) and
314 *E2f1* ^{β -/-} isolated islets. As expected, the floxed region of the *E2f1* gene spanning exon 2 and
315 3 was not covered in *E2f1* ^{β -/-} isolated islets compared to *E2f1*^{fl/fl} isolated islets, indicating
316 specific and efficient gene deletion through the *Cre* recombinase activity in *E2f1* ^{β -/-} isolated

317 islets (Supplementary figure S6A). Transcriptome analysis revealed that 692 annotated
318 genes were differentially expressed across the two groups (adjusted P Value (AdjP) <0.05).
319 Interestingly, a majority of genes were upregulated in *E2f1*^{β-/-} isolated islets (493 genes,
320 Figure 4A and Supplementary Table S4), with only 199 down-regulated genes associated
321 with the loss of *E2f1* expression in β-cells (Figure 4A and Supplementary Table S4). This
322 first observation suggests that *E2f1* expression is not only necessary to activate, but also to
323 repress gene transcription within β-cells. Analyses of the RNA-seq data of downregulated
324 genes with Ingenuity Pathway Analysis (IPA) software revealed an enrichment of gene
325 networks involved in insulin secretion pathway or Maturity Onset Diabetes of the Young
326 (MODY) signaling (Figure 4B). Conversely, upregulated genes in *E2f1*^{β-/-} isolated islets were
327 mostly associated with inflammatory response, including the hepatic fibrosis signaling
328 pathway, iNOS signaling or toll-like receptor signaling (Figure 4C). RNA-seq data were then
329 analyzed using the “upstream regulator analysis” function of IPA to identify potential
330 contributors that could be associated to the transcriptional reprogramming observed in
331 *E2f1*^{β-/-} isolated islets. Among the most significant upstream regulators of the upregulated
332 genes, Tumor Necrosis Factor, interferon gamma, Myd88 were identified (Supplementary
333 Table S5). Conversely, analysis of the downregulated genes suggested that Xbp1, Hnf1a,
334 Neurod1 and Pdx1, transcription factors previously shown to control β-cell identity or
335 function, were found to be potential upstream regulators that were predicted to be inhibited
336 (Supplementary Table S5). To better understand the relationship between the observed
337 metabolic phenotype (*i.e.* glucose intolerance and defective insulin secretion), increased
338 glu+ cells and *E2f1* deficiency, we filtered gene sets to focus on β- and α-cell-specific genes
339 being conserved between zebrafish, mouse and human (42). Notably, a total of 15 genes
340 from 109 conserved genes (82 and 27 for α-cell and β-cell genes, respectively) were
341 differentially expressed. Interestingly, most of the conserved β-cell markers were found to
342 be decreased in *E2f1*^{β-/-} isolated islets (Figure 4D and Supplementary figure S6B), whereas

343 most of the conserved α -cell genes were upregulated upon *E2f1* deficiency (Figure 4D and
344 Supplementary figure S6C). Gene Set Enrichment Analysis (GSEA) further confirmed an
345 enriched signature of increased expression of α -cell markers (Figure 4E) and conversely, a
346 decreased expression of β -cell markers in *E2f1* ^{β -/-} isolated islets (Figure 4F). We further
347 confirmed these changes in the expression of selected α - and β -cell markers at the
348 transcriptional level by qPCR in an independent experiment: accordingly, we observed a
349 strong decrease in transcript levels of *Pdx1*, *Ins2*, *Pcsk9*, *Foxo1* and *Glp1r* in *E2f1* ^{β -/-} islets
350 (Supplementary figure S6D). Conversely, α -cell specific Aristaless-related homeobox (*Arx*)
351 mRNA levels were increased in *E2f1* ^{β -/-} islets (Supplementary figure S6E). Altogether these
352 results suggest that the β -cell specific deletion of *E2f1* induces a transcriptional
353 reprogramming characterized by a loss of β -cell identity genes associated to an increased
354 expression of non β -cell markers.

355

356 **The treatment with the E2F inhibitor HLM006474 inhibits glucose-stimulated insulin**
357 **secretion and alters β - and α -cell gene expression in Min6 cells and human islets.**

358

359 To assess the effect of E2F1 activity on β -cell identity markers in Min6 cells and human
360 islets, we made use of the E2F pan-inhibitor HLM006474 previously shown to inhibit the
361 binding of E2Fs to their DNA target genes and E2F1 transcriptional activity (35). Consistent
362 with our previous findings in HEK293 cells (35), a 48h treatment of Min6 cells with this
363 inhibitor triggered a decrease in *E2f1* transcriptional activity, as measured by transient
364 transfection experiments using an E2F reporter gene (Figure 5A). In addition, the treatment
365 of Min6 cells with this inhibitor induced a marked decrease in glucose-stimulated insulin
366 secretion (Figure 5B) and in the expression of several β -cell markers, including *Ins1*, *Pdx1*,
367 and *Pax4* and ~~*Nkx2.2*~~ (Figure 5C). The treatment of human islets with the E2F inhibitor for
368 48 hours also decreased GSIS (Figure 5D) and β -cell marker expression levels with a

369 concomitant increase in the expression of α -cell genes (Figure 5E). Therefore, the
370 pharmacological inhibition of E2F activity impairs β -cell function and gene expression in both
371 mouse cell line and human islets, suggesting that E2F1 activity is also required in human
372 islets to maintain proper insulin secretion and β -cell identity genes, as observed in mice.

373

374 **Maintenance of β -cell identity is dependent on E2F1 transcriptional activity.**

375

376 Our transcriptome analysis revealed a 2.5-fold more up- than downregulation of global gene
377 expression in *E2f1* ^{β -/-} isolated islets. Comparative analysis of log10 transcripts per million
378 levels (Log10(TPM+1)) of up- and downregulated genes values demonstrated that the
379 expression of upregulated genes in *E2f1* ^{β -/-} islets was significantly increased upon *E2f1*
380 deficiency compared to wild-type controls whereas the expression of downregulated genes
381 was not significantly modulated (Figure 6A). Considering that *E2f1* could play a dual role in
382 the regulation of gene expression in pancreatic β -cells, we postulated that this mechanism
383 could be related to a distinct epigenomic profile within promoter of genes that are up- and
384 down-regulated in *E2f1* ^{β -/-} islets. Using a recently published chromatin-state segmentation
385 model (12), we probed the active/repressive level of these promoters by monitoring several
386 epigenome marks such as active and poised promoters (tri-methylation of lysine 4 in histone
387 H3 [H3K4me3]) and enhancers (acetylation of lysine 27 in histone H3 [H3K27ac]).
388 Intersecting publicly available data of chromatin immunoprecipitation followed by next-
389 generation sequencing (ChIP-seq) from healthy C57Bl6/J mouse pancreatic islets (GSE
390 110648 (12)) and our RNA-seq data, we grouped up- and down regulated genes according
391 to their chromatin state (Figure 6B and Supplementary Table S4). We observed that 61% of
392 the upregulated genes in *E2f1* ^{β -/-} pancreatic islets were associated to a silent chromatin state
393 in healthy C57Bl6/J mouse pancreatic islets characterized by bivalent H3K4me3/H3K27me3
394 and Polycomb-repressed (H3K27me3) marks. Conversely, 82% of the down-regulated

395 genes showed an enrichment in active chromatin state characterized by RNA-Pol2
396 recruitment, H3K4me3 and H3K27ac histone marks.

397

398 While H3K4me3, H3K27ac and H3K27me3 ChIP-seq data were available for mouse islets,
399 we then performed ChIP-seq experiments in Min6 cells as a surrogate of β -cell. H3K4me3,
400 H3K27ac and H3K27me3 ChIP-seq signals were thus interrogated within promoter
401 (centered to transcription start site [TSS] +/- 1 kb) of up- and downregulated genes both in
402 Min6 cells and mouse pancreatic islets (Figures 6C-D and Supplementary figures S7A-B).
403 H3K4me3 as well as H3K27ac signals were stronger within promoter of genes that are
404 downregulated in *E2f1* ^{β -/-} isolated islets compared to upregulated genes, both in Min6 cells
405 and mouse pancreatic islets (Figure 6C and Supplementary figures S7A-B). Conversely,
406 H3K27me3 ChIP-seq signals were lower in the promoter region of downregulated genes
407 compared to upregulated genes (Figure 6D and Supplementary figures S7A-B). Altogether,
408 these results suggest that the transcriptome of *E2f1* ^{β -/-} islets is associated to a specific
409 epigenomic pattern that may be involved in the control of E2f1-mediated transcriptional
410 activation or repression.

411

412 **E2f1 cistrome profiling by ChIP-seq identifies potential direct E2f1 target genes**
413 **involved in β -cell function.**

414

415 Having demonstrated that the transcriptome of *E2f1* ^{β -/-} isolated islets was altered compared
416 to controls, we next asked whether these up and down regulated genes identified in isolated
417 islets from *E2f1* ^{β -/-} mice were direct or indirect E2f1 target genes. To reach this aim, we
418 performed ChIP-seq experiments to determine chromatin-bound E2f1 target genes.

419 In a first series of experiments, ChIP-seq experiments targeting endogenous E2f1 were
420 conducted in pancreatic islets but failed to profile the endogenous E2f1 cistrome due to lack

421 of antibody specificity (data not shown). Alternatively, E2f1 was over-expressed in Min6 cells
422 as surrogate of β -cells through transfection of a plasmid encoding E2f1 fused to Flag tag
423 (E2f1-flag). As expected, E2f1-flag protein was overexpressed in Min6 cells transfected with
424 plasmid encoding E2f1-flag compared to those transfected with empty plasmid
425 (Supplementary figure S8A). These results prompted us to perform a ChIP-seq analysis
426 using an anti-flag antibody to profile E2f1-flag cistrome at genome-wide level in Min6 cells.
427 Among the E2f1-bound genomic regions, 94.5% were localized within promoter (≤ 1 kb)
428 whereas other genomic locations were marginally represented (Supplementary figure S8B)
429 confirming that E2f1 is a transcription factor mainly bound within GC-rich proximal promoter
430 (43). Indeed, a DNA motif enrichment analysis was performed within E2f1-enriched
431 promoter regions showing that E2f motif was the most significant enriched motif within these
432 regions suggesting that E2f1 was directly bound on promoter (Supplementary figure S8C).
433 Next, we consolidated our results in an independent experiment by performing a ChIP-qPCR
434 analysis targeting two E2f1-flag-bound promoters (from *Ezh2* and *Ccne1* genes) detected
435 by ChIP-seq (Supplementary figures S8D and E, respectively). As expected, ChIP-qPCR
436 performed with anti-Flag antibody led to a significant enrichment of E2f1-flag within both
437 *Ezh2* (Supplementary figure S8F) and *Ccne1* (Supplementary figure S8G) promoters
438 compared to ChIP-qPCR conducted with unspecific antibody (IgG). In addition, none E2f1-
439 flag enrichment was detected within an unspecific intergenic chromatin region (negative
440 control, Supplementary figure S8H), validating our E2f1 cistrome analysis.

441 After ChIP-qPCR-based validation of our anti-flag antibody approach in Min6 cells
442 (Supplementary figure S8), E2f1-flag ChIP-seq signal was interrogated within promoter
443 (centered to TSS +/- 1kb) of dysregulated genes identified in pancreatic islets isolated from
444 *E2f1* ^{β -/-} mice to identify E2f1-bound (*i.e.*, direct E2f1 target genes) and E2f1-unbound (*i.e.*,
445 indirect E2f1 target genes) genes. Among the upregulated genes in *E2f1* ^{β -/-} islets, we
446 identified 197 genes harboring E2f1-bound proximal promoters and 297 genes with E2f1-

447 unbound proximal promoters (Supplementary table S6). Among the downregulated genes,
448 95 genes harbored a E2f1-bound proximal promoter whereas 106 genes were identified as
449 E2f1-unbound proximal promoters (Supplementary table S6). This ChIP-seq and RNA-seq
450 intersecting analysis was exemplified by a series of genes including *Nkx6-1* (Supplementary
451 figure S9A) and *Tcf7* (Supplementary figure S9B) displaying E2f1 enrichment in the close
452 vicinity of TSS. Concerning E2f1-unbound promoters, we could observe that *Ins1*
453 (Supplementary figure S9C) and *Gzma* (Supplementary figure S9D), although differentially
454 regulated at the mRNA level, were not bound by E2f1 at the chromatin level. Altogether,
455 these results suggested that E2f1 could have a dual role on the regulation of gene
456 expression by acting either as a transcriptional activator or repressor in pancreatic islets,
457 through both indirect and direct mechanisms at the chromatin level.

458 To better appreciate the potential role of E2f1 in the control of gene expression, canonical
459 pathway analysis was performed using the different clusters of genes identified above. Our
460 analysis revealed that E2f1-unbound downregulated genes were mostly associated to
461 insulin secretion signaling pathway (Supplementary figures S9E-H). IPA could not reveal
462 any enrichment of pathways involved in insulin secretion in E2f1-bound promoters.
463 However, a detailed analysis of ChIP-seq data from down- and upregulated genes revealed
464 that E2f1 was associated to the chromatin region of several genes involved in β -cell function,
465 such as *Glis3*, *Glp1r*, *Manf*, *Nkx6-1*, *Ppp1r1a* or *Wfs1* or β -cell dysfunction, such as *Bcl11a*
466 or *Cxcl14* (Supplementary figure S9A and Supplementary table S6).

467

468 Since E2f1-bound genes in Min6 cells are predicted to be potential E2f1 direct target genes,
469 we next investigated whether there were differences in the epigenomic activation level of
470 these promoters. Therefore, we conducted a ChromHMM analysis (Chromatin Hidden
471 Markov Model) allowing characterization of chromatin states based on differential
472 enrichment levels of histone marks as well as transcription factor at genome-wide level (44).

473 ChromHMM analysis was thus performed by combining ChIP-seq data obtained in Min6
474 cells from both E2f1-Flag and a selection of histone marks related to the active/repressive
475 state of promoter (i.e., H3K4me3, H3K9ac, H3K27ac, and H3K27me3) and enhancers (i.e.,
476 H3K4me1, H3K27ac and H3K27me3). By applying a 16-state ChromHMM analysis, we
477 demonstrated that only 3 states were enriched with E2f1-Flag (states 6, 14 and 15) (Figure
478 7A). Whereas states 14 and 15 displayed the typical features of active promoter (i.e.,
479 H3K4me3, H3K9ac and/or H3K27ac), chromatin state related to state 6 was more
480 associated with repressed promoter (H3K4me3 and H3K27me3). The TSS-centered
481 genomic distribution analysis of these 16 chromatin states confirmed that states 6, 14 and
482 15 corresponded to proximal promoter of genes (Supplementary figure S10A).

483 To go further in the characterization of the role of E2f1 in the β -cell, we next decided to
484 analyze the differential transcriptomic data from *E2f1* ^{β -/-} isolated islets in the light of this
485 ChromHMM analysis by determining whether the promoter of deregulated genes belonged
486 to one of the chromatin states described above. This analysis showed that 23.4% of the
487 upregulated genes (109 on 465 genes) harbored a state 6-promoter indicating that the
488 expression of these genes could be repressed by E2f1 in β -cells *in vivo* (Supplementary
489 Table S7). Conversely, promoters of downregulated genes were more associated with state
490 14 (46.5%, 87 out of 187 genes, Supplementary Table S7) and 15 (41.1%, 77 out of 187
491 genes, Supplementary Table S7) indicating that E2f1 could play a positive role in the
492 regulation of expression of these genes in β -cell. Although pathway analysis of the different
493 chromatin states of the direct down- and upregulated genes could not precisely demonstrate
494 a specific enrichment of pathways involved in insulin secretion or β -cell function
495 (Supplementary figures S10B to G), we could observe that most of the non β -cell markers,
496 such as *Cxcl12* (Figure 7B) or the β -cell disallowed genes *Gab1* (Figure 7C), *Mgll*, *Oat*
497 (Supplementary Table S7), *Slc25a33* (Figure 7D) or *Yap1* (Figure 7E), were mostly
498 associated to segment 6 and were upregulated in *E2f1* ^{β -/-} isolated islets (Supplementary

499 Table S7). Interestingly, genes related to β -cell function, such as *Glis3* (Figure 7F), *Glp1r*
500 (Figure 7G), *Manf* (Figure 7H), *Nkx6-1* (Supplementary Table S7), *P2ry1* (Figure 7I) or *Wfs1*
501 (Supplementary Table S7), were downregulated and associated to state 14 or 15
502 (Supplementary Table S7). Altogether, these results support a potential dual active and
503 repressive role for E2f1 on transcriptional regulation within β -cells. Importantly, our data
504 suggest that E2f1 modulates β -cell and non β -cell transcriptional programs in pancreatic
505 islets through direct, epigenomic based-mechanisms as well as indirect processes probably
506 through the upstream regulation of β -cell enriched transcriptional regulators, such as Pdx-1
507 or Hnf1a.

508 **Discussion**

509

510 In the present study, we show that the transcription factor E2F1 plays an essential role in
511 maintaining β -cell function and identity through the control of transcriptomic and epigenetic
512 programs within the pancreatic islets. Our study is the first one to demonstrate a direct, cell-
513 autonomous contribution of *E2f1* in controlling not only *in vivo* insulin secretion but also β -
514 cell identity maintenance, without affecting the pancreatic islet cell number and β -cell mass.
515 The role of E2F1 in the control of cell cycle and proliferation has been extensively studied,
516 particularly in the context of cancer (18). However, its function in non-proliferating fully
517 differentiated cells, including β -cells, remains to be precisely deciphered. The observation
518 that cell cycle regulators, including E2F1, are expressed in cells that are not proliferating,
519 suggest that they may be involved in adaptive pathways that are independent of cellular
520 proliferation. We and others have demonstrated that this pathway plays a key role in post-
521 natal β -cell proliferation (45-47), glucose homeostasis and insulin secretion (20; 48; 49).
522 Studies also revealed that the Cdk4-E2F1-pRb pathway controls the fate of pancreatic
523 progenitors through the transcriptional control of the expression of *Ngn3* and *Pdx1* as well
524 as *Pdx1* protein stability (50; 51). Most of these studies were performed using germline *E2f1*
525 deficient mice, which precludes to ascertain a cell-autonomous role of *E2f1* in the endocrine
526 pancreas and β -cell functions. To better appreciate the specific role of E2F1 in β -cells, we
527 specifically knocked-down *E2f1* in the β -cell using the Cre/loxP technology. Although we
528 cannot rule out an early role for *E2f1* in pancreatic progenitors due to the use of the RIP-
529 Cre mice (28), our data demonstrate that *E2f1* expression within the β -cell is necessary to
530 maintain a proper gene expression program to regulate insulin secretion and glucose
531 homeostasis. Moreover, we observe that the specific *E2f1* deficiency in adult, mature β -cells
532 results in glucose homeostasis impairments and failure in glucose-stimulated insulin
533 secretion. Since E2F1 overexpression stimulates β -cell proliferation and function (48), our

534 results further suggest that targeting *E2f1* might be of interest to maintain β -cell functions in
535 the context of diabetes.

536

537 The complexity of E2f1 biology resides in the fact that it can positively or negatively regulate
538 the expression of its target genes. Our data suggest that E2f1 may be part of a repressor
539 complex that regulates β -cell identity. In line with this, we observe that genes mostly
540 upregulated in *E2f1* ^{β -/-} isolated islets, including *Gab1*, *Slc25a33* or *Yap1*, were identified as
541 β -cell “ disallowed ” genes, *i.e.* genes that are repressed in β cells (52), or genes involved
542 in the inflammatory response such as *Cxcl12*, *Cxcl14* or *Irf5*. This suggests that the
543 repressive effects of E2f1 are key in maintaining β -cell identity and subsequent β -cell
544 function. Accordingly, repression of non β -cell programs is crucial for maintaining β -cell
545 identity. Pdx1 (14), Pax6 (15), Nkx6.1 (16) and Nkx2.2 (17) are key transcription factor
546 required to maintain gene repression of non- β -cell programs. Interestingly, *Nkx6.1* mRNA
547 levels are decreased in *E2f1* ^{β -/-} isolated islets, and *Nkx6.1* promoter is directly bound by
548 E2f1, suggesting that E2f1 could modulate β -cell functions through *Nkx6.1* regulation.
549 Chromatin regulators and epigenomic features play important roles in the control of β -cell
550 identity and plasticity (53-55). Indeed, the modulation of islet-enriched transcription factor
551 activity, including Pdx1 or Nkx2.2, involves their interaction with coregulators such as
552 Dnmt1, Dmnt3a or Hdac1 (56-58) or their accessibility to chromatin, as demonstrated for
553 the β -cell specific deletion of protein arginine methyltransferase 1 (Prmt1) that results in the
554 loss of β -cell identity and diabetes development (59). In addition, recent studies also indicate
555 that loss of Polycomb silencing in human and mouse β -cells contributes to the loss of β -cell
556 identity in diabetes (12). Indeed, the β -cell specific deletion of *Eed*, a component of the
557 Polycomb repressive complex (PRC)-2, triggers β -cell dysfunction, dedifferentiation and
558 diabetes development associated to chromatin-state-associated transcriptional
559 dysregulation (12). In addition, as PRC2 loss induces β -cell plasticity through epigenomic

560 reprogramming at both active and silent genes suggest that maintaining proper and specific
561 histone marks and chromatin state at precise loci is crucial to maintain normal β -cell
562 functions and avoid T2D development. Interestingly, most of the upregulated genes in $E2f1^{\beta-/-}$
563 β pancreatic islets were characterized by bivalent H3K4me3/H3K27me3 and Polycomb-
564 repressed (H3K27me3) marks. In addition, epigenomic interventions triggering ectopic
565 acetylation and gene derepression contribute to β -cell dysfunctions. Indeed, blocking HDAC
566 activity through the use of the HDAC inhibitor SAHA, impairs glucose intolerance in mice
567 fed a HFD (12). Here we show that the loss of $E2f1$ function triggers transcriptional
568 dysregulation of specific genes that are in a bivalent (*i.e.* H3K4me3/H3K27me3 and
569 Polycomb-repressed (H3K27me3) marks) and active (*i.e.* RNA-Pol2 recruitment, H3K4me3
570 and H3K27ac histone marks) state in healthy pancreatic islets. This suggests a potential
571 ectopic acetylation in the promoter region of upregulated genes in $E2f1^{\beta-/-}$ islets and
572 decreased activation of the promoter region of downregulated genes. Interestingly, we
573 demonstrate in this study that $Ezh2$, a member of the PRC2 complex, is also a direct $E2f1$
574 target gene. Although $E2f1$ is a ubiquitous transcription factor that is weakly expressed
575 within β -cell compared to *bona fide* β -cell genes, we speculate that this transcriptional
576 regulator may cooperate with β -cell transcription factors and/or the chromatin machinery
577 such as HDAC or the PRC2 complex to integrate some signals necessary for β -cell
578 maintenance in physiological conditions. Since $E2f1$ regulates gene expression through its
579 interaction with repressor complexes including pRb, SWI/SNF and HDACs (18), our finding
580 that $E2f1$ mediates repression of non β -cell programs deserves deeper investigations to
581 identify the $E2f1$ complexes that can trigger these transcriptomic and epigenomic effects in
582 the β -cell and their patho(physio)logical consequences.

583 The current study has a number of limitations. First, the use of RipCre transgenic mice to
584 delete $E2f1$ in the β cells may also contribute to side-effects on glucose homeostasis.
585 Although we observed that these mice do not have a metabolic phenotype (Figure 1 and

586 (22; 31)), it cannot be excluded that the transgene *per se* could exert specific deleterious
587 functions in β cells.

588 Second, over-expression studies in Min6 and pharmacological treatment with the E2F
589 inhibitor may display adverse side-effects and induce off-target actions, such as non-specific
590 inhibition of other cell-cycle/E2f related proteins or modulation of cofactor activity due to
591 overexpression of transcription factors (60).

592 Third, the use of bulk RNA-seq on total pancreatic islets does not allow to perfectly address
593 the effect of *E2f1* deletion on the β -cell transcriptome. Transcriptomic analyses using sorted
594 β cells or single-cell RNA-sequencing will provide direct evidences regarding the alteration
595 of β -cell identity within specific pancreatic cell populations.

596 Finally, we observe increased α -cell positive staining associated with decreased endocrine
597 cell proliferation in *E2f1* ^{β -/-} islets, and lineage tracing experiments demonstrate that α -cells
598 do not originate from β -cell. The origin of the supernumerary α cells observed in *E2f1* ^{β -/-}
599 islets remains unknown and requires further investigations.

600 In summary, the present data highlight that E2f1 transcriptional activity within pancreatic
601 islets is key for maintaining glucose homeostasis and insulin secretion through the
602 regulation of key β -cell identity genes and the repression of non β -cell programs, both in
603 mouse and human islets. The observation that E2F1 levels are decreased in human T2D
604 islets (24) suggests that a reduced E2F1 expression or activity may contribute to β -cell
605 failure in diabetes.

606

607 **Author contributions.** F.O., C.B., M.E.F., E.C., L.R., X.G., M.M., C.C., N.R., E.B. and
608 S.A.H. contributed to the *in vivo* and cellular experiments. F.O., M.M., C.B., E.D., S.A., L.B.,
609 M.D. and A.B. performed the RNA-seq and ChIP-seq experiments and analysis. P.D.D.,
610 Z.B., P.M., L.F., J.K.C., F.P., B.P. and P.C. provided reagents and data and discussed the
611 results from the study. J.-S.A. designed the study, supervised the project and contributed to
612 experiments and/or their analysis and the funding of this project. F.O., C.B., M.E.F., E.C.,
613 N.R., P.F., A.B. and J.-S.A. wrote and/or edited the manuscript. F.O., C.B., M.E.F. and E.C.
614 contributed equally to this work. J.-S.A. is the guarantor of this work and, as such, had full
615 access to all of the data in the study and take responsibility for the integrity of the data and
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617

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639

640 **Conflict of interest.** The authors declare no competing financial interests.

641

642 **References**

643

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- 836

837 **Figure legends**

838

839 **Figure 1. The β cell-specific deletion of *E2f1* impairs glucose tolerance and insulin**
840 **secretion in mice. (A)** Intraperitoneal glucose tolerance test (IPGTT) was performed on
841 *E2f1* ^{β -/-} (n=12), RIP-Cre^{+/+} (n=7) and *E2f1*^{fl/fl} (n=8) male mice at 12 weeks of age. **(B)** Area
842 under the curve (AUC) calculated from (B). **(C)** Plasma insulin levels at 0 and 30 min after
843 intraperitoneal glucose injection in *E2f1* ^{β -/-} (n=12), RIP-Cre^{+/+} (n=7) and *E2f1*^{fl/fl} (n=8) male
844 mice at 12 weeks of age. **(D)** IPGTT was performed on 5-month-old adult *E2f1*^{MIP-CreERT β -/-}
845 (n=12) and *E2f1*^{fl/fl} (n=8) male mice 3 months after tamoxifen administration. **(E)** Area under
846 the curve (AUC) calculated from (D). **(F)** Plasma insulin levels at 0 and 20 min after
847 intraperitoneal glucose injection in *E2f1*^{MIP-CreERT β -/-} (n=11) and *E2f1*^{fl/fl} (n=11) male mice at
848 5 months of age 3 months post tamoxifen treatment. All values are expressed as mean \pm
849 s.e.m. and were analysed by one-way analysis of variance (ANOVA) with Tukey's test (B,
850 C), two-way ANOVA with Tukey's test (A, D, F) or two-tailed unpaired *t*-test (E). **p* < 0.05;
851 ***p*<0.01.

852

853 **Figure 2. Normal β -cell mass but altered α -to- β cell ratio in β cell-specific *E2f1***
854 **deficient mice. (A to D)** Morphometric analysis revealed comparable islet density (A), mean
855 islet size (B), β -cell fraction (C), and mass (D), area (E) and proliferation (F) in pancreata of
856 3-month-old *E2f1* ^{β -/-} (n=5) and control *E2f1*^{fl/fl} (n=5) male mice. **(G)** Representative
857 immunofluorescent staining of insulin and glucagon in pancreatic sections from 3-month-old
858 *E2f1* ^{β -/-} and control *E2f1*^{fl/fl} male mice. **(H)** Ratio of glucagon labelled cells (Glucagon +) over
859 pancreatic islets in *E2f1* ^{β -/-} and *E2f1*^{fl/fl} male mice calculated from (F) (n=5). **(I)**
860 Representative immunofluorescent staining of insulin and somatostatin in pancreatic
861 sections from 3-month-old *E2f1* ^{β -/-} and control *E2f1*^{fl/fl} male mice. **(J)** The ratio of
862 somatostatin labelled cells over pancreatic islets in *E2f1* ^{β -/-} and *E2f1*^{fl/fl} male mice was

863 calculated from (G) (n=5). All values are expressed as mean \pm s.e.m. and were analysed by
864 two-tailed unpaired Mann-Whitney test (A, B, C, D, E, F, G, H, J). *p < 0.05; **p<0.01.

865

866 **Figure 3. Lineage tracing of β cells reveals that *E2f1*-deficient β cells are not converted**
867 **into α cells. (A-B)** Representative immunofluorescent staining of Dapi, Tomato, insulin (A)
868 and Dapi, Tomato, glucagon (B) in pancreatic sections from 12-week-old Rip-
869 *Cre⁺::E2f1^{+/+}::tdTomato* (*E2f1 ^{β +/+}*) and *E2f1 ^{β -/-}::tdTomato* (*E2f1 ^{β -/-}*) mice. **(C-D)**
870 Representative immunofluorescent staining of Dapi, red fluorescent protein (RFP), insulin
871 (C) and Dapi, RFP, glucagon (D) in pancreatic sections from 12-week-old *E2f1 ^{β -/-}::ECFP*
872 (*E2f1 ^{β -/-}*) mice.

873

874 **Figure 4. RNA-seq analysis of *E2f1* β cell-specific knockout islets reveal altered**
875 **transcriptional programs. (A)** Volcano plot providing adjusted P value (*i.e.*, FDR, false
876 discovery rate) and fold change for all gene transcripts in islets from *E2f1 ^{β -/-}* mice. Genes
877 that are differentially expressed compared to *E2f1^{fl/fl}* with an AdjP<0.05 are indicated by two-
878 level color coding. 199 downregulated protein-coding genes are highlighted in red. 493
879 upregulated protein-coding genes are highlighted in green (n=3 per genotype for RNA-seq
880 analysis). **(B-C)** Ingenuity Pathway Analysis of downregulated (B) and upregulated (C)
881 genes in *E2f1 ^{β -/-}* compared to *E2f1^{fl/fl}*. Histogram of enriched terms across input gene lists
882 are shown. **(D)** Evolutionary conserved α - and β -cell markers were recovered from Tarifeno-
883 Saldivia E *et al.* (42) and were used to filter our RNA-seq dataset. Volcano plots provides
884 AdjP values (*i.e.*, FDR, false discovery rate) and fold change for both α - and β -cell marker
885 transcripts in islets from *E2f1 ^{β -/-}* mice. The α - and β -cell markers are displayed as orange
886 square and blue triangle, respectively. Gene symbols of differentially expressed α - and β -
887 cell markers are displayed (AdjP<0.05). **(E-F)** Enrichment plot from Gene Set Enrichment

888 Analysis (GSEA) was conducted with 82 probe sets specifically expressed in α -cells (E) and
889 with 26 probe sets specifically expressed in β -cells (F).

890

891 **Figure 5. The pharmacological inhibition of E2f transcription factor activity induces a**
892 **loss of β -cell function in mouse and human islets. (A)** Min6 cells were transiently co-
893 transfected with the E2F-RE-Tk promoter luciferase construct in the absence (PCDNA3) or
894 presence of E2F1:DP1 heterodimer (E2F1/DP1) and were subsequently treated with DMSO
895 (0.1 %, 48h) or HLM006474-treated (10 μ M, 48h). Raw data for luciferase activity were
896 normalized to β -galactosidase activity. **(B)** Glucose stimulated insulin secretion (GSIS) at
897 indicated glucose concentration on DMSO (0.1 %, 48h) or HLM006474-treated (10 μ M, 48h)
898 Min6 cells (n=6). **(C)** qPCR-based analysis of β -cell specific mRNA expression in DMSO
899 (0.1 %, 48h) or HLM006474-treated (10 μ M, 48h) Min6 cells (n=3). **(D)** Glucose stimulated
900 insulin secretion (GSIS) at indicated glucose concentration on human islets treated with
901 DMSO (0.1 %, 48h) or HLM006474 (10 μ M, 48h) (n=3) (see supplementary Table S1 for
902 donor information). **(E)** qPCR-based analysis of β -cell specific (*INS*, *PDX1*, *PAX4*, *MAFA*
903 and *NEUROD1*) and α -cell specific (*ARX* and *GCG*) mRNA expression in DMSO (0.1 %,
904 48h) or HLM006474-treated (10 μ M, 48h) human islets (n=3). Data are represented as mean
905 \pm s.e.m. and were analyzed by two-way ANOVA with Tukey's test (A, B, D) and two-tailed
906 unpaired *t*-test (C, E). **p* < 0.05; ***p*<0.01; ****p*<0.001.

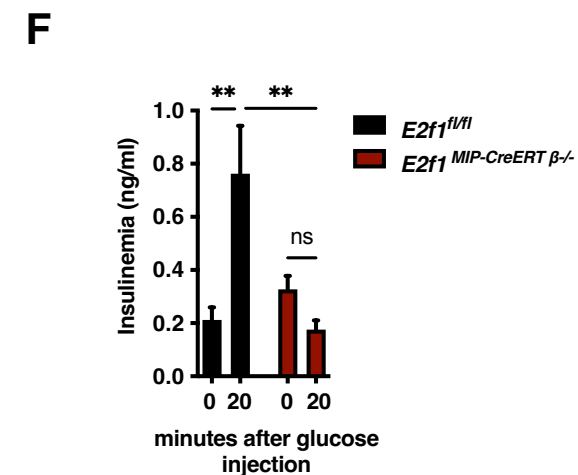
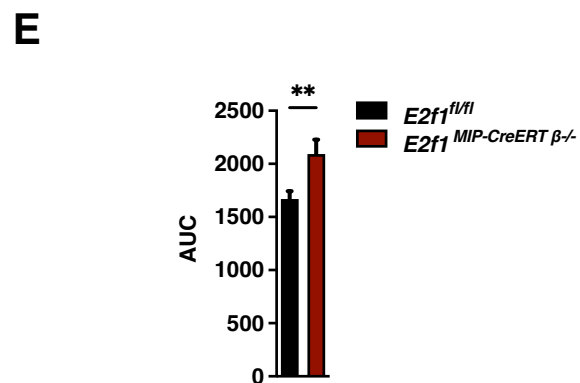
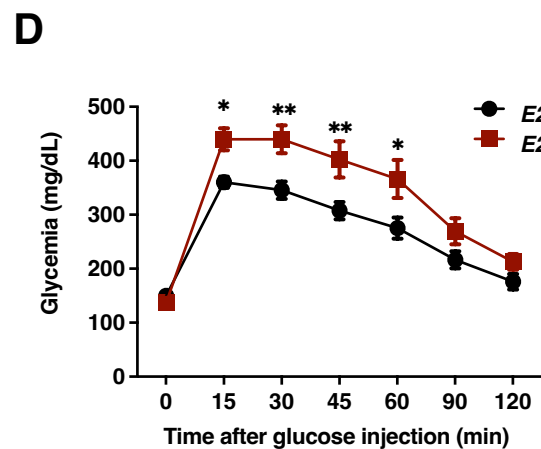
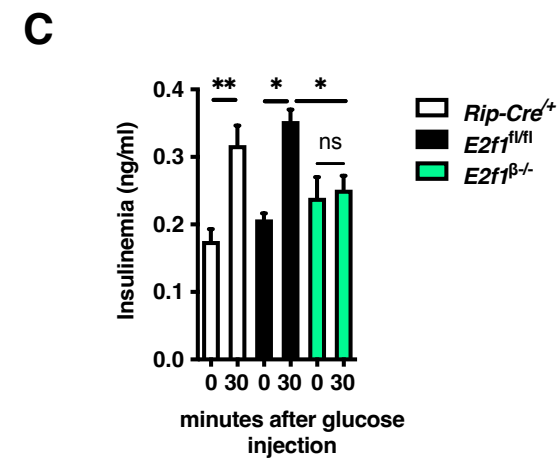
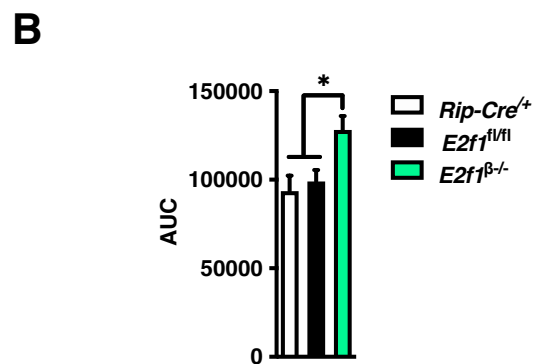
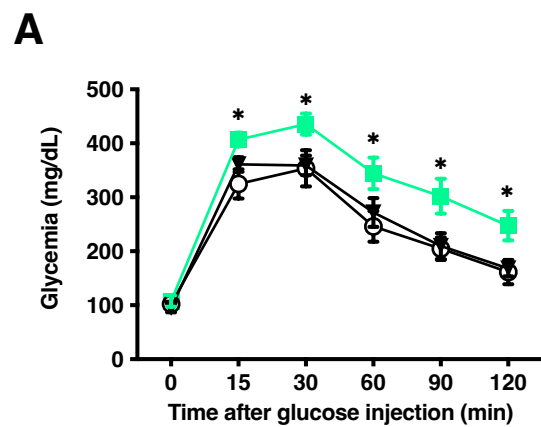
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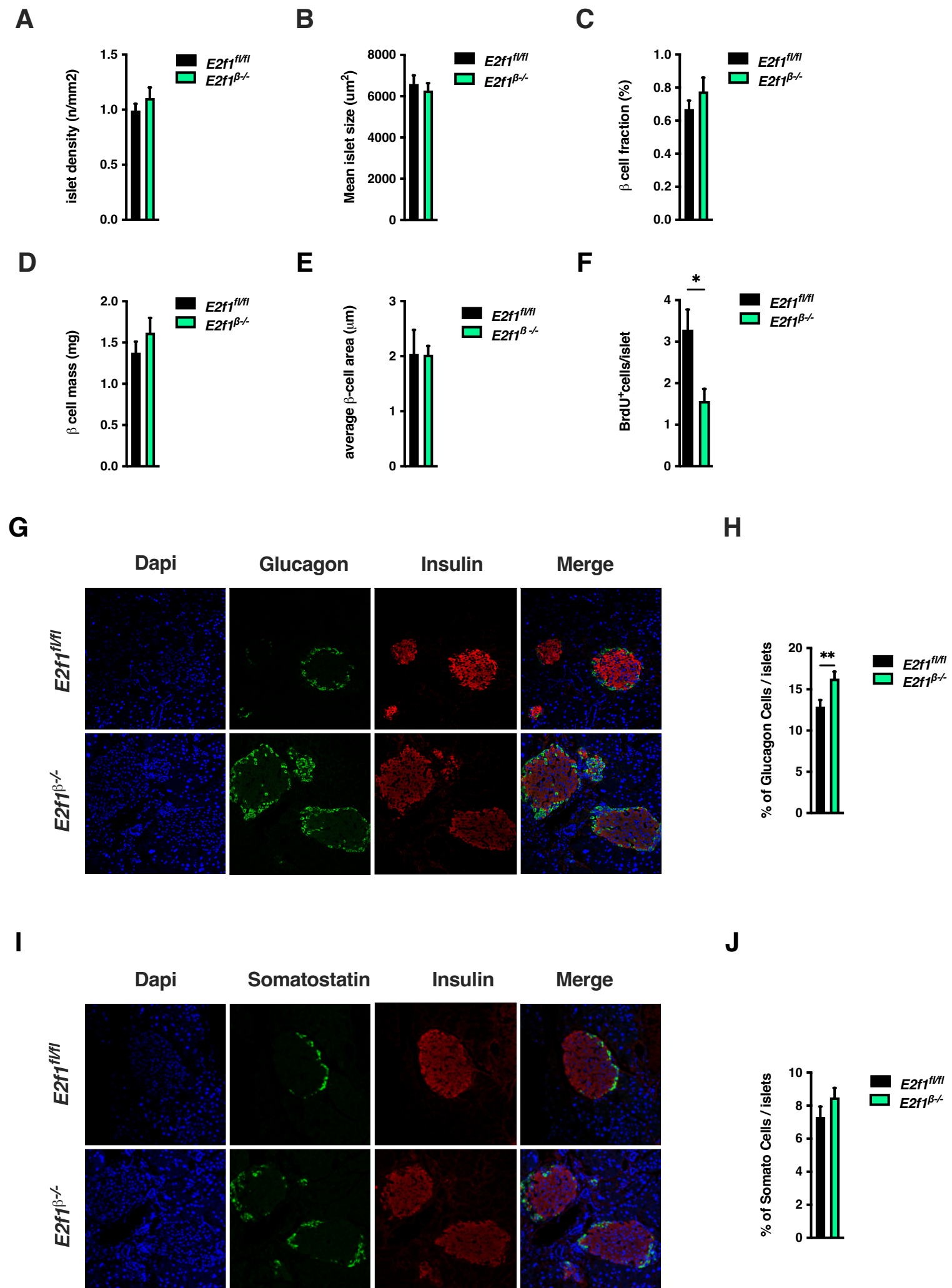
908 **Figure 6. The transcriptome of *E2f1* ^{β -/-} islets is associated to a specific epigenomic**
909 **pattern. (A)** Expression level of *E2f1* ^{β -/-} up- and down- regulated genes both in pancreatic
910 islets from control (WT) and *E2f1* knock-out (*E2f1* ^{β -/-}) mice. Results are displayed as
911 Log₁₀(TPM+1) calculated from TPM obtained from RNA-seq data. Data are represented as
912 mean s.e.m and were analyzed by unpaired *t*-test (**** *p*<0.0001). **(B)** Pie-chart displaying
913 chromatin state of *E2f1* ^{β -/-} up- and down- regulated genes according to pancreatic islets

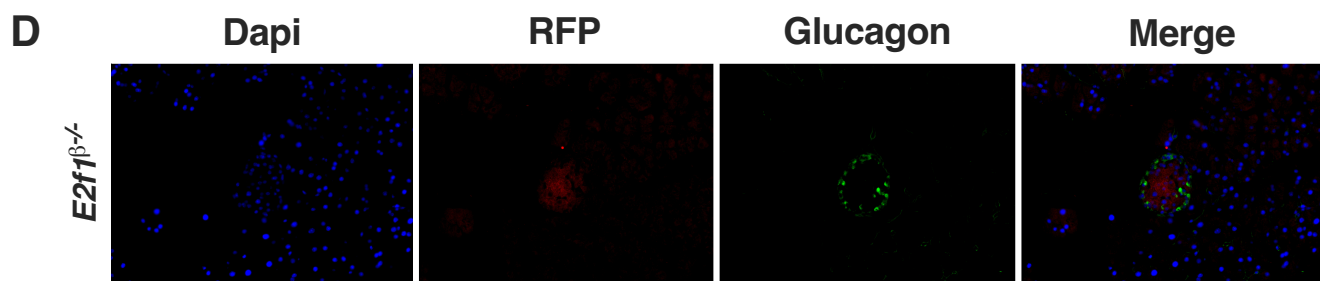
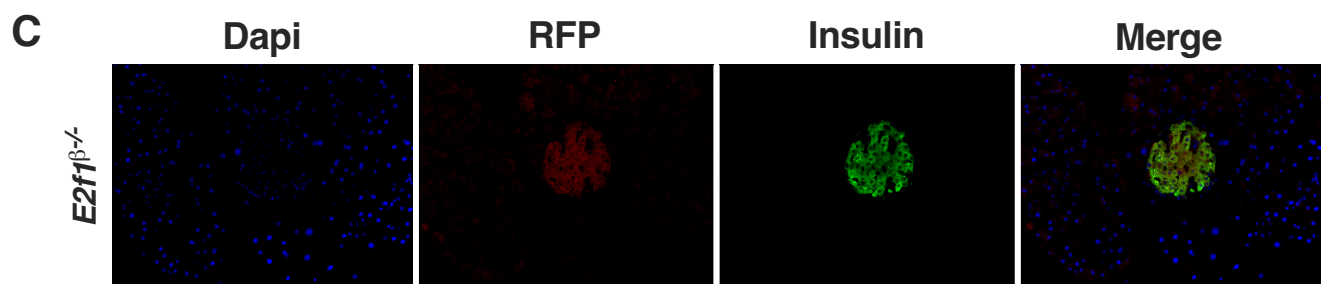
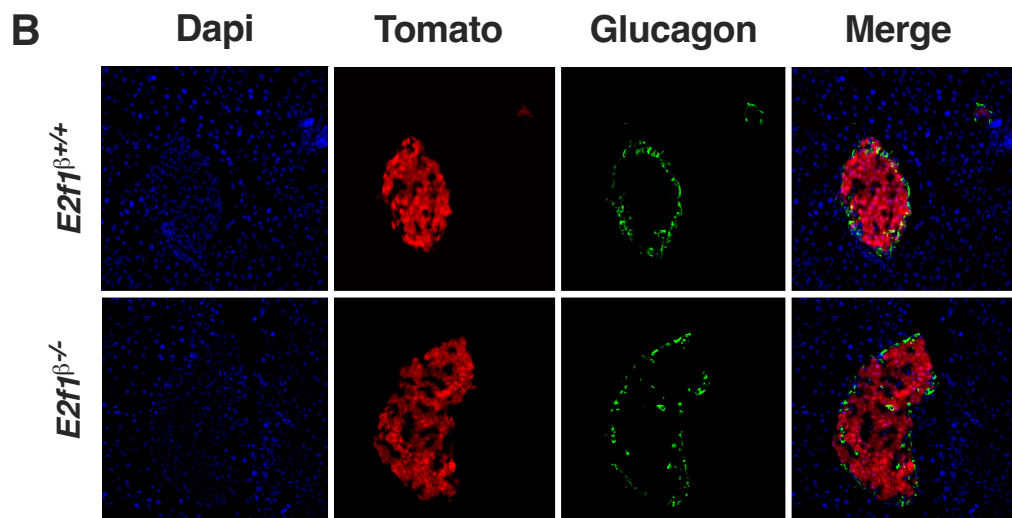
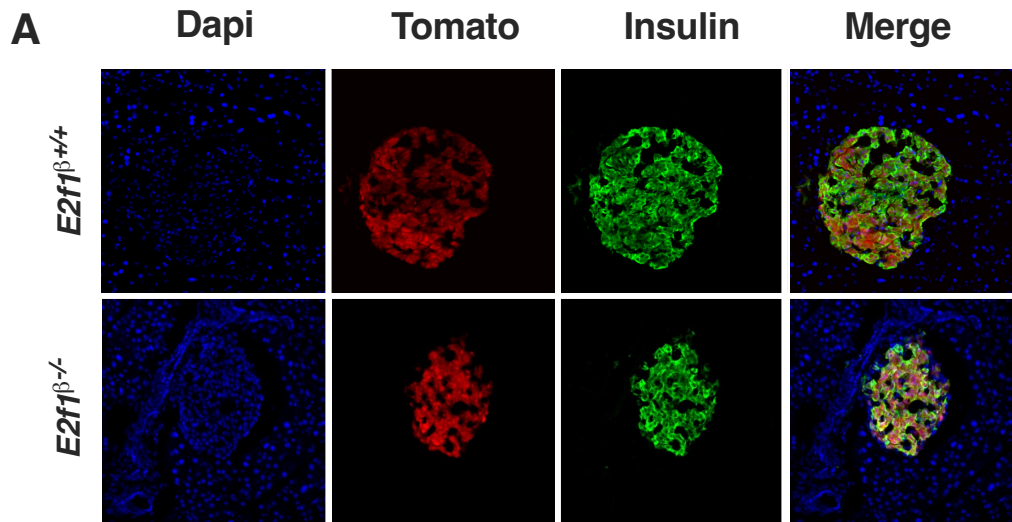
914 genes-associated chromatin state stratification from Lu TT *et al.* (12) **(C)** H3K4me3 and
915 H3K27ac ChIP-seq mean signal within promoter (centered to TSS +/- 1kb) of *E2f1*^{β-/-}-up- and
916 down- regulated genes both in Min6 cells and mouse pancreatic islets (12). **(D)** H3K27me3
917 ChIP-seq mean signal within promoter (centered to TSS +/- 1kb) of *E2f1*^{β-/-}-up- and down-
918 regulated genes both in Min6 cells and mouse pancreatic islets (12).

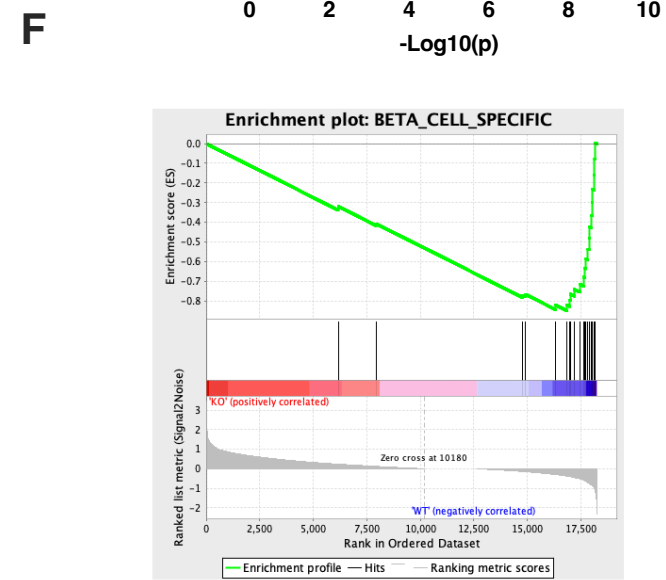
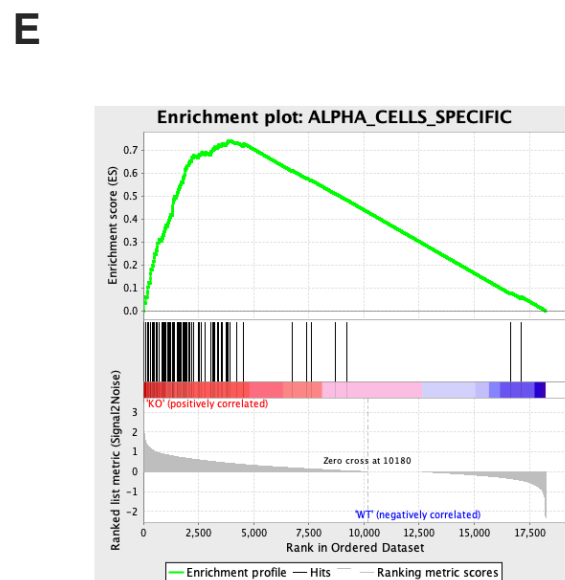
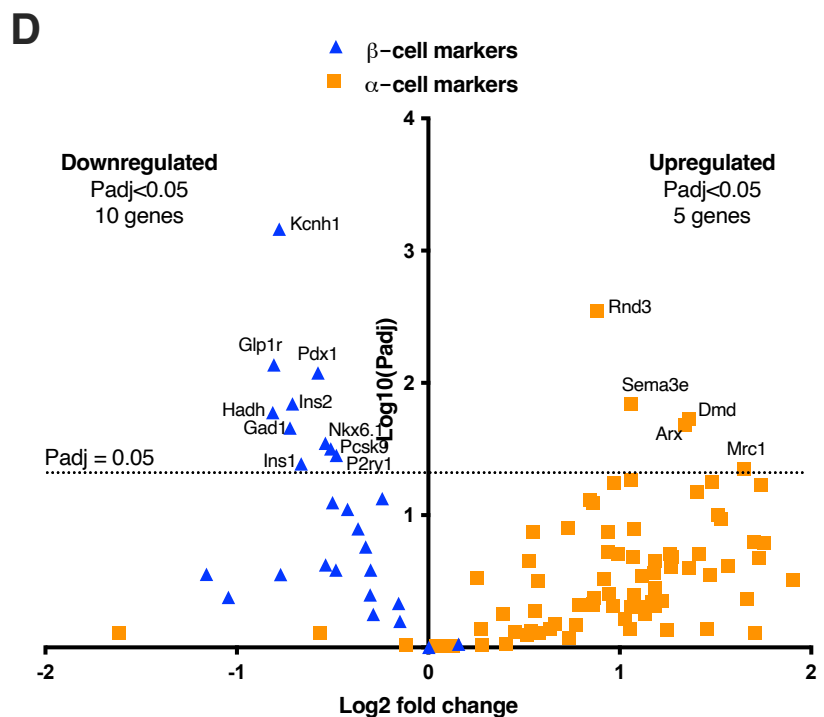
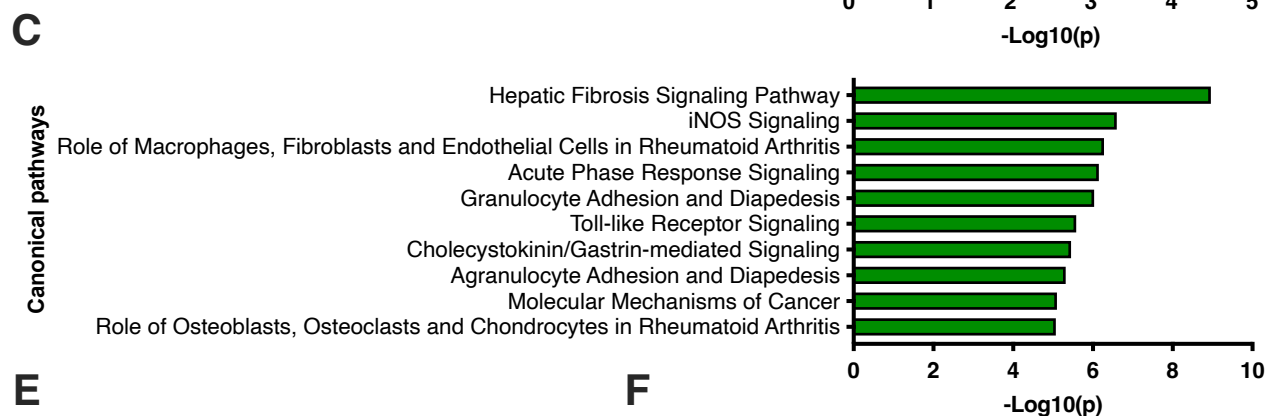
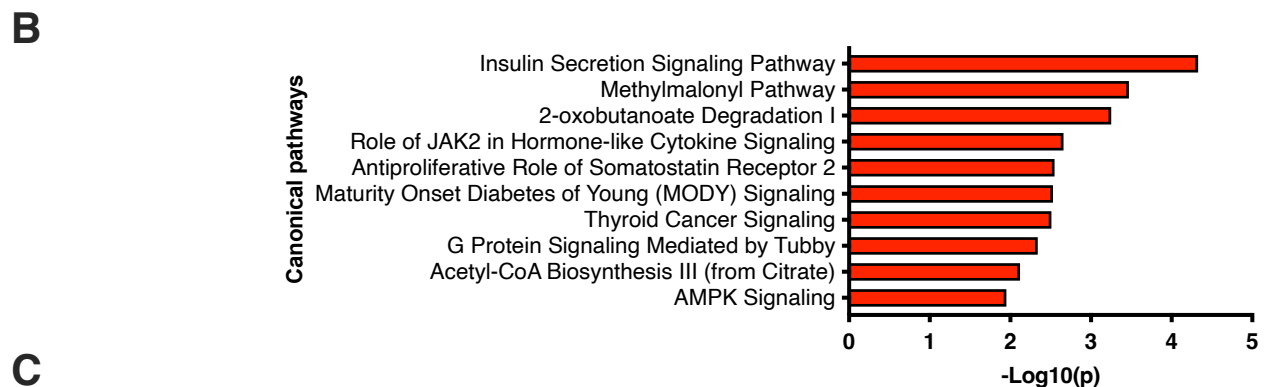
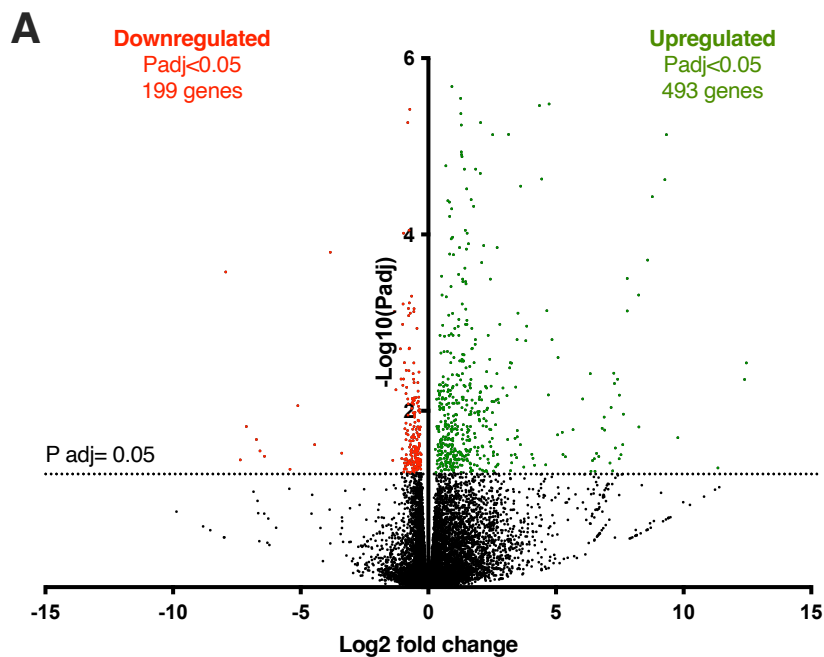
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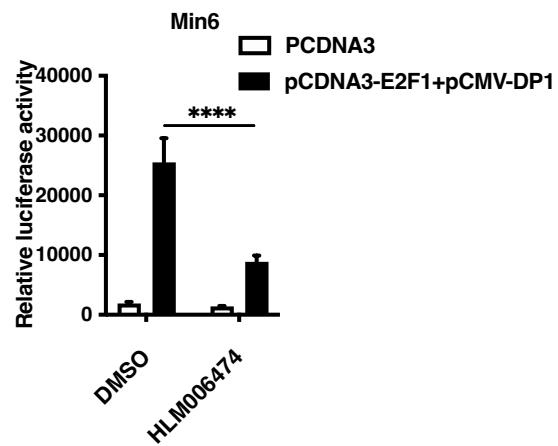
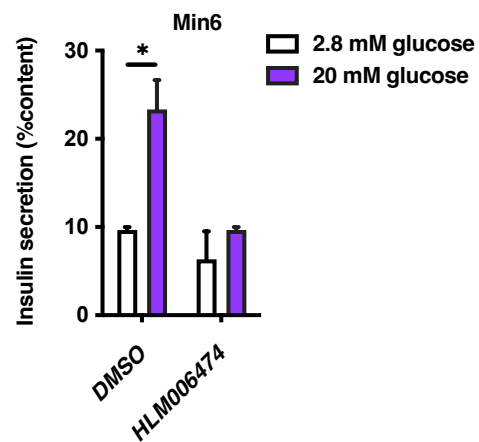
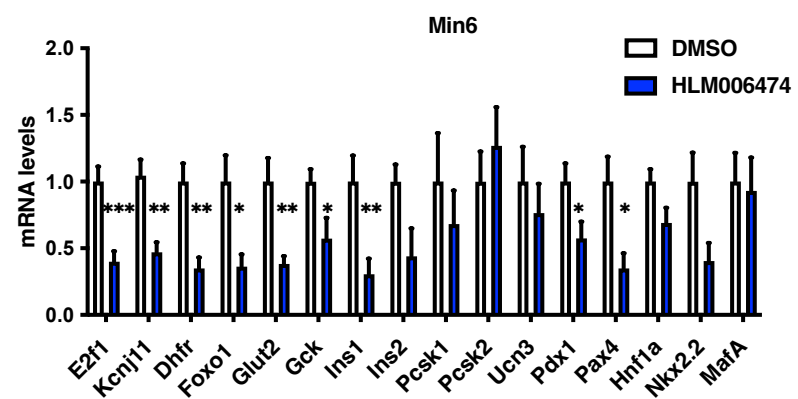
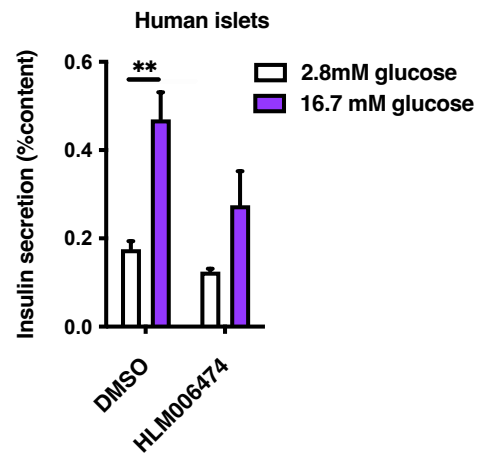
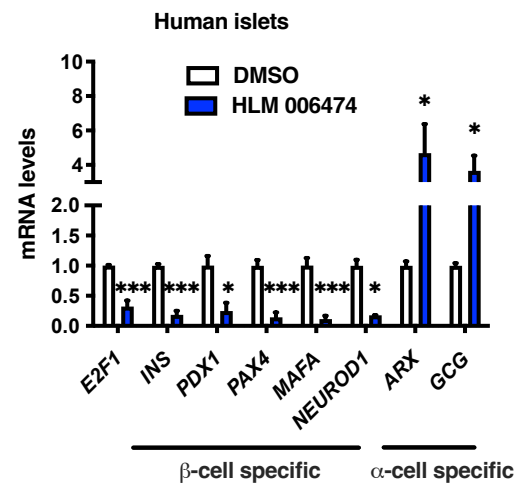
920 **Figure 7. Integrating ChIP-seq and RNA-seq data reveals that E2f1 modulates β-cell**
921 **and non-β-cell genes associated to different epigenomic marks. (A)** ChromHMM model
922 based on Min6 cells. Heatmap displays ChromHMM 16-state model obtained with ChIP-seq
923 data sets for H3K4me3, H3K27ac, H3K9ac, H3K4me1, H3K27me3 and E2f1. ChromHMM
924 identifies functionally distinct chromatin states representing both repressive, bivalent and
925 active domains. **(B to I)** Integrated Genome Browser profiles displaying H3K4m3, H3K27ac
926 and H3K27me3 ChIP-seq signal intensities from Min6 cells and mouse pancreatic islets and
927 E2f1 ChIP-seq signal intensity at selected promoters of *E2f1*^{β-/-} upregulated (B to E) and
928 downregulated (F to I) genes.

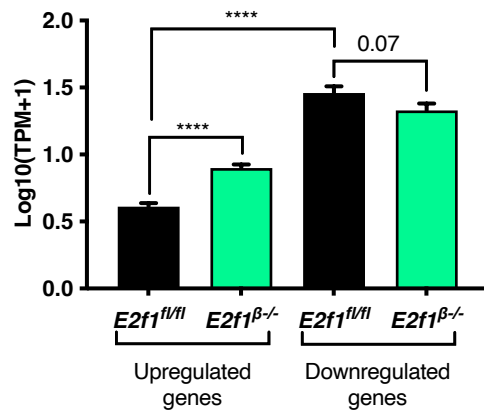
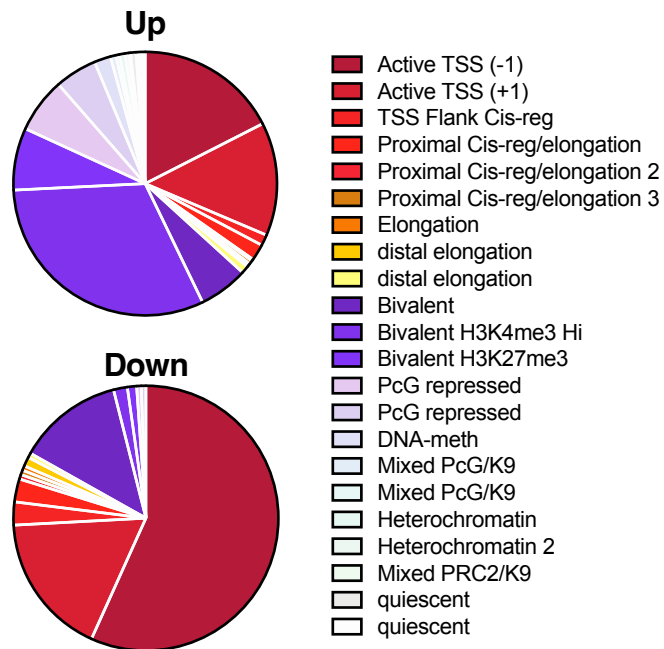
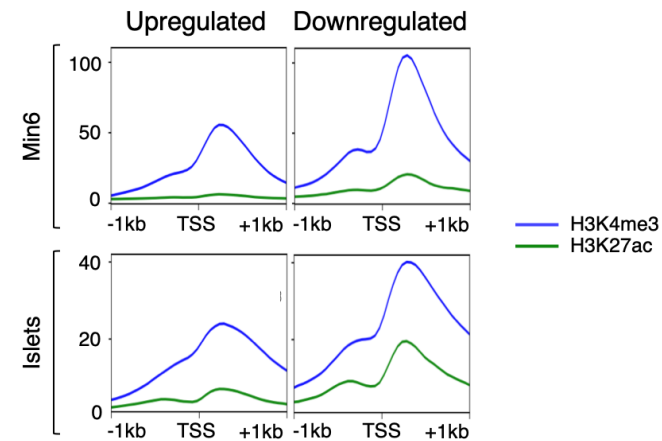
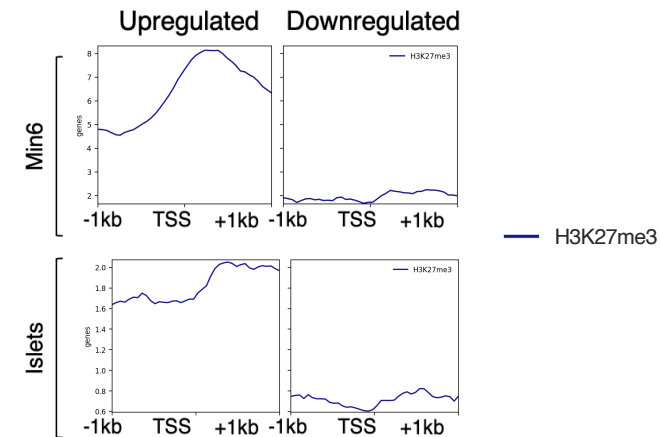




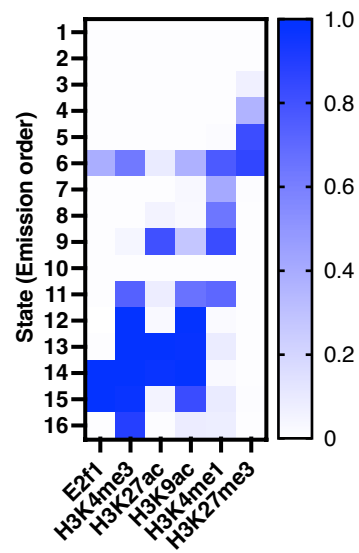




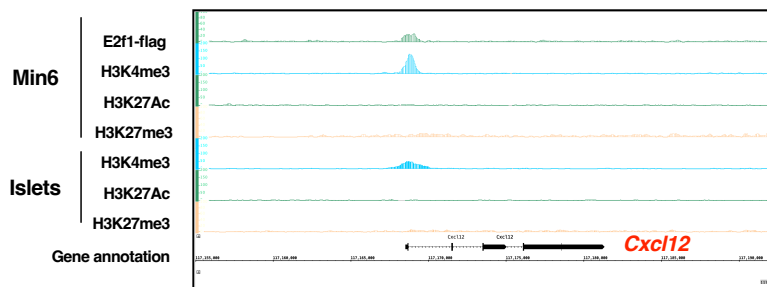
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A**B****C****D**

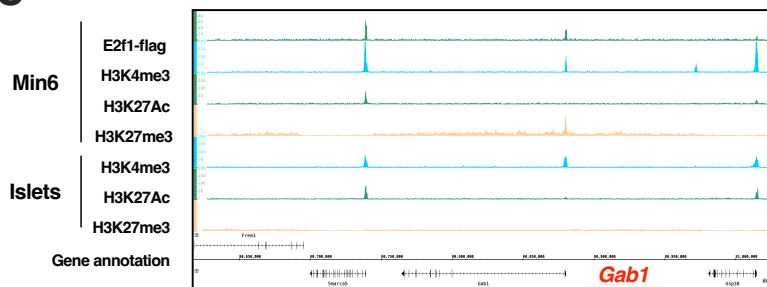
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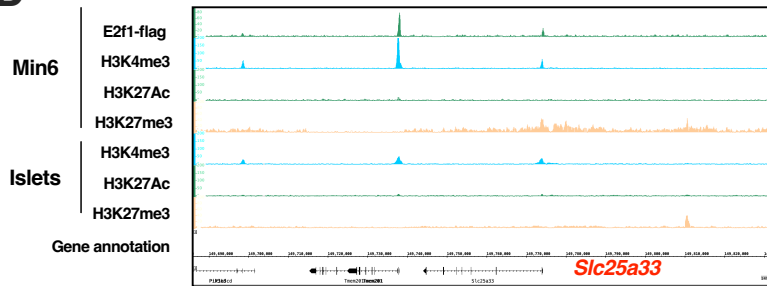
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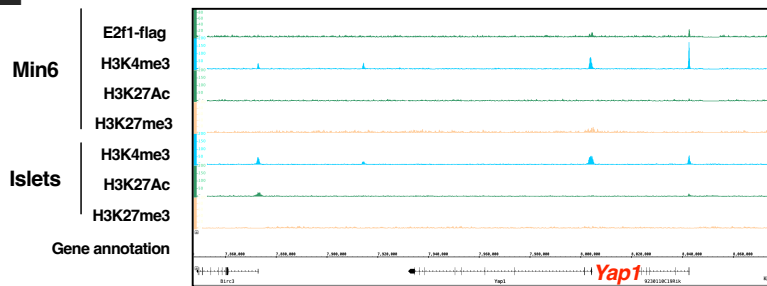
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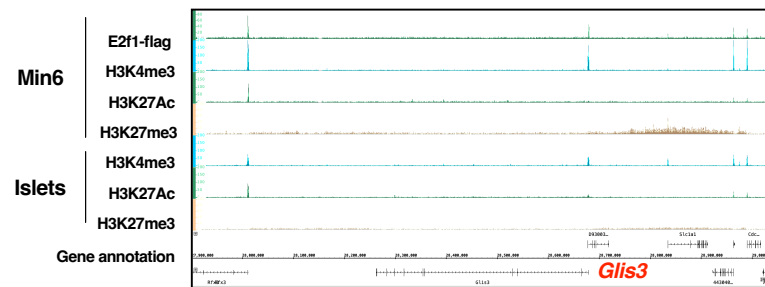
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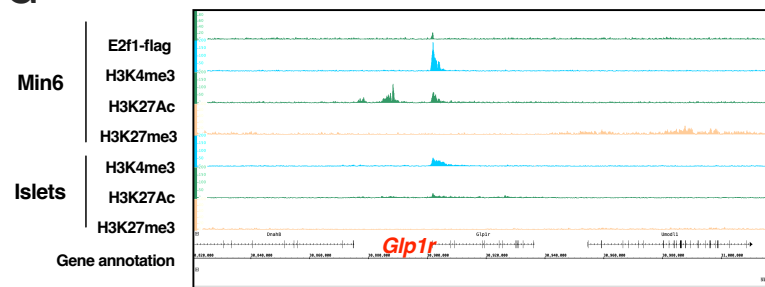
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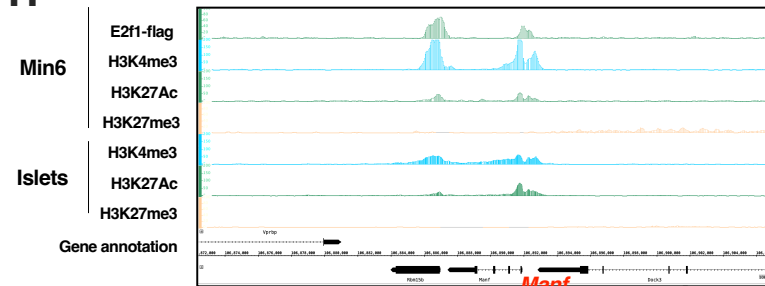
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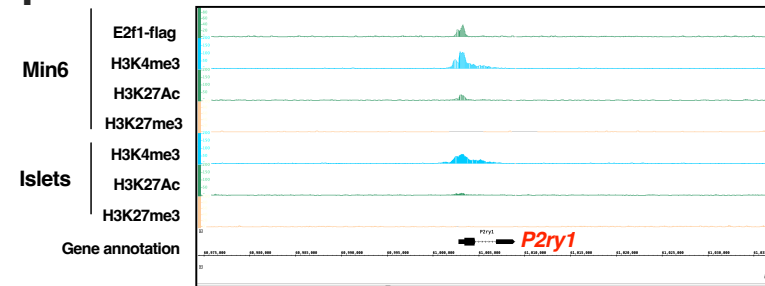
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H



I



Supplemental material

Supplementary methods

Materials and Oligonucleotides. Anti-BrdU (ab6326), anti-insulin (guinea pig, ab7842), anti-glucagon (rabbit, ab92517), anti-RFP (ab124754) and IgG (ab37415 ChIP grade for ChIP-seq experiments) antibodies were from Abcam; H3K4me3 (#61379), H3K27ac (#39685) and H3K27me3 (#61017) antibodies were from Active motif; anti-Glut2 (#07-1402-1) was from Merck; anti-cleaved caspase 3 antibody (#9661S) was from Cell Signaling; anti-PC1/3 (AB10553) was from Millipore. Anti-glucagon (mouse, G2654) and anti-FLAG (clone M2) were from Sigma-Aldrich. The HLM006474 compound was first described in (1) and synthesized as previously described (2). The list of primers used in this study is presented in Supplementary Table S2.

Animal Experiments. Mice were maintained according to European Union guidelines for the use of laboratory animals. Mice were housed under a 12-hr light/dark cycle and given a regular chow (A04;Safe).

E2f1^{-/-} (B6; 129S4-*E2f1*^{tm1Meg/J}) mice and *db*^{+/+} mice (Janvier Labs) were crossed to obtain *db/db::E2f1*^{+/+} and *db/db::E2f1*^{-/-} mice and were previously described in (3). *CMV-CDK4*^{R24C} (4) and *Cdkn2a*^{-/-} (5) were described elsewhere and were crossed with *E2f1*^{-/-} mice to obtain *E2f1*^{-/-::CMV-CDK4^{R24C} and *E2f1*^{-/-::Cdkn2a}^{-/-}.}

The congenic mice carrying the floxed *E2f1* allele were thereafter mated with rat insulin II promoter (RIP)-Cre (6) to generate RIPcre^{Tg/+::E2f1}^{flox/flox} mice. To delete *E2f1* in adult β cells, we developed a mouse model allowing targeted recombination of *E2f1* in

β cells through the use of a tamoxifen inducible strategy. To this end, $E2f1^{flox/flox}$ were crossed with MIP-CreERT mice (Jax Lab, stock number #024709). $E2f1^{flox/flox}$, Rip-Cre^{+/+} and MIP-CreERT were intercrossed to generate pure mutant Rip-Cre^{Tg/+}/ $E2f1^{flox/flox}$ and MIP-CreERT^{Tg/+}/ $E2f1^{flox/flox}$ mice. A PCR genotyping strategy was subsequently used to identify RIP-cre^{Tg/+}:: $E2f1^{+/+}$ (Rip-Cre^{+/+}), Rip-cre^{+/+}:: $E2f1^{flox/flox}$ or MIP-CreERT^{+/+}:: $E2f1^{flox/flox}$ ($E2f1^{fl/fl}$), RIPcre^{Tg/+}:: $E2f1^{flox/flox}$ ($E2f1^{\beta-/-}$) and MIP-CreERT^{Tg/+}:: $E2f1^{flox/flox}$ ($E2f1^{MIP-CreERT \beta-/-}$) mice. Tamoxifen was dissolved in corn oil (stock solution, 20mg/mL) at 52°C in agitation for 15min and was then administrated to both 2-month-old $E2f1^{fl/fl}$ control and $E2f1^{MIP-CreERT \beta-/-}$ transgenic animals by gavage once per day for 7 days at the dose of 4mg/day. After gavage, a stock solution of 1 mg/mL (stored at 4°C) was prepared in advance by dissolving 100mg of Tamoxifen Citrate (Biogaran) in 100 mL of drinking water. This solution was then diluted 1:20 in drinking water and provided to the animals for 1 week after the gavage induction in black bottles to prevent any alteration of the drug.

Metabolic phenotyping experiments were performed according to the EMPRESS protocols. For in vivo insulin secretion, $E2f1^{fl/fl}$ and $E2f1^{MIP-CreERT \beta-/-}$ mice were starved for 5/6 hours prior Glucose-Stimulated Insulin Secretion (GSIS) to evaluate the basal insulinemia. Blood was collected from mice anesthetized with isoflurane delivered in oxygen at a flow rate of 1l/min. Whole blood samples were collected from the retro-orbital cavity into blood collection tubes containing EDTA, using sterile glass capillaries. To assess insulin secretion level, a second blood sample was collected 20 minutes after an intraperitoneal injection of 2g/kg of body weight of D-(+)-glucose. Plasma was obtained by centrifuging at 2000g for 10 minutes at 4°C. Thereafter, it was transferred into pre-cooled tubes and directly frozen in liquid nitrogen and then stored at -80°C.

Plasma insulin concentration was evaluated by using Enzyme-Linked Immunosorbent Assay (ELISA) Ultrasensitive immunoassay (Mercodia, Uppsala, Sweden), following manufacturer's instructions. All reagents and samples were pre-warm at room temperature before use. The optical density was read at 450 nm, using a spectrophotometer ELISA reader (Sunrise BasicTecan, Crailsheim, Germany), supported by the Tecan's Magellan data analyses software. Insulin concentration was calculated using the online analyses software (myAssay.com), as suggested from the provider.

Measurement of cell proliferation, apoptosis and β -cell size. To assess cellular proliferation, 5-bromo-2'-deoxyuridine (BrdU, B9285, Sigma Aldrich) was administered to 4 *E2f1* ^{$\beta^{-/-}$} mice and 4 *E2f1*^{*fl/fl*} control littermates. BrdU was dissolved in drinking water (1mg/ml) and provided to mice in dark bottles to protect the solution from the light. The solution was prepared fresh and it was changed every two days for 8 days prior to analyses. Pancreata were harvested, embedded in paraffin, and sectioned at 5 μ m. The pancreatic sections were co-stained with anti-BrdU and anti-PC1/3, and slides were mounted with DAPI mounting-medium for nuclei-staining. Islet numbers and area were calculated with Axiovision software in squared-Pixel (PC1/3 positive area), and BrdU+/DAPI+ nuclei were counted. To measure apoptosis and β -cell size, pancreatic tissues were fixed with 10% formalin solution, dehydrated and embedded in paraffin. Immunofluorescence analysis were performed on 5 μ m tissue sections. The sections were first de-paraffinized and re-hydrated, followed by a heat-induced antigen retrieval in citrate buffer. Sections were then incubated with blocking buffer for 30minutes and primary anti-Glut2 (for measuring β -cell size) or anti-cleaved caspase 3 antibodies (for measuring apoptosis) diluted at 1:100 in blocking buffer solution over night at +4°C. Immunofluorescent stainings were revealed using an

alexa-conjugated anti-rabbit secondary antibody (for Glut-2) or fluorescein-isothiocyanate-conjugated anti-rabbit (for cleaved caspase-3). Nuclei were stained with Dapi (SigmaAldrich, D9542). For cleaved caspase 3 immunostaining, intestinal FFPE sections from murine trinitrobenzene sulphonic acid (TNBS)-induced model of colitis (a kind gift of Dr Laurent Dubuquoy, Lille) was a positive control. Image acquisitions were done using a Spinning disk confocal microscope (Zeiss). 20 islets per mice were analyzed and 5 mice from each genotype were used to analyze β -cell size and apoptosis. Analysis and quantification were performed on ImageJ software using a macro program (developed in the lab and available upon request).

RNA-Sequencing. RNA quality was verified using RNA 6000 nanochips (Agilent, 5067-1511) on the Agilent 2100 bioanalyzer (Agilent, G2939A). Purified RNA (50ng) with RNA integrity number ≥ 6.5 was subsequently used for library preparation (TruSeq Stranded mRNA Library Preparation Kit, #20020594, Illumina) and sequenced on a HiSeq2500 system (Illumina). 3 biological replicates per condition were sequenced using paired-end mode. The demultiplexing of sequence data (from BCL files generated by Illumina sequencing systems to standard FASTQ file formats) was performed using bcl2fastq Conversion Software (Illumina; version 2.19.1). Trimming of residuals adapters and low-quality reads was performed using Cutadapt software (version 1.7.1). A mean of 54 million paired-end reads of 75 bp were generated for each sample. After initial checks and validation of sequence quality, RNA-seq reads were aligned to the mouse reference genome (mm10) using TopHat2 or STAR Aligner (version 2.5.2b). Subsequently, both quantification and annotation of the reads were performed using Bioconductor package Rsubread. The counting of the different genes

and isoforms was performed using RSEM (version 1.3). Finally, the differential gene expression analyses were performed using Bioconductor package DESeq2.

ChIP sequencing. 1 ng of eluted and purified DNA was used to prepare DNA sequencing library with the Nextflex rapid DNA seq kit 2.0 (Perkin Elmer, NOVA-5188-01) on the NextSeq 500 system (Illumina) using single read 100 base pairs mode. Sequence reads from FASTQ files were mapped to the mouse genome (mm10) using Bowtie2 Aligner (version 2.3.5.1). The demultiplexing of sequence data (from BCL files generated by Illumina sequencing systems to standard FASTQ file formats) was performed using bcl2fastq Conversion Software (Illumina; version 2.20). Trimming of residuals adapters and low-quality reads was performed using TrimGalore (version 0.4.5). Finally, peak-calling was performed with MACS2 software (version 2.2.7.1).

Bioinformatic analysis. Bioinformatic analysis were mainly performed using the open web-based platform Galaxy Europe (<https://usegalaxy.eu>). Motif search was performed using Pscan Web Interface (7).

Supplementary References

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Supplementary figures and legends

Supplementary Figure S1, related to Figure 1. Validation of the *E2f1* ^{β -/-} mouse model. (A) qPCR-based analysis of *E2f1* mRNA expression in different tissues (pancreatic islets, hypothalamus (Hypo), heart, epididymal white adipose tissue (eWAT), brown adipose tissue (BAT) and muscle) isolated from 3-month-old male *E2f1* ^{β -/-}, RIP-Cre^{+/+} and *E2f1*^{fl/fl} control mice (n=3-6). (B and C) Body weight (B, n=5-8) and fasting glycaemia (C, n=7-12) of 3-month-old male *E2f1* ^{β -/-}, RIP-Cre^{+/+} and control *E2f1*^{fl/fl} mice. Statistical analysis were performed using one-way analysis of variance (ANOVA) with Tukey's test. **p<0.01. Results are represented as mean \pm s.e.m.

Supplementary Figure S2, related to Figure 1. Metabolic phenotyping of the *E2f1* ^{β -/-} and *E2f1*^{MIP-CreERT β -/-} mouse models. Body weight (A, F, n=5-7), fasting

glycaemia (**B, G**, n=5-7), ipGTT (**C, H**, n=5-7) and its corresponding AUC (**D, I**, n=5-7), and plasma insulin levels at 0 and 30 min after intraperitoneal glucose injection (**E, J**, n=5-7) of 6-week-old (**A to E**) and 8-week-old (**F to J**) male *E2f1* ^{$\beta^{-/-}$} and control *E2f1*^{fl/fl} mice. (**K**) Intraperitoneal insulin tolerance test (IPITT) of *E2f1* ^{$\beta^{-/-}$} (n=8), RIP-Cre^{+/+} (n=8) and *E2f1*^{fl/fl} (n=8) male mice at 12 weeks of age. (**L**) qPCR-based analysis of *E2f1* mRNA expression in pancreatic islets isolated from 5-month-old male *E2f1*^{MIP-CreERT $\beta^{-/-}$} and *E2f1*^{fl/fl} control mice 3 months after tamoxifen administration (n=9-10). (**M-N**) ipGTT (**M**, n=9-10) and its corresponding AUC (**N**, n=9-10) was performed one month after tamoxifen administration in *E2f1*^{MIP-CreERT $\beta^{-/-}$} and *E2f1*^{fl/fl} control mice. All values are expressed as mean \pm s.e.m. and were analysed by two-tailed unpaired Mann-Whitney test (A, B, D, F, G, I, L, N) or two-way ANOVA with Bonferroni's multiple comparisons test (C, H, K, M). *p < 0.05; **p<0.01; ***p<0.001.

Supplementary Figure S3, related to Figure 2. The E2f1-CDK4-Cdkn2a pathway is required to maintain normal α -to- β cell ratio. (**A**) Representative immunofluorescent staining of Glut-2 in pancreatic sections from 3 months old *E2f1* ^{$\beta^{-/-}$} and control *E2f1*^{fl/fl} male mice. Quantification of β -cell size was performed as described in the supplemental material using confocal images from 20 islets and 5 mice per genotype and ImageJ macro. (**B-D**) Representative immunofluorescent staining of cleaved caspase 3 (B-C) and BrdU staining (D) in pancreatic sections from 3 months old *E2f1* ^{$\beta^{-/-}$} and control *E2f1*^{fl/fl} male mice (B-D). Small intestine FFPE sections from control C57bl6/J mice treated with TNBS were used as a positive control for apoptotic cell detection through cleaved caspase 3 staining (C). Nuclei were stained with Dapi.

Supplementary Figure S4, related to Figure 2. The E2f1-CDK4-Cdkn2a pathway is required to maintain normal α -to- β cell ratio. (A, B). Representative immunofluorescent staining of insulin and glucagon in pancreatic sections from 16-week-old global *E2f1* knockout male mice (*E2f1*^{-/-}, B) compared to littermate controls (*E2f1*^{+/+}, A). **(C)** Quantification of glucagon (Glucagon +) and insulin (Insulin +) labelled cells from the different mouse models (n=3 per genotype). **(D)** Scheme representing the different genetically-engineered mouse models used in this study. **(E to H)** Representative immunofluorescent staining of insulin and glucagon in pancreatic sections from male CMV-CDK4^{R24C} (E), *E2f1*^{-/-}::CMV-CDK4^{R24C} (F), *Cdkn2a*^{-/-} (G), *E2f1*^{-/-}::*Cdkn2a*^{-/-} (H) mice. Values in C are expressed as mean \pm s.e.m. and were analysed by one-way ANOVA with Tukey's test. ***p<0.001 and ****p<0.0001 compared to *E2f1*^{+/+}; #####p<0.0001 compared to *E2f1*^{-/-}.

Supplementary Figure S5, related to Figure 2. Altered α -to- β cell ratio in germline *E2f1*-deficient mice. (A) Representative immunofluorescent staining of insulin and glucagon in pancreatic sections from 14 to 15 week old global *E2f1* knockout male mice in a *Db/Db* background (*Db/Db*::*E2f1*^{-/-}) compared to littermate control (*Db/Db*::*E2f1*^{+/+}). **(B)** Quantification of glucagon (Glucagon +) and insulin (Insulin +) labelled cells in *Db/Db*::*E2f1*^{-/-} and *Db/Db*::*E2f1*^{+/+} mice calculated from C (n=4 per genotype). Values in B are expressed as mean \pm s.e.m. and were analysed by two-tailed unpaired *t*-test. *p < 0.05; **p<0.01.

Supplementary Figure S6, related to Figure 4. Gene expression analysis of pancreatic islets isolated from β cell-specific *E2f1* knockout mouse (*E2f1* ^{β -/-}) compared to littermate controls (*E2f1*^{fl/fl}). (A) Aligned reads and sequencing

coverage of *E2f1* gene exons in *E2f1^{fl/fl}* and *E2f1^{β-/-}* isolated islets in RNA-sequencing experiments. **(B and C)** Heatmap from gene set enrichment analysis (GSEA) displaying differentially expressed β-cell specific genes **(B)** and α-cell specific genes **(C)** in islets isolated from *E2f1^{β-/-}* and *E2f1^{fl/fl}* mice. **(D)** qPCR-based analysis of *E2f1*, *Pcsk9*, *Foxo1* and some β-cell specific genes (*Pdx1*, *Mafa*, *Ins2*, *Glp1r*) in islets isolated from 6-month-old *E2f1^{β-/-}* and *E2f1^{fl/fl}* control male mice (n=5-11). **(E)** qPCR-based analysis of *Arx* (α-cell specific gene) in islets isolated from 6-month-old *E2f1^{β-/-}* and *E2f1^{fl/fl}* control male mice (n=3-5). Results are represented as mean ± s.e.m. Statistical analysis for D and E were performed using one-way ANOVA with Tukey's test. *p < 0.05; **p<0.01; ***p<0.001.

Supplementary Figure S7, related to Figure 6. Chromatin state of specific examples of *E2f1^{β-/-}* up- and down- regulated genes in pancreatic islets and Min6 cells. **(A-B)** Integrated Genome Browser (IGB, (8)) was used to visualize H3K4m3, H3K27ac and H3K27me3 ChIP-seq signal intensities from Min6 cells and mouse pancreatic islets (9) within a series of **(A)** *E2f1^{β-/-}* down-regulated genes and **(B)** *E2f1^{β-/-}* up-regulated genes.

Supplementary Figure S8, related to Figure 7. E2f1 ChIP-seq validation. **(A)** Western blot assay showing efficacy of pCMV-hE2F1-Flag plasmid transfection using a Flag antibody in Min6 cells transfected during 24h with the empty pCMV plasmid (Empty plasmid) and pCMV-hE2F1-Flag (E2f1 Flag) plasmid during 24h and 48h. **(B)** Pie-chart showing localization of E2F1 binding in the genome divided in proximal promotor (<1kb), distal promotor (between 1 and 3 kb), gene body, downstream and distal intergenic region. **(C)** Transcription factor binding motifs enriched in ChIP-Seq

from Min6 cells transfected with pCMV-hE2F1-Flag plasmid. **(D)** Integrated genome browser (IGB) representation of hE2F1-Flag fixation site in the promoter region of *Ezh2* in Min6 cells transfected with pCMV plasmid (Empty-Flag) or pCMV-hE2F1-Flag (E2f1-Flag) plasmid (n=2). **(E)** Representation of hE2F1-Flag fixation site in the promoter of *Ccne1* in Min6 cells transfected with pCMV plasmid or pCMV-hE2F1-Flag plasmid realized using IGB software (n=2). **(F, G, H)** ChIP-qPCR showing fixation of hE2F1-Flag in *Ezh2* (F), *Ccne1* (G) and an intergenic region in Min6 cells transfected with pCMV plasmid or pCMV-hE2F1-Flag after an immunoprecipitation with IgG or Flag antibodies (n=2).

Supplementary Figure S9, related to Figure 7. Pathway analysis of direct and indirect E2f1 target genes. (A-D) IGB profiles of E2f1 bound (A-B) and unbound (C-D) genes identified through E2f1-Flag Chip-seq analysis. (E-H) Ingenuity Pathway Analysis (IPA) of E2f1 bound and unbound downregulated (E-G) and upregulated (F-H) genes in *E2f1*^{β-/-} compared to *E2f1*^{fl/fl}. Histogram of the 10 top enriched canonical pathways across input gene lists are shown.

Supplementary Figure S10, related to Figure 7. Pathway analysis of E2f1 direct and indirect target genes. (A) Genomic localisation of 16-state ChromHMM model. Heatmap displays the fold enrichment for each state for each 200-bp bin position within 2 kb around a set of transcription start sites (TSSs). **(B to G)** Ingenuity pathway analysis identified 10 top canonical pathways of *E2f1*^{β-/-} up- and down-regulated genes belonging to segment 6 (B-C), 14 (D-E) and 15 (F-G).

Supplementary Table S1, related to Figure 5. Donor information.

Supplementary Table S2, related to Figures 5, S1, S2, S6 and S8. List of oligonucleotides used in this study.

Supplementary Table S3, related to Figures 4, 6, 7, S6, S7, S8, S9 and S10. List of ChIP-seq and RNA-seq data sets used in this study.

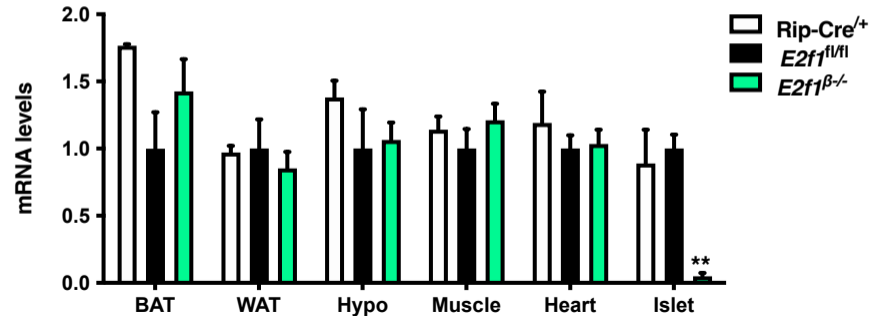
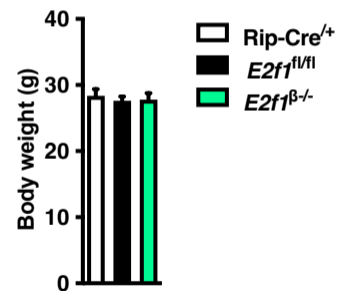
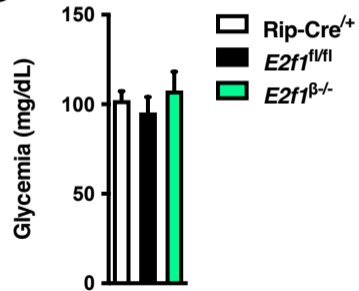
Supplementary Table S4, related to Figures 4, 6 and S6. List of transcripts differentially regulated in *E2f1* ^{β -/-} and *E2f1*^{fl/fl} pancreatic islets identified by RNA-sequencing and their chromatin state.

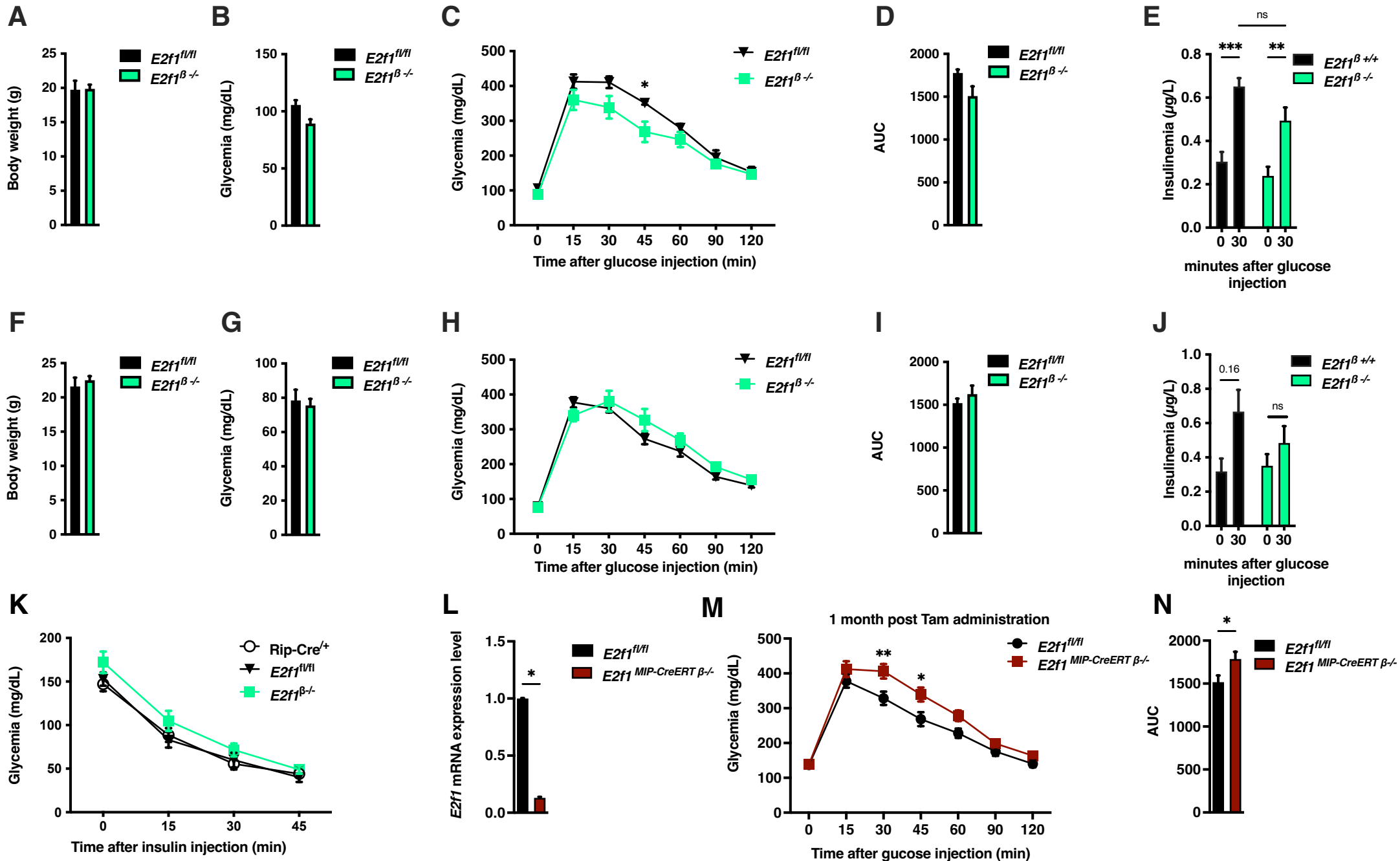
Supplementary Table S5, related to figure 4. Pathway analysis of RNA-sequencing data in pancreatic islets isolated from control *E2f1*^{fl/fl} and β -cell specific *E2f1* ^{β -/-} deficient mice identifies potential upstream regulators associated to *E2f1* deficiency.

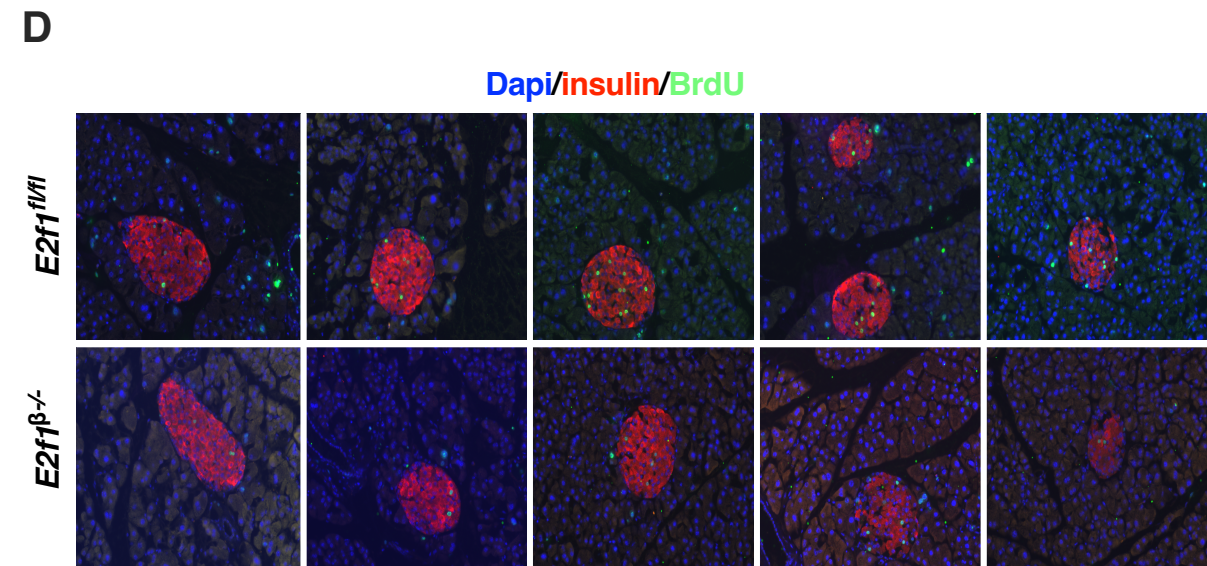
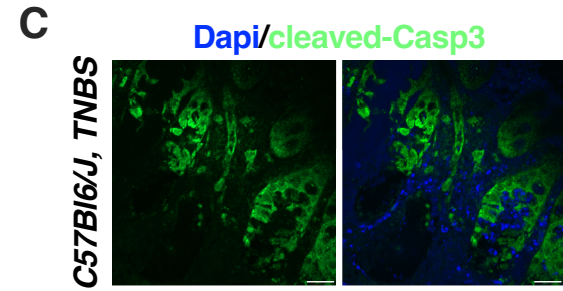
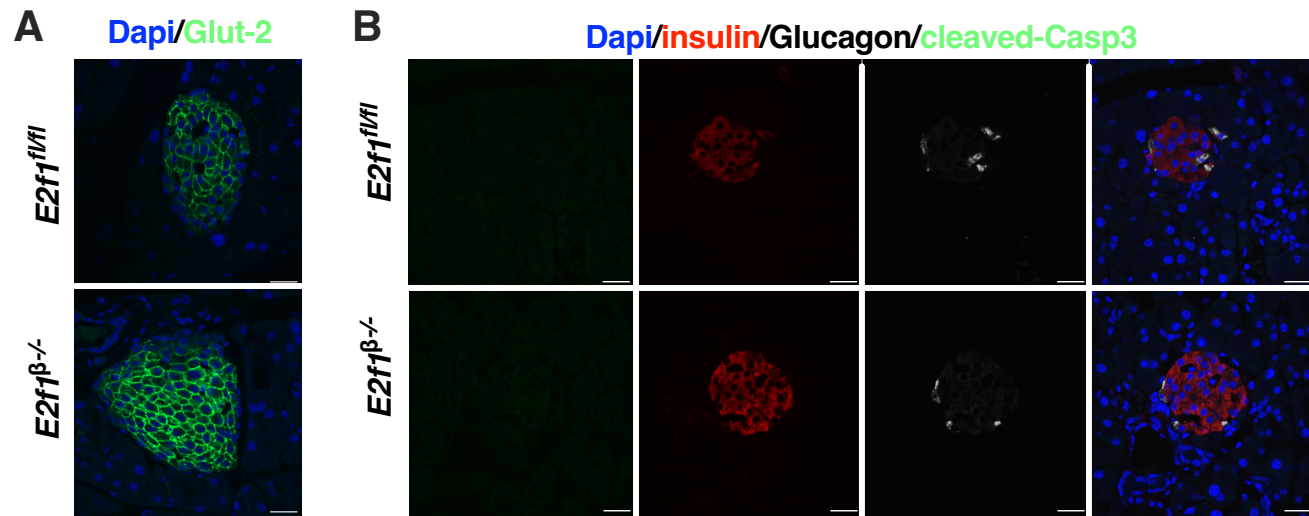
Supplementary Table S6, related to figure 7, S9 and S10. E2f1-flag ChIP-seq in Min6 cells reveals direct and indirect E2f1 target genes involved in beta cell function. Download the excel file at : <https://nextcloud.univ-lille.fr/index.php/s/ATYtizjgHkQCEpb>

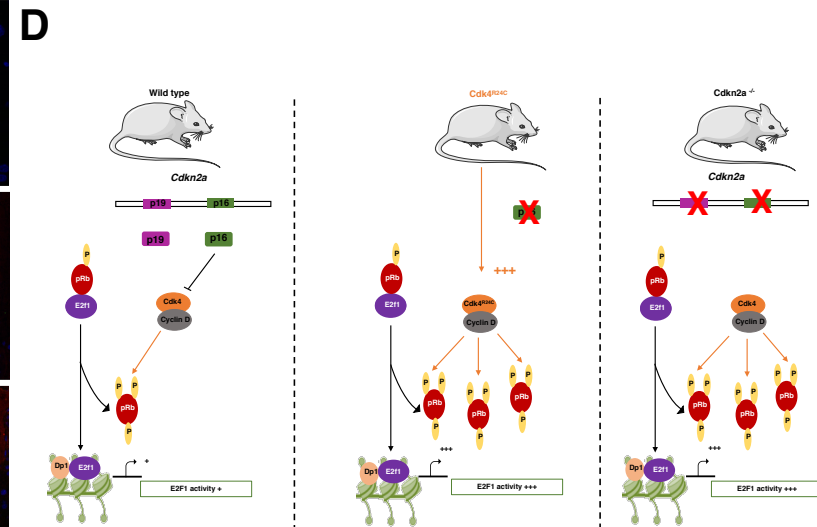
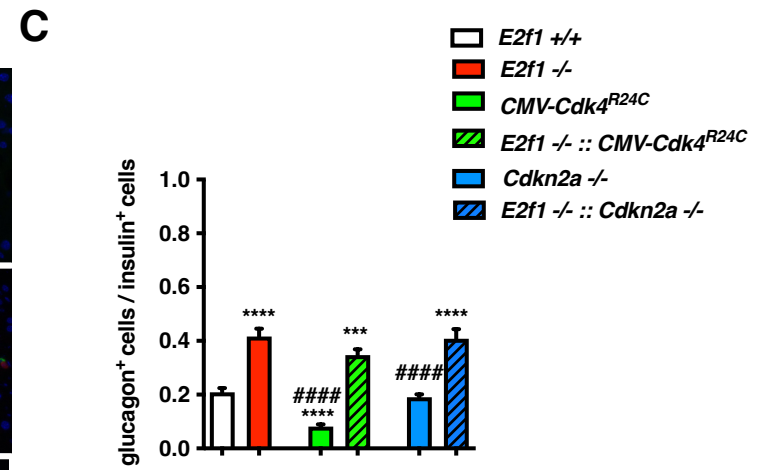
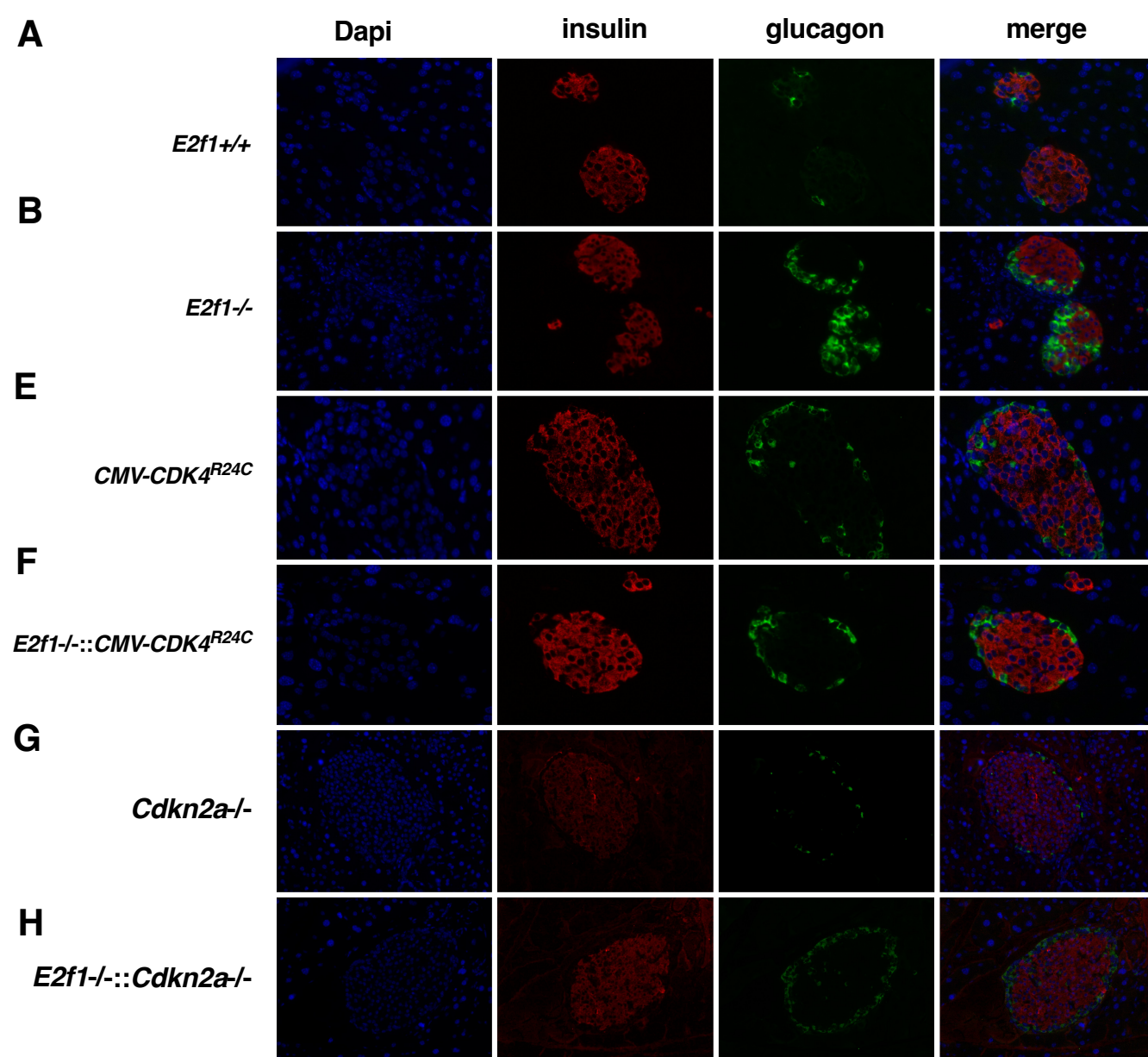
Supplementary Table S7, related to figure 7 and S10. List of the up- and downregulated genes that are bound by E2f1 at the chromatin level identified through ChromHMM 16-state segmentation (10). Chromatin state of E2f1 target genes were identified through intersecting E2f1-flag ChIP sequencing and RNA-sequencing data in pancreatic islets isolated from control *E2f1*^{fl/fl} and β -cell specific *E2f1* ^{β -/-} deficient mice. Genes belonging to segment 6, 14 and 15 are listed with their corresponding

adjPval and Log2FC. Download the excel file at: <https://nextcloud.univ-lille.fr/index.php/s/cgxD5gQjqKbwZpQ>

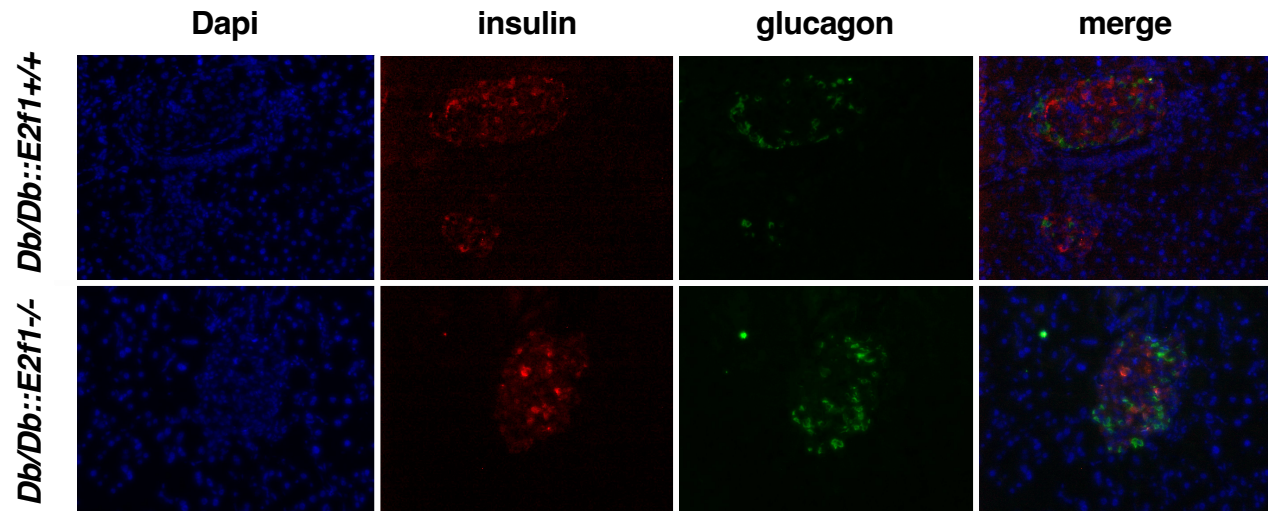
A**B****C**



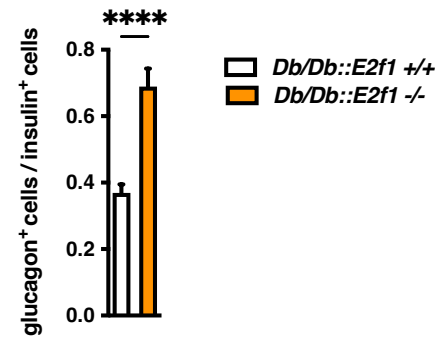


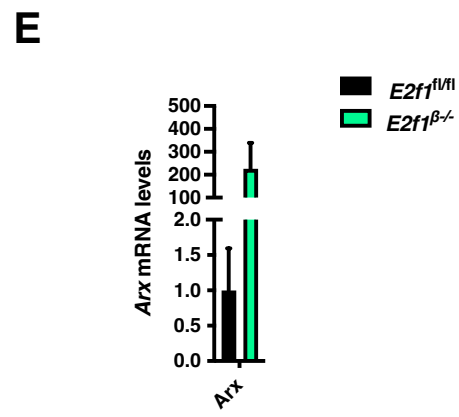
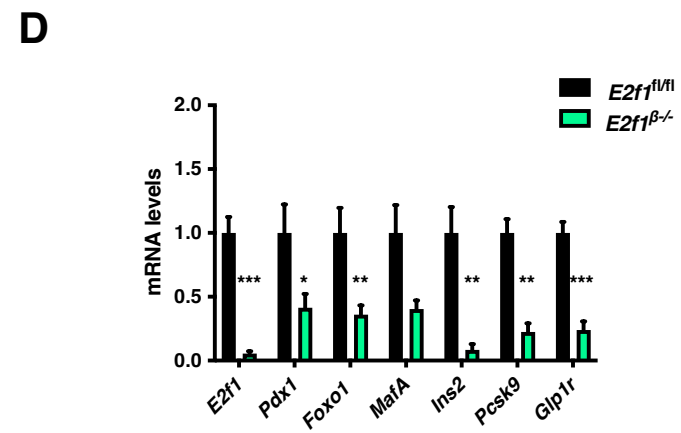
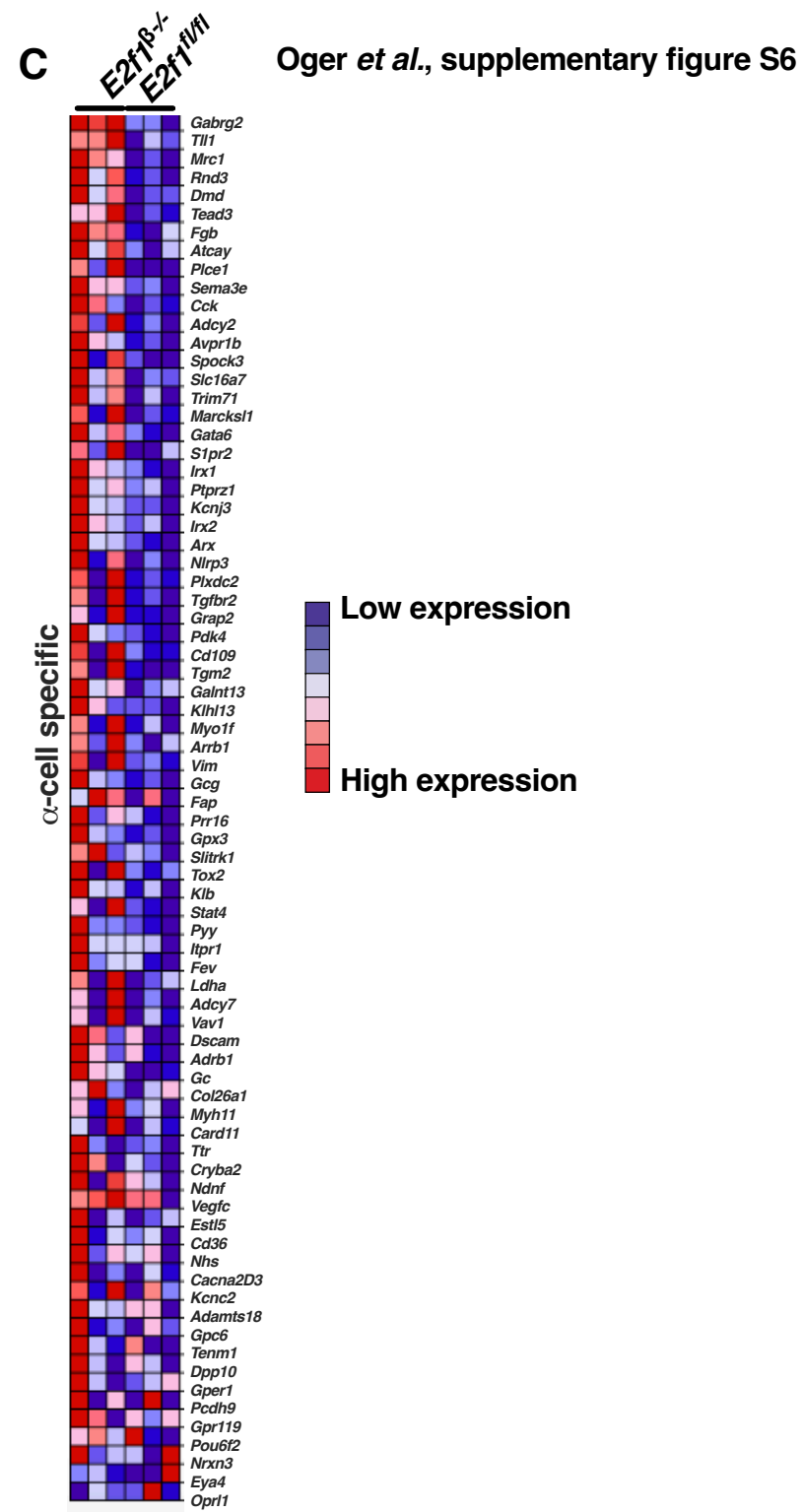
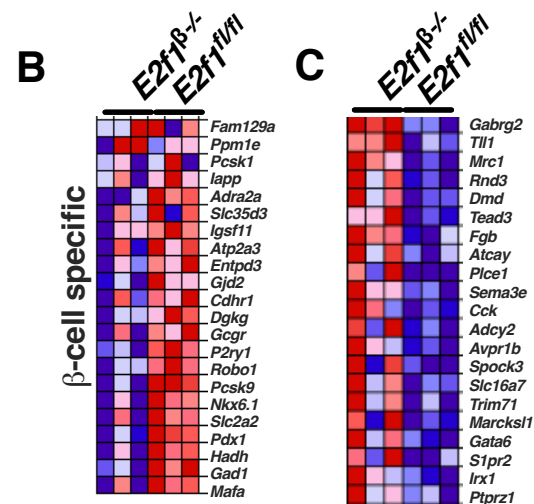
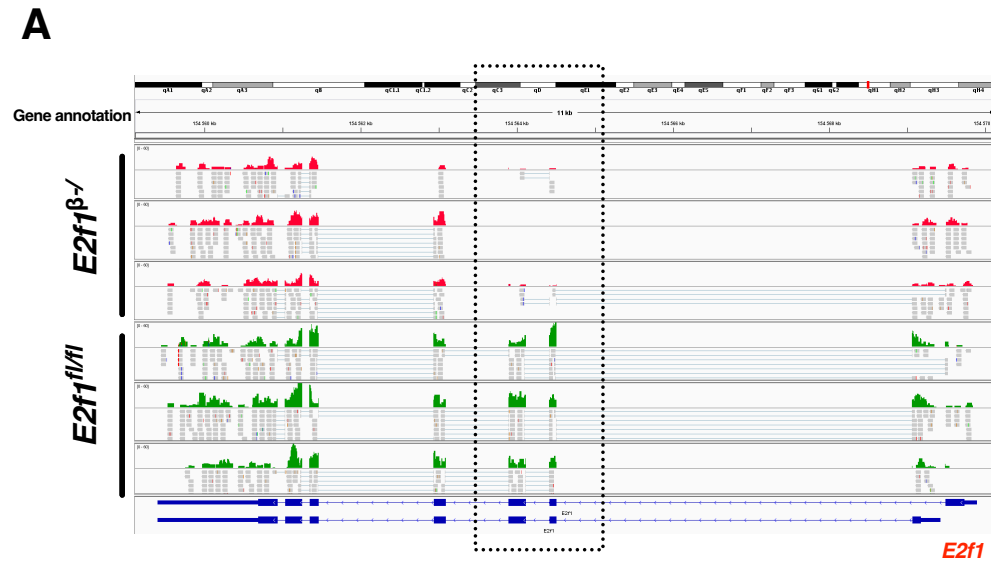


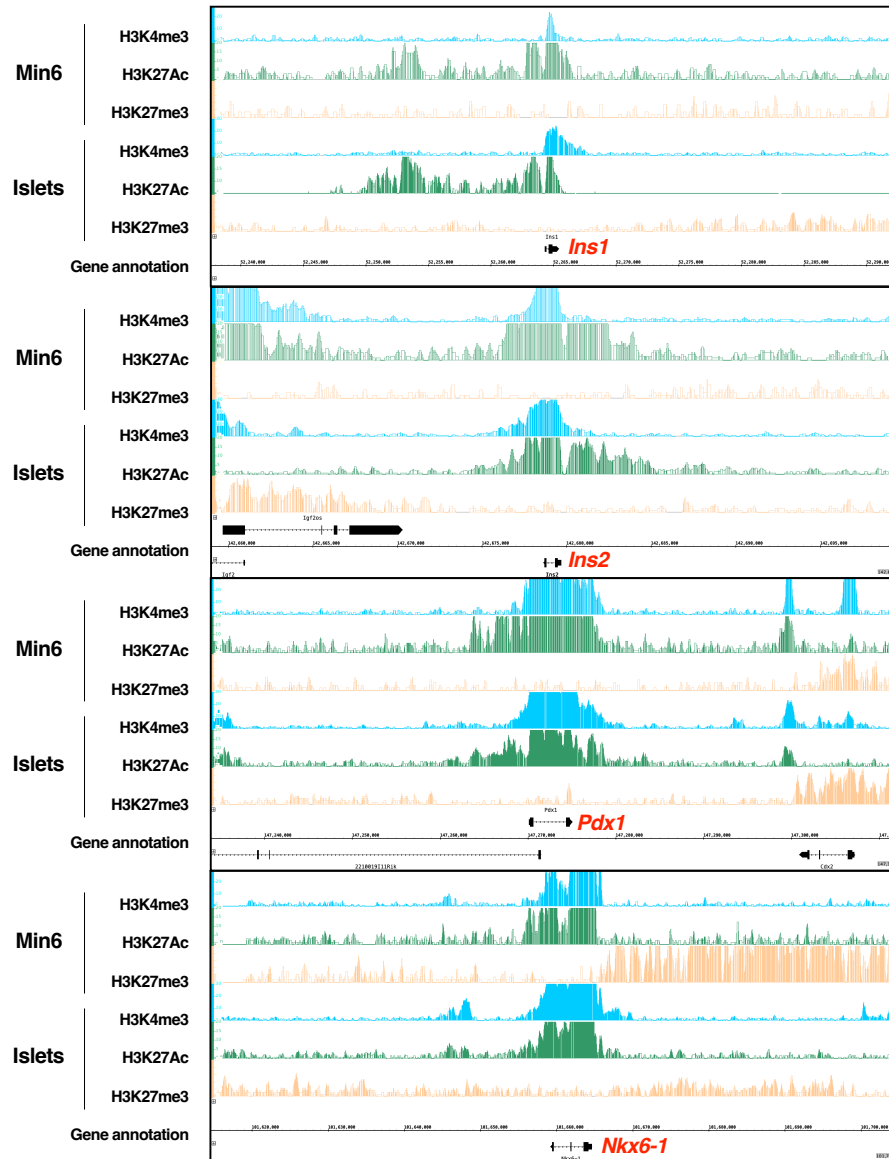
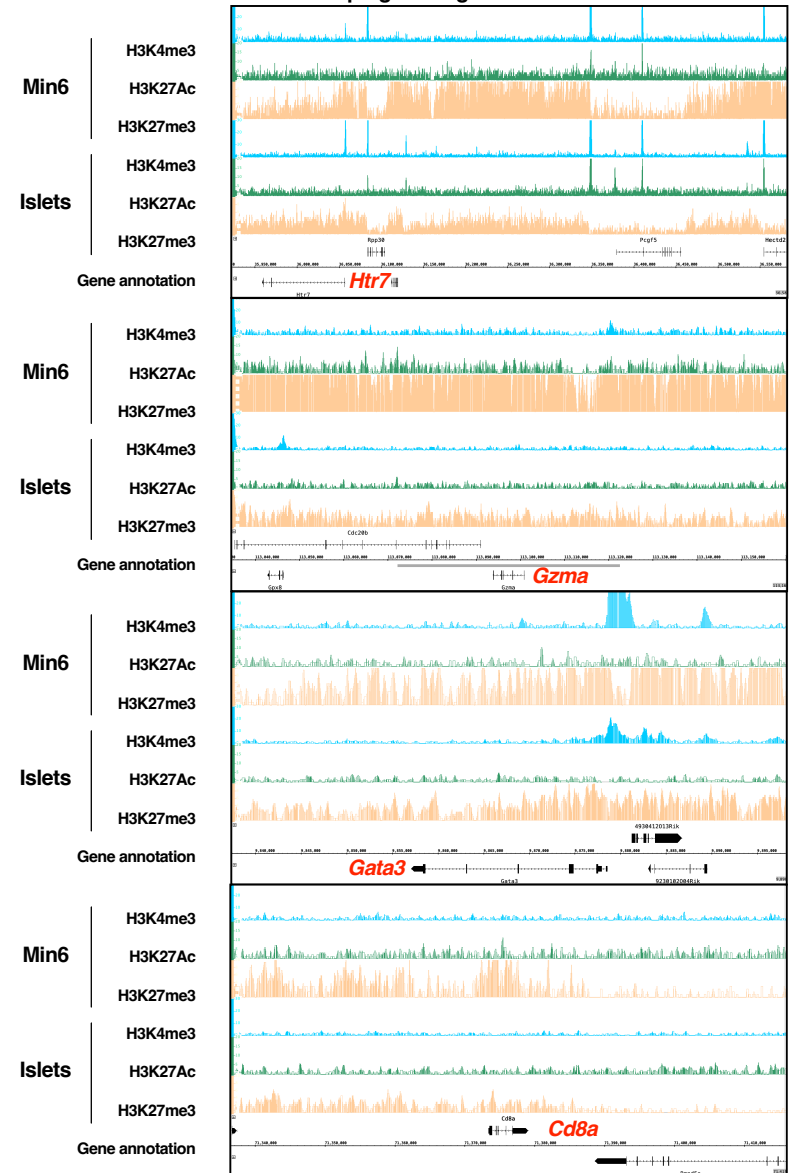
A



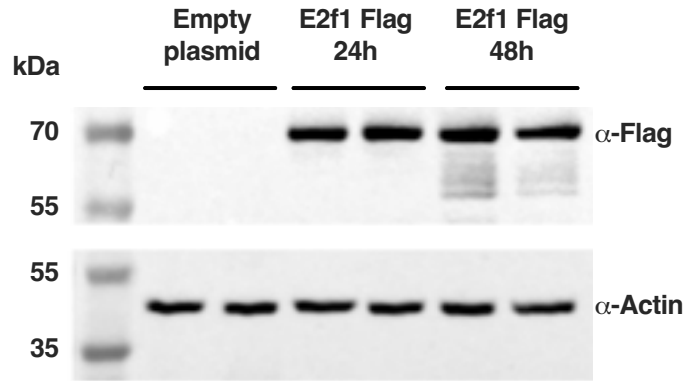
B



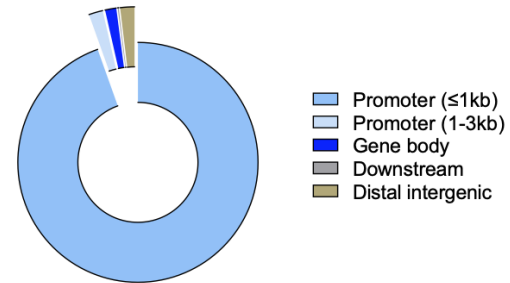


ADownregulated genes in *E2f1*^{β-/-} islets**B**Upregulated genes in *E2f1*^{β-/-} islets

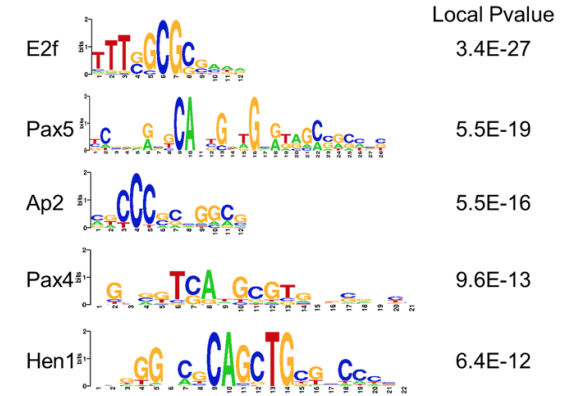
A



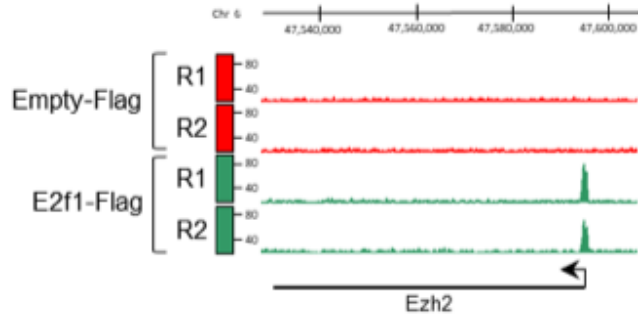
B



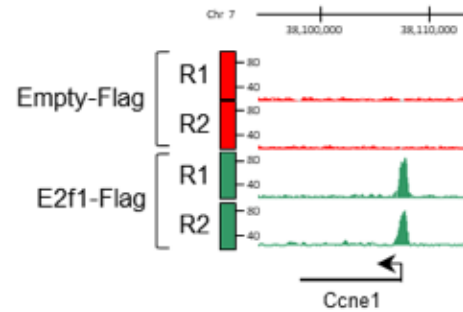
C



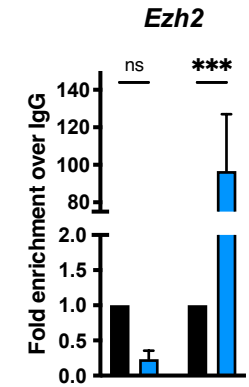
D



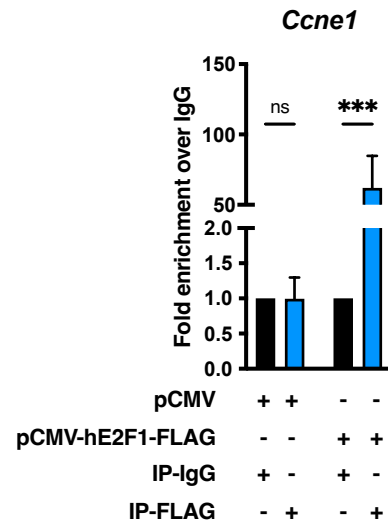
E



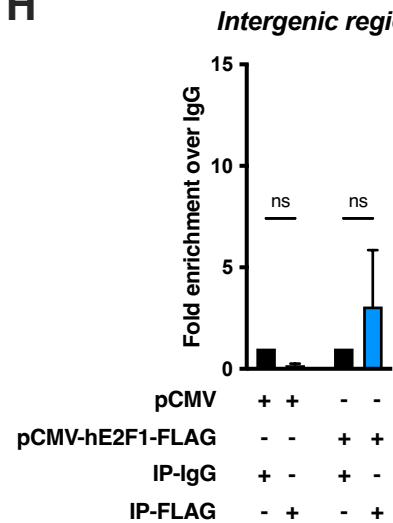
F



G

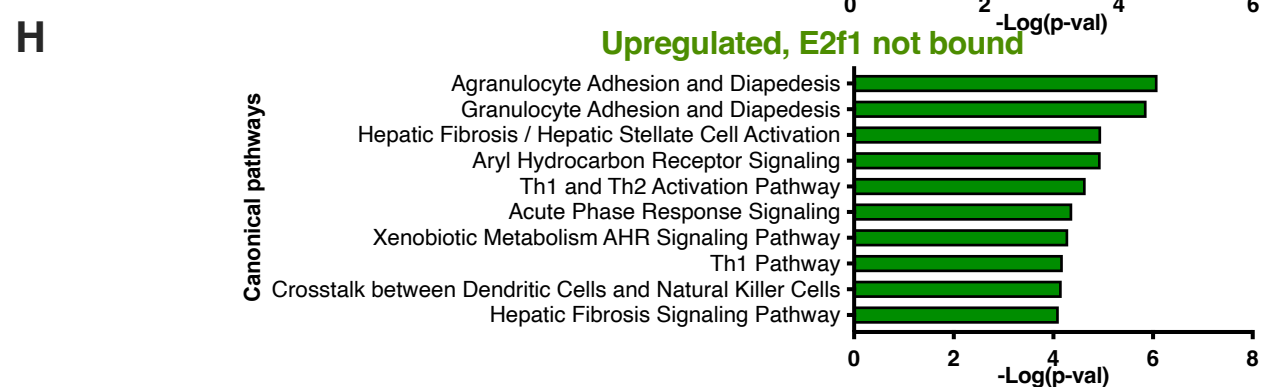
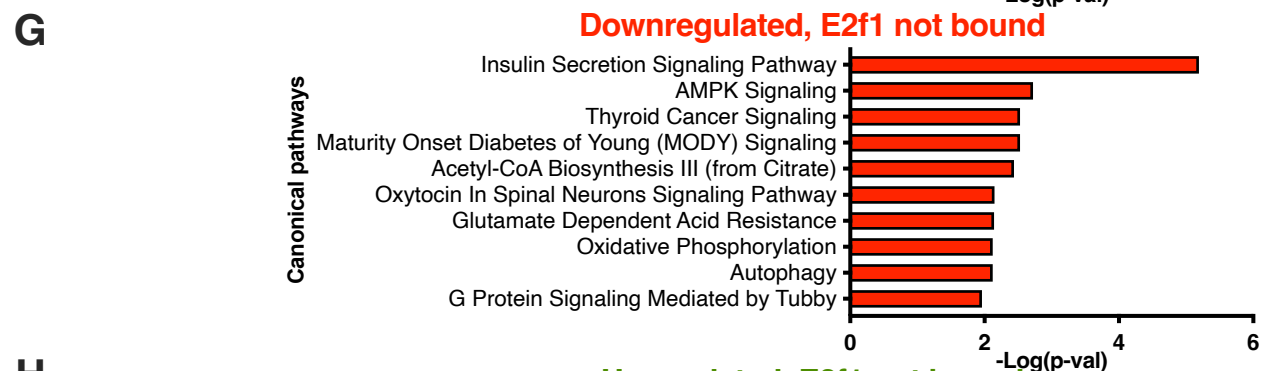
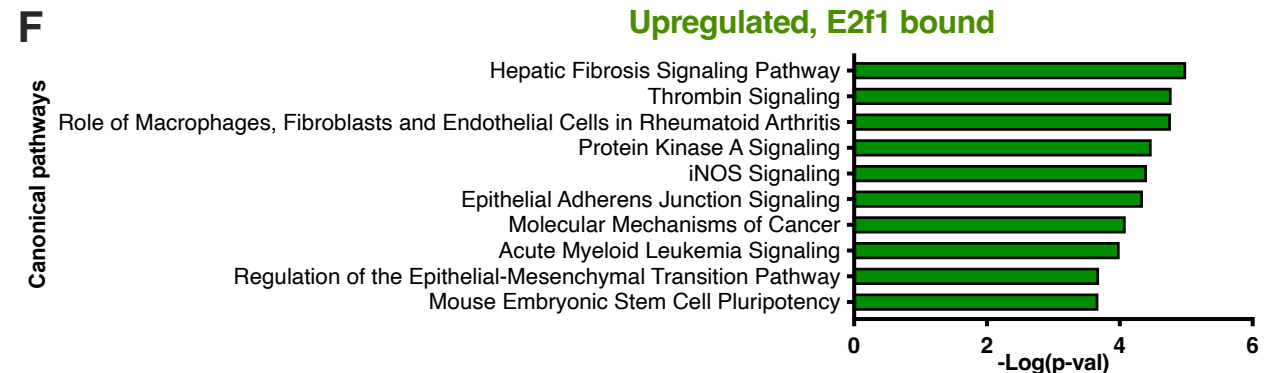
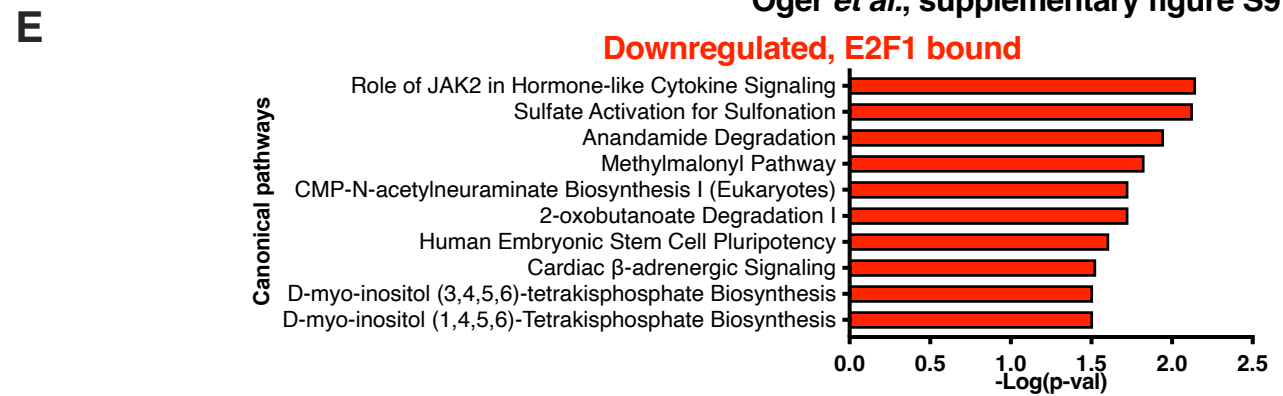
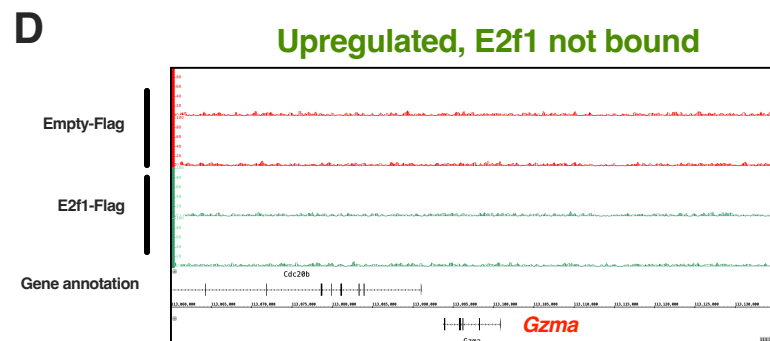
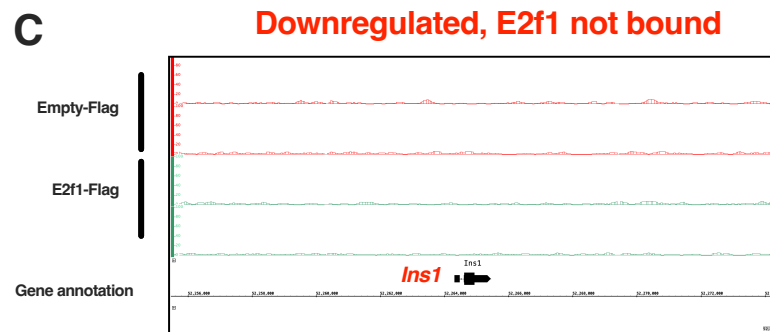
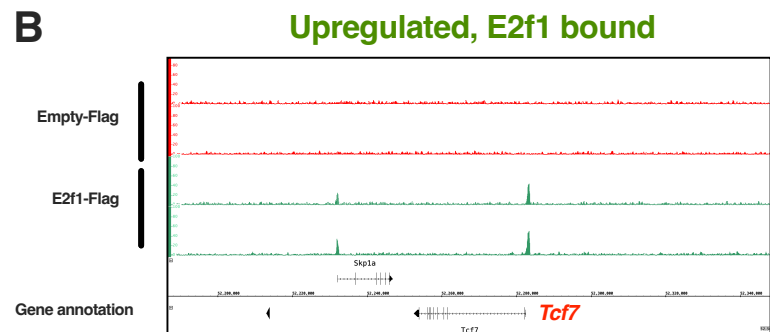
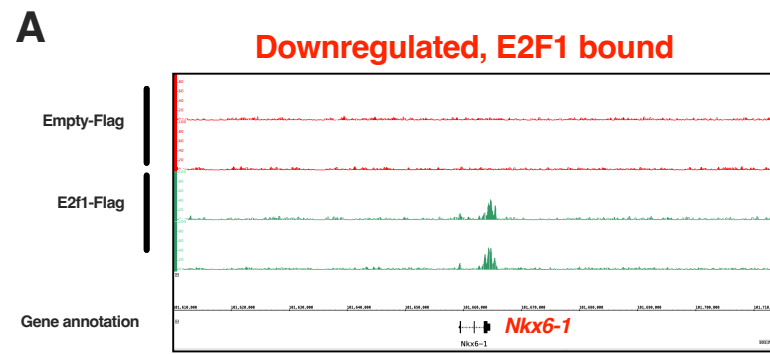


H

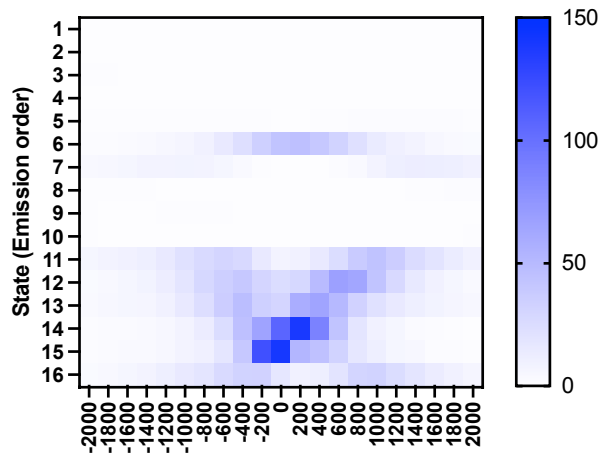


I

	pCMV	+	+	-	-
pCMV-hE2F1-FLAG	-	-	+	+	
IP-IgG	+	-	+	-	
IP-FLAG	-	+	-	+	

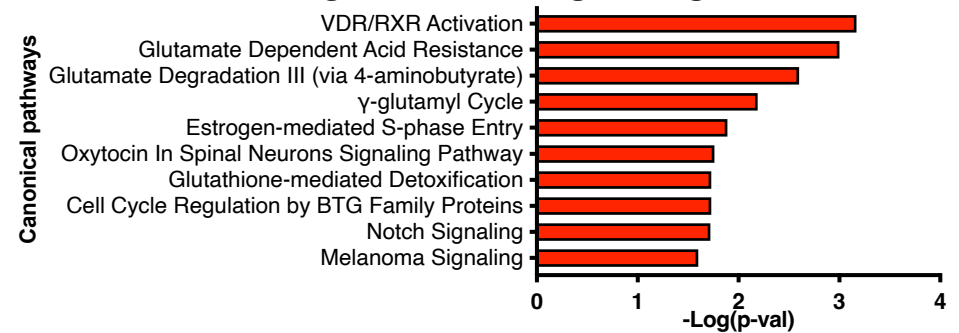


A



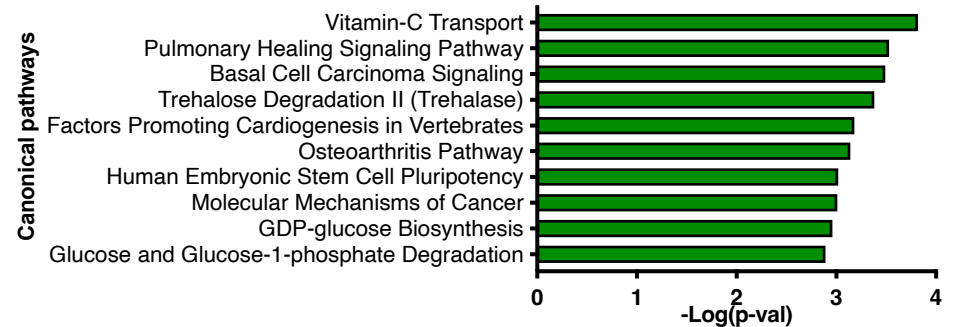
B

Segment 6, downregulated genes



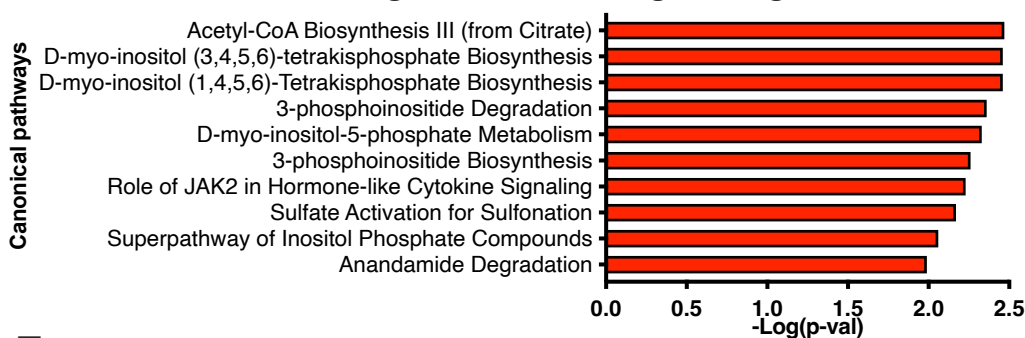
C

Segment 6, upregulated genes



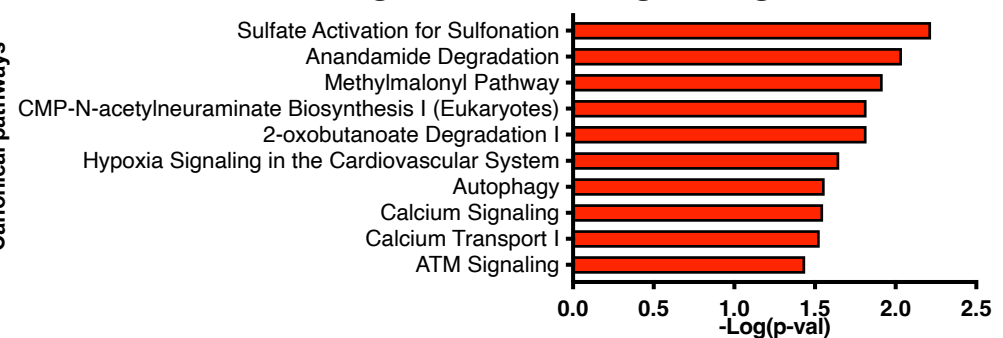
D

Segment 14, downregulated genes



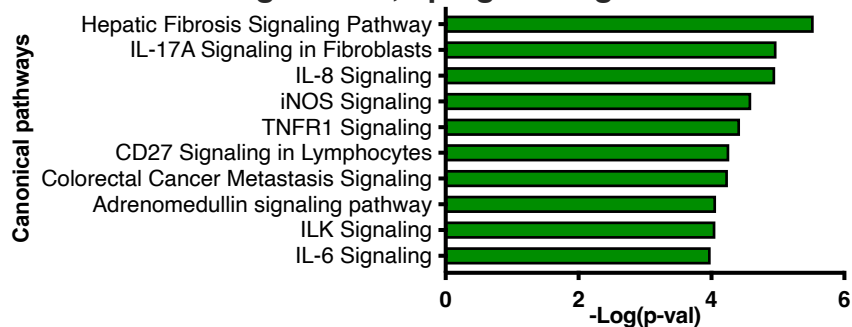
F

Segment 15, downregulated genes



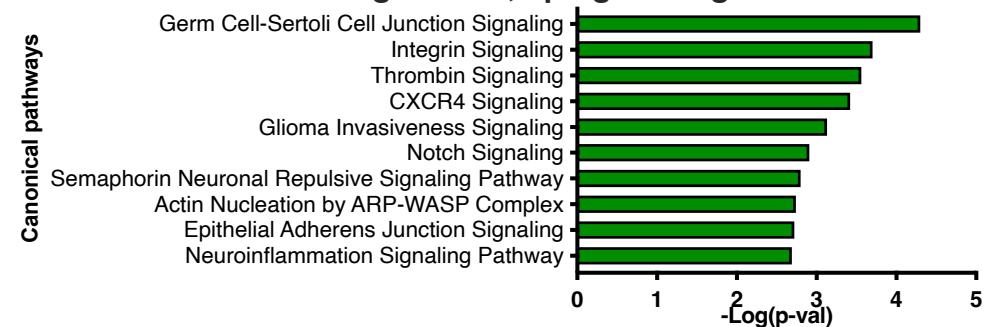
E

Segment 14, upregulated genes



G

Segment 15, upregulated genes



Continues on the next page

RECOMMENDED INFORMATION								
Donor cause of death	Hémorragie Méningée	AVC	AVC					
Warm ischaemia time (h)	0	0	0					
Cold ischaemia time (h)	3H38	6H20	6H35					
Estimated purity (%)	80	80	80					
Estimated viability (%)	98,1	93,7	95,3					
Total culture time (h) ^d	18	18	36					
Glucose-stimulated insulin secretion or other functional measurement ^e	1,18	3,67	1,56					
Handpicked to purity? Please select yes/no from drop down list	No	No	No					
Additional notes								

^aIf you have used more than eight islet preparations, please complete additional forms as necessary

^bFor example, IIDP, ECIT, Alberta IsletCore

^cPlease specify the therapy/therapies

^dTime of islet culture at the isolation centre, during shipment and at the receiving laboratory

^ePlease specify the test and the results

Supplementary Table S2, related to Figure 5, S1, S2, S5 and S7 . List of oligonucleotide used in this study. (To modify for publication)

Gene Name	Gene symbol	Species	Primer
Cyclophilin	Cyclo	Mouse	ATGGCACTGGCGGCAGGTCC
			TTGCCATTCCTGGACCCAAA
E2f1	E2f1	Mouse	GATCGAAGCTTTAATGGAGCG
			CCCTTGCTTCAGAGAACAGG
E2f1 Exon3	E2f1 Exon3	Mouse	ACAGCTGCAACTGCTTTCGGAG
			AGCTTGTAGTTGGTCTCAGGAGG
Paired Box 4	Pax4	Mouse	GTGTACCCTCAGCTGCCTTG
			ATAGGCCTGGGATGAGGTGT
Pancreatic and duodenal homebox 1	Pdx1	Mouse	ATTGTGCGGTGACCTCGGGC
			GATGCTGGAGGCTGTGGCG
Aristaless-related homebox	Arx	Mouse	GCGGGCTTCCAGAAGACGC
			CTGGAACCACTGGACTCGG
Homebox protein Nkx2.2	Nkx2.2	Mouse	GTGCAGGAGTATTGGAGGC
			GAAGGGCCAGAGGAGGAGA
Forkhead box protein O1	Foxo1	Mouse	TGCCAACCAAGCTTCCACA
			TGGACTGCTCCTCAGTTCCTGCT
Insulin1	Ins1	Mouse	GCCAAACAGCAAAGTCCAGG
			GTTGAAACAATGACCTGCTGC
Insulin2	Ins2	Mouse	CAGCAAGCAGGAAGCCTATCT
			CAGGTGGGAACCAAAAGGT
Glucagon	Gcg	Mouse	AGGCCGAGGAAGGCGAGACT
			GGAGCCATCAGCGTGCCTGC
Potassium voltage-gated channel subfamily J member 11	Kcnj11	Mouse	CACAAGCTGGGTTGGGGGCTC
			TGCCCTCAGCTGGGTTCTGC
Dihydrofolate reductase	Dhfr	Mouse	ATGGTTCGACCATGAACTGCATCG
			TCTTCTCAGGAATGGAGAACCAGG
Glucokinase	Gck	Mouse	GCTCAGTGAACCCCGTCAAGC
			TGTGCGCAGCTGCTGAGG
v-maf musculoaponeurotic fibrosarcoma oncogene family, protein A	MafA	Mouse	CCTGTAGAGGAAGCGGAGGAA
			CCTCCCCAGTCGAGTATAGC
v-maf musculoaponeurotic fibrosarcoma oncogene family, protein B	MafB	Mouse	TTAGCGCAGACAGACTACCCAAA
			ATACTTTTACACTCCACCCTCG
Solute carrier family 2 (facilitated glucose transporter)	Slc2a2	Mouse	AACCGGATGATTGGCATGT
			GGCGAATTTATCCAGCAGCA
Proprotein convertase subtilisin/kexin type1	Pcsk1	Mouse	CCGGAGGGCAAGAAGCTGCC
			TGTTACGCCACGTCACACGAT
Proprotein convertase subtilisin/kexin type2	Pcsk2	Mouse	AAAGATGGCGCTGCAACAAG
			TTGCCAGTGTGAACAGGT
Proprotein convertase subtilisin/kexin type9	Pcsk9	Mouse	TTGCAGCAGCTGGAACTT
			CCGACTGTGATGACCTCTGGA
Urocortin 3	Ucn3	Mouse	TGATGCCACCTACTTCTCTG
			CTGTGTTGAGGCAGCTGAAG
Hepatocyte nuclear factor 1 homeobox a	Hfn1a	Mouse	ACCGTACACCGTGGACCTTA
			CCTGAGATCTACAGCACCTG
Glucagon like peptide 1 receptor promoter	Glp1r	Mouse	CTGCGGCTCTAAACCTGAG
			CTGCTCTTCGCGCTGG
Enhancer of zeste homolog 2 promoter	Ezh2	Mouse	TTCGCCCTCTGATTGGAC
			CATCGCTTTATTTGGCCCC
Cyclin E1 promoter	Ccne1	Mouse	GTTCTTAACCTCGGGCCCT
			CAAGTGAATGTCAGCAGGG
Intergenic region (Chromosome 7)	Chr7	Mouse	ACTCTGCCTGTACCCTTTT
			GGGTCAAGAGAGTGTGGGA
E2F1	hE2F1	Human	ATGGCACTGGCGGCAGGTCC
			TTGCCATTCCTGGACCCAAA
Paired Box 4	hPAX4	Human	AGCAGAGGCACTGGAGAAAGATT
			CAGCTGCATTTCCACTTTCAGCTT
Pancreatic and duodenal homebox 1	hPDX1	Human	CGTCCAGCTGCCTTTCCTAT
			CCGTGAGATGTACTTGTGAATAGGA
Aristaless-related homebox	hARX	Human	CTGCTGAAACGCAAACAGAGGC
			CTCGGTCAAGTCCAGCCTCATG
v-maf musculoaponeurotic fibrosarcoma oncogene family, protein A	hMAFA	Human	TTGTACAGGTCCCGCTCTTT
			AGCAGAGGCACTGGAGAAAGATT
Neurogenic Differentiation	hNEUROD1	Human	GCCCCAGGGTTATGAGACTAT
			GAGAAGTGAAGACTCGTCTGT
Insulin	hINS	Human	AGCCTTTGTGAACCAACACC
			GCTGGTAGAGGGAGCAGATG
Glucagon	hGCG	Human	CATTACAGGGCACATTCAC
			CGGCCAAGTTCTTCAACAAT

Supplementary Table S3, related to Figures 4, 5, 6, 7, S5, S6, S7, S8 and S9 . List of ChIP-seq and RNA-seq data sets used in this study.

References	Experiment	Mouse strain	Genotype	Biological samples	Antibody	Accession number	Database	Related figures
Lu et al., Cell Metab, 2018	ChIP-seq	C57B6/J (8-10 weeks)	WT	Pancreatic islets	H3K4me3 H3K27ac H3K27me3	GSE110648	Gene expression omnibus (https://www.ncbi.nlm.nih.gov/geo/)	Figure 6, Figure 7 and Figure S6 Figure 6, Figure 7 and Figure S6 Figure 6, Figure 7 and Figure S6
This study	ChIP-seq	N/A	N/A	Min6 cells (DMSO)	H3K4me3 H3K27ac H3K27me3 Flag M2	In progress In progress In progress In progress		Figure 6, Figure 7 and Figure S6 Figure 6, Figure 7 and Figure S6 Figure 6, Figure 7 and Figure S6 Figure 7, Figures S7, S8 and S9
This study	RNA-seq	C57B6/J (12 weeks) C57B6/J (12 weeks) N/A	E2f1 ^{fl/fl} (ctrl) E2f1 ^{β-/-} (KO) N/A	Pancreatic islets (n=3) Pancreatic islets (n=3) Min6 cells (n=3)	N/A	In progress In progress In progress		Figure 4, Figure 6, Figure 7, Figures S5, S6, S8 and S9 Figure 4, Figure 6, Figure 7, Figures S5, S6, S8 and S9 Figure 6

ENSMUSG00000042203	5472,431258	-0,423803738	0,12666124	-3,3472531	0,00081617	0,03040838	ENSMUSGOC Tbc1d22b	A
ENSMUSG00000029467	91654,93969	-0,420004883	0,13163128	-3,1907681	0,00141895	0,0413992	ENSMUSGOC Atp2a2	A
ENSMUSG00000032557	7881,072312	-0,416455263	0,12999674	-3,2050617	0,00135034	0,04025087	ENSMUSGOC Uba5	A
ENSMUSG00000017764	1951,666245	-0,415361445	0,12765493	-3,253783	0,00113879	0,03658842	ENSMUSGOC Zswim1	C
ENSMUSG00000020260	14551,26937	-0,413337849	0,11369729	-3,635424	0,00027752	0,01520599	ENSMUSGOC Pofut2	A
ENSMUSG00000066900	5646,041715	-0,412707629	0,130862	-3,1537623	0,0016118	0,04530275	ENSMUSGOC Sude3	A
ENSMUSG00000039263	8166,600461	-0,41124954	0,10065138	-4,0858808	4,291E-05	0,00478835	ENSMUSGOC Npep1	A
ENSMUSG00000029629	2563,479544	-0,410790686	0,12147788	-3,3816089	0,00072063	0,02834773	ENSMUSGOC Pfh14	A
ENSMUSG00000023915	4774,617527	-0,403332537	0,12400434	-3,2525679	0,00114367	0,03661742	ENSMUSGOC Trfrs21	A
ENSMUSG00000042178	4184,20181	-0,401835106	0,12229858	-3,285689	0,00101733	0,0346194	ENSMUSGOC Armc5	B
ENSMUSG00000052942	5713,177341	-0,400983075	0,1202595	-3,3343152	0,0008551	0,03117295	ENSMUSGOC Glis3	A
ENSMUSG00000067924	4911,838402	-0,3980071725	0,09960195	-3,9966257	6,425E-05	0,00598827	ENSMUSGOC Rtl8b	A
ENSMUSG00000032120	7883,8877	-0,397379363	0,10718423	-3,7074425	0,00020936	0,01276282	ENSMUSGOC C2cd2l	A
ENSMUSG00000022769	10645,89718	-0,395391387	0,11129131	-3,5527607	0,00038121	0,01865366	ENSMUSGOC Sdf21l	A
ENSMUSG00000032839	2979,579928	-0,39196468	0,11525528	-3,4008391	0,00067179	0,0271818	ENSMUSGOC Trpc1	A
ENSMUSG00000023921	2998,880766	-0,388505658	0,09994953	-3,8870182	0,00010148	0,00779176	ENSMUSGOC Mut	A
ENSMUSG00000030780	2842,428676	-0,388439033	0,10682712	-3,6361461	0,00027675	0,01520599	ENSMUSGOC BC017158	B
ENSMUSG00000034850	12587,35693	-0,38443241	0,11255733	-3,4154365	0,0006368	0,02611017	ENSMUSGOC Tmem127	A
ENSMUSG00000041891	50559,83839	-0,382473545	0,10077414	-3,7953541	0,00014743	0,00990598	ENSMUSGOC Lman1	A
ENSMUSG00000029086	18314,63456	-0,380380144	0,11619043	-3,2737649	0,00106125	0,03529294	ENSMUSGOC Prom1	B
ENSMUSG00000028976	19224,79516	-0,379554251	0,09891521	-3,8371677	0,00012446	0,00888115	ENSMUSGOC Slc2a5	D
ENSMUSG00000057530	46918,95336	-0,375862178	0,09537694	-3,9408077	8,1208E-05	0,00697732	ENSMUSGOC Ece1	A
ENSMUSG00000039474	21446,12834	-0,375383165	0,1014726	-3,699355	0,00021615	0,0130042	ENSMUSGOC Wfs1	B
ENSMUSG00000020256	20384,87856	-0,373202713	0,11684915	-3,1938846	0,00140372	0,04121615	ENSMUSGOC Aldh1l2	A
ENSMUSG00000031634	6575,896164	-0,372847598	0,11477619	-3,248475	0,00116025	0,03687281	ENSMUSGOC Ufsp2	A
ENSMUSG00000070754	23405,25567	-0,370032438	0,10471225	-3,6338026	0,00040963	0,01970234	ENSMUSGOC Hsp94	L
ENSMUSG00000061306	38242,00441	-0,367326377	0,08790389	-4,1787274	2,9314E-05	0,00362201	ENSMUSGOC Slc38a10	A
ENSMUSG00000041997	7979,776404	-0,367221429	0,11385062	-3,2254672	0,00125767	0,03886665	ENSMUSGOC Tik1	A
ENSMUSG00000018102	7365,912236	-0,360880958	0,11308403	-3,1912637	0,00141652	0,04139384	ENSMUSGOC Hist1h2bc	A
ENSMUSG00000028032	7794,246647	-0,35198861	0,10154982	-3,4661666	0,00052794	0,0233637	ENSMUSGOC Paps1	A
ENSMUSG00000032575	34023,93709	-0,349883098	0,09193823	-3,8056323	0,00014144	0,00964427	ENSMUSGOC Manf	A
ENSMUSG00000022685	4281,025535	-0,348980733	0,1011102	-3,451489	0,0005575	0,02410638	ENSMUSGOC Parn	A
ENSMUSG00000030500	10383,75467	-0,347431309	0,10108855	-3,4369006	0,00058841	0,0251165	ENSMUSGOC Impdh1	A
ENSMUSG00000032743	2602,916463	-0,34623877	0,10607501	-3,2640936	0,00109815	0,03590927	ENSMUSGOC D430042009A	A
ENSMUSG00000042298	2422,136369	-0,344725972	0,10893669	-3,1644615	0,0015537	0,04414145	ENSMUSGOC Ttc19	A
ENSMUSG00000027230	8366,127433	-0,341784841	0,10448123	-3,2712558	0,00107071	0,03534136	ENSMUSGOC Creb3l1	A
ENSMUSG00000043733	20117,70888	-0,341021098	0,10586577	-3,2212592	0,00127629	0,03902319	ENSMUSGOC Ptpn11	A
ENSMUSG00000035227	26177,87793	-0,340455569	0,09448867	-3,6031366	0,0003144	0,01630453	ENSMUSGOC Spcs2	A
ENSMUSG00000025935	29617,13461	-0,33999618	0,09387831	-3,6216693	0,00029271	0,01589604	ENSMUSGOC Tram1	A
ENSMUSG000000202845	5684,630611	-0,332542156	0,09342382	-3,5595009	0,00037156	0,01848763	ENSMUSGOC Tmem39a	N
ENSMUSG00000045752	7764,694737	-0,332314013	0,10320283	-3,2200088	0,00128187	0,03902319	ENSMUSGOC Tssc4	A
ENSMUSG00000032042	69776,49007	-0,329953801	0,08732525	-3,7784465	0,00015781	0,01038523	ENSMUSGOC Srpr	A
ENSMUSG00000029472	14016,66516	-0,319355737	0,09521643	-3,3539984	0,00079653	0,02998791	ENSMUSGOC Anapc5	A
ENSMUSG00000026307	12454,39985	-0,308271842	0,08476792	-3,6366569	0,0002762	0,01520599	ENSMUSGOC Scy	A
ENSMUSG00000074102	4761,144515	-0,307006184	0,09619548	-3,1914823	0,00141545	0,04139384	ENSMUSGOC Rbm15b	A
ENSMUSG00000079487	7484,02724	-0,297935911	0,0913629	-3,2610162	0,00111014	0,0360222	ENSMUSGOC Med12	A
ENSMUSG00000028173	13310,53768	-0,295379867	0,09378537	-3,1495302	0,00163533	0,04568507	ENSMUSGOC Wis	A
ENSMUSG00000034586	27057,80754	-0,293478881	0,09071823	-3,2350597	0,00121617	0,03823	ENSMUSGOC Hid1	A
ENSMUSG00000030282	11812,57743	-0,276735176	0,08295817	-3,33584	0,00085042	0,03117295	ENSMUSGOC Cmas	A

MCHR1		g-protein coupled receptor					0.0242
MCGAT2		enzyme					0.0242
NDUFAF3		other					0.0242
NIBAN2		transcription regulator					0.0242
NOP58		enzyme					0.0242
NPTX1		other					0.0242
NSD3		enzyme					0.0242
NUCKS1		kinase					0.0242
OLA1		enzyme					0.0242
PSMD14		peptidase					0.0242
PTGDS		enzyme					0.0242
PTTG1IP		other					0.0242
RAD50		enzyme					0.0242
RANBP9		other					0.0242
RDH16		enzyme					0.0242
RIMS2		other					0.0242
SERP1		other					0.0242
SERTAD1		transcription regulator					0.0242
SH2B2		other					0.0242
SLC39A4		transporter					0.0242
SNW1		transcription regulator					0.0242
SRGAP1		other					0.0242
THRSF		other					0.0242
UZAF2		other					0.0242
WAPL		other					0.0242
WIF1		other					0.0242
ZIC1		transcription regulator					0.0242
EGF		growth factor					0.0245
ADAM10		peptidase					0.0246
BTG2		transcription regulator					0.0246
GTF2B		transcription regulator					0.0246
SFRP1		transmembrane receptor					0.0246
RETNLB		other					0.0258
ROR2		kinase					0.0258
Hmgn3		other					0.0262
Ihht		enzyme					0.0262
TCF		group					0.0267
INS	-0.71	other	-0.277	-0.041	-0.197	0.0276	
Nr1h		group	0.152 bias	0.382	-0.606	0.0276	
AZM		transporter				0.0278	
CTNWB1		transcription regulator	-1.147 bias	-0.507	-0.152	0.0283	
EIF2AK3		kinase	-1.969 bias	-0.843	-0.31	0.0283	
HIF1A		transcription regulator	-1.352 bias	-0.444	-0.198	0.0292	
CXCR4		g-protein coupled receptor				0.0294	
DK1		other				0.0311	
RAF1		kinase				0.0311	
MAPK1		kinase	-0.816	0.088	-1.033	0.0321	
ADRA2B		g-protein coupled receptor				0.0321	
AGAP2-AS1		other				0.0321	
AGTRAP		g-protein coupled receptor				0.0321	
AKAP5		other				0.0321	
AP2M1		other				0.0321	
ARF1		enzyme				0.0321	
ATP2A1		transporter				0.0321	
BRS3		g-protein coupled receptor				0.0321	
CACNA1D		ion channel				0.0321	
CDC25B		phosphatase				0.0321	
CHN1		other				0.0321	
CPT1		group				0.0321	
Cathepsin		group				0.0321	
DDX19B		enzyme				0.0321	
DKK2		other				0.0321	
FFAR2		g-protein coupled receptor				0.0321	
GALR1	-0.816	g-protein coupled receptor				0.0321	
GH2		other				0.0321	
IGFBP4		other				0.0321	
ITPR1D2		other				0.0321	
Irs3		other				0.0321	
KRT10		other				0.0321	
LAMB1		other				0.0321	
MIR3662		microma				0.0321	
MUCL1		other				0.0321	
MYBPC3		other				0.0321	
NASP		other				0.0321	
NRZF1-AS1		other				0.0321	
ORAI3		other				0.0321	
PITPNA		transporter				0.0321	
PPP1R3C		phosphatase				0.0321	
PRKAB2		kinase				0.0321	
RAB11A		enzyme				0.0321	
SEMA3E		other				0.0321	
SGMS1		enzyme				0.0321	
SHBG		other				0.0321	
SIDT2		transporter				0.0321	
SLC2A8		transporter				0.0321	
SLC11B3		transporter				0.0321	
SNRK		kinase				0.0321	
STEAP4		enzyme				0.0321	
SUFU		transcription regulator				0.0321	
TACS1D2		other				0.0321	
TBC1D4		other				0.0321	
TCF4LEF		group				0.0321	
TEX11		other				0.0321	
VTCN1		other				0.0321	
ZFP42		transcription regulator				0.0321	
mi-194		microma				0.0321	
GSK3B		kinase				0.0321	
IGF2		growth factor				0.0328	
Mapk		group				0.0328	
FOXA1		transcription regulator	-1.982	0.02	-2.023	0.0329	
HMGAT1		transcription regulator				0.0341	
PTH		other				0.0341	
SMAD2		transcription regulator				0.0341	
PDPK1		kinase				0.0364	
GLI1		transcription regulator	-0.227	0.204	-0.792	0.0369	
IL10RA		transmembrane receptor	-1.633	-0.024	-1.575	0.0369	
DSCAML1		other				0.0371	
GH1		growth factor				0.0382	
KDM3A		transcription regulator				0.0382	
MLX		transcription regulator				0.0382	
MYBL2		transcription regulator				0.0382	
mi-30		microma				0.0382	
SLC13A1		transporter				0.0392	
ACACA		enzyme				0.04	
AKIRIN2		other				0.04	
APBB1		transcription regulator				0.04	
ARAF		kinase				0.04	
AXIN1		other				0.04	
CDH16		enzyme				0.04	
CHR3		ectoderm coupled receptor				0.04	
CXCL14		cytokine				0.04	
FZR1		kinase				0.04	
GATM		enzyme				0.04	
GNR01		enzyme				0.04	
GPR99		g-protein coupled receptor				0.04	
GYS2		enzyme				0.04	
HCFC1		transcription regulator				0.04	
HINFP		transcription regulator				0.04	
HTR2C		g-protein coupled receptor				0.04	
INSL5		other				0.04	
UGALST2	-0.797	other				0.04	
MIR3936HG		other				0.04	
Muc1		transmembrane receptor				0.04	
NDN		transcription regulator				0.04	
Nesf		other				0.04	
PITX1		transcription regulator				0.04	
PORCN		enzyme				0.04	
PRMT2		enzyme				0.04	
PXN		other				0.04	
RAD51C		enzyme				0.04	
RBBP8		enzyme				0.04	
RNF187		enzyme				0.04	

RUVBL2		transcription regulator					0.04
SIK3		transcription regulator					0.04
STX2		transporter					0.04
TPPP2		other					0.04
WFS1	-0.375	enzyme					0.04
WNT7B		other					0.04
WRN		enzyme					0.04
ZMY2		transcription regulator					0.04
miR-193a-3p (and other		mature microma					0.04
miR-455-3p (miRNAs w/		mature microma					0.04
miR-455		microma					0.04
miR-489		microma					0.04
HDL-cholesterol		complex					0.04
LGALS3		other					0.0403
CYP11A1		enzyme					0.0414
CYP27B1		enzyme					0.0419
DRD2		g-protein coupled receptor					0.0419
AKT1		kinase					0.0425
DSCAM		other					0.0425
TSC2		other					0.0427
EGFR		kinase	-1.503 bias	-0.714	0.061		0.0427
MECP2		transcription regulator					0.0435
SILC25A13		transporter					0.0435
PIK3CA		kinase					0.0435
Grb		group					0.044
IFNG		cytokine	0.43 bias	-0.474	1.887		0.0454
SNAI2		transcription regulator					0.0458
TOB1		transcription regulator					0.0458
RGS2		enzyme					0.0459
KLF4		transcription regulator	Inhibited	-2.19 bias	-0.588	-0.88	0.0461
EIF2S1		translation regulator					0.0478
NRG1		growth factor					0.0478
ACOT13		enzyme					0.0478
AKAP12		transporter					0.0478
ANK3PTL6		other					0.0478
ANKHD1/ANKHD1-EIF4		other					0.0478
CBR3-AS1		other					0.0478
CCND2		other					0.0478
CDKSR1		kinase					0.0478
CTNBP1		other					0.0478
DLX1		transcription regulator					0.0478
DMTF1		transcription regulator					0.0478
EOG1		enzyme					0.0478
ERVW-1		other					0.0478
FSTL3		other					0.0478
GLP1R	-0.806	g-protein coupled receptor					0.0478
GPAM		enzyme					0.0478
GUCY2C	-0.658	kinase					0.0478
HPRT1		enzyme					0.0478
IGFBP7		transporter					0.0478
MC3R		g-protein coupled receptor					0.0478
MEIT1		enzyme					0.0478
NRAS		enzyme					0.0478
Npy4r		g-protein coupled receptor					0.0478
OBP2B		transporter					0.0478
PDCD5		other					0.0478
PDE3A		enzyme					0.0478
PLSCR1		enzyme					0.0478
PRKAB1		kinase					0.0478
PRKG2		kinase					0.0478
Pdgf Ab		complex					0.0478
SH2D5		other					0.0478
SILC7A11-AS1		other					0.0478
TEF2		other					0.0478
VEGF		growth factor					0.0478
miR-637		microma					0.0478
PI3K (complex)		complex	-1.091 bias	-0.714	0.312		0.0486
Raf		group					0.0498

PDLIM2	other		-1.890	bias	3.41E-03	BST1, CRISP1, D2, FBP1, RTN1, SCAR3, SLC43A3, STC2	
mir-210	miRNA	Inhibited	-2.368	bias	3.41E-03	CD8B, CXCL12, FGFRL1, KLF6, LAMP1, RADS2, SCAR3	
FOXO4	transcription regulator		0.692	bias	3.41E-03	ANXA3, FABP5, GADD45B, JAG1, LCP2, SERPINE1, SOD2	150 (7)
ciprofibrate	chemical drug		0.174	bias	3.47E-03	CXCL12, GSTP1, KRT8, MGLL, NFKBIA, OAT, Saa3, SLC44A, Vnn3	114 (8)
L-tryptophan	chemical - endogenous mammal		-0.730	bias	3.49E-03	APOA1, BMP4, CAMK4, CD44, CEBA, CXCL12, FAS, GDF15, HSPD, ID1	190 (19)
UGAI S1	other		-3.533	bias	3.533E-03	ANG2, CXCL12, CXCL16, IJN, IJN2, IL1B, SERPINE1	213 (23)
GW3965	chemical reagent		-1.039	bias	3.57E-03	APOA1, Cc2, CCA2, CD86, CSF3, FABP5, IL1B, NFKBIA	148 (12)
RPTOR	other		-0.136	bias	3.62E-03	Cc2, CCR7, CD86, HK2, IL1B, LY75, MRC1	188 (21)
TRAP	other		0.762	bias	3.68E-03	CD40, CD86, ICAM1, IL1B	148 (17)
VTN	other		1.199	bias	3.68E-03	IL1B, RUNX2, SERPINE1, SFN	154 (20)
TAB1	enzyme		-0.782	bias	3.68E-03	BIRC3, IL1B, JUN, SERPINE1	143 (18)
bisulfated hydroxyanisole	chemical toxicant		1.896	bias	3.68E-03	GSTA3, GSTP1, JUN, NQO1	46 (3)
selenium	chemical drug		-0.152	bias	3.68E-03	APOA1, CEBA, KLF3, MRC1	114 (7)
Hedgehog	group		3.68E-03	bias	3.68E-03	CCN2, JAG1, KLF4, KLF3, KRT19	
isoleucic acid	chemical drug		-1.000	bias	3.68E-03	APOA1, CSF1, CSF3, GDF15, IL1B	161 (20)
AMPK	complex		1.195	bias	3.75E-03	BMP2, BMP2, Cc2, CXCL12, LITAF, OAT, RUNX2, SERPINE1	202 (21)
3M402	chemical reagent	Activated	2.204	bias	3.75E-03	ACOD1, BCL2L1, CD40, CD83, CD86, FOSL1, IL1B, Saa3	140 (15)
staurosporine	chemical - kinase inhibitor		-1.238	bias	3.75E-03	CASP3, CD28, FAS, FOSL1, ICAM1, IL1B, NQO1, SERPINE1	169 (20)
flamain	chemical drug	Activated	2.412	bias	3.79E-03	ALAS1, CD14, CSF1, CYP3A7, GSTP1, IL1B, PADI2, SERPINE1, UGT1A7 (includes others)	26 (4)
H89	chemical - kinase inhibitor		-1.796	bias	3.79E-03	Cc2, CD14, CD83, GSTP1, IL1B, NFKBIA, SDC1, SERPINE1, SOD2	209 (16)
dasidzain	chemical drug		0.816	bias	3.84E-03	CASP3, CD86, CXCR3, HLA.A, LCP2, NQO1, RAS, GRP1	169 (17)
ARNT	transcription regulator		0.277	bias	3.95E-03	CCR7, CD81, CSF3, CXCR3, HK2, NQO1, SERPINE1, SLC2A3	182 (13)
vorinostat	chemical drug		-1.356	bias	3.99E-03	BIRC3, BMP2, CASP3, CD8A, CEBA, FAS, ICAM1, IL1B, JUN, KLF4	204 (18)
9-10-dimethyl-1,2-benzanthracene	chemical toxicant		1.350	bias	4.02E-03	IL1B, JUN, MRC1, NQO1, SERPINE1	182 (20)
beta-naphthoflavone	chemical toxicant		1.350	bias	4.02E-03	FTH1, GSTP1, NQO1, Saa3, UGT1A7 (includes others)	208 (17)
HDAC5	transcription regulator		4.05E-03	bias	4.05E-03	HK2, HMGCS2, JUN, KLF6, PTFN13, RUNX2	
AGER	transmembrane receptor		1.449	bias	4.05E-03	Cc2, CSF1, FAS, ICAM1, IL1B, SERPINE1	186 (21)
SHARPIN	other		4.05E-03	bias	4.05E-03	IL1B, MUKL, TNFAIP3	120 (14)
GAS2L3	other		4.05E-03	bias	4.05E-03	FAS, PTFN14, TM6SF1	
BMP10	growth factor		4.05E-03	bias	4.05E-03	ICAM1, ID1, NFKBIA	149 (7)
PRF1	transporter		4.05E-03	bias	4.05E-03	Cc2, CD44, IL1B	137 (12)
MAFG	transcription regulator		4.05E-03	bias	4.05E-03	GST3, GSTP1, NQO1	
EPHX2	enzyme		4.05E-03	bias	4.05E-03	Cc2, ICAM1, IL1B	190 (19)
MAPK10	kinase		4.05E-03	bias	4.05E-03	CASP3, CD44, JUN	184 (17)
CXCL2	cytokine		4.05E-03	bias	4.05E-03	Cc2, ICAM1, IL1B	182 (18)
VIPR1	G-protein coupled receptor		4.05E-03	bias	4.05E-03	Cc2, CD40, CD86	119 (13)
SMURF2	enzyme		4.05E-03	bias	4.05E-03	JUN, RUNX2, SERPINE1	196 (17)
NAM1	transcription regulator		4.05E-03	bias	4.05E-03	IL1B, IL7R, RND3	182 (20)
EFNB2	kinase		4.05E-03	bias	4.05E-03	IL7R, RUNX2, TIAM1	66 (7)
DSP	other		4.05E-03	bias	4.05E-03	Cc2, CEBA, JUP	
BHLHA15	transcription regulator		4.05E-03	bias	4.05E-03	CCKAR, GJB2, RRT19	
cyclohexanoic acid	chemical - endogenous non-mammal		4.05E-03	bias	4.05E-03	BCL2A1, Cc2, FAS	86 (7)
silicon dioxide	chemical drug		4.05E-03	bias	4.05E-03	FOSL1, IL1B, JUN	208 (21)
erythromycin	chemical drug		4.05E-03	bias	4.05E-03	CD86, ICAM1, IL1B	148 (17)
CDK19	kinase		-1.414	bias	4.07E-03	CD81, FAS, JUN, RHD2F, SDC1, SFN, UPP1	
atorvastatin	chemical drug		-1.671	bias	4.09E-03	APOA1, BMP2, BMP6, Cc2, CD40, CYBA, GADD45B, ICAM1, IL17RD, JUN	204 (21)
p38 Sapp	group		4.11E-03	bias	4.11E-03	CD83, CD86	
Msi/Krs	group		4.11E-03	bias	4.11E-03	RELB, YAP1	
ATPase	group		4.11E-03	bias	4.11E-03	CD40, ICAM1	
Em	group		4.11E-03	bias	4.11E-03	CD44, ICAM1	
CYP	group		4.11E-03	bias	4.11E-03	CD86, NQO1	
olmesartan	chemical drug		4.11E-03	bias	4.11E-03	CYBA, ICAM1	
FOXK2	transcription regulator		4.11E-03	bias	4.11E-03	MOG3, SERPINE1	
ZM22	transcription regulator		4.11E-03	bias	4.11E-03	CD44, JUN	
Nilotinib	group		4.11E-03	bias	4.11E-03	CD83, CD86	
DCB 3503	chemical reagent		4.11E-03	bias	4.11E-03	Cc2, IL1B	
TDP2	transcription regulator		4.11E-03	bias	4.11E-03	IL7R, SYT1	
HADHA	enzyme		4.11E-03	bias	4.11E-03	Cc2, IL1B	95 (7)
MAPKAPK5	kinase		4.11E-03	bias	4.11E-03	MAPK6, TNFAIP3	
Gim1 (includes others)	other		4.11E-03	bias	4.11E-03	Cc2, IL1B	
EIF2AK1	kinase		4.11E-03	bias	4.11E-03	Hamp/Hamp2, IL1B	
BCAR3	other		4.11E-03	bias	4.11E-03	RALA, RRAS	
CES1	enzyme		4.11E-03	bias	4.11E-03	Cc2, IL1B	
Cxcl3	cytokine		4.11E-03	bias	4.11E-03	CEBA, CEBPD	
ELF2	transcription regulator		4.11E-03	bias	4.11E-03	KLK3, VTN	
4,4'-disothiocyanostilbene-2,2'-dimethine	chemical drug		4.11E-03	bias	4.11E-03	CASP3, Cc2	128 (13)
cimetidine	chemical drug		4.11E-03	bias	4.11E-03	FAS, GDF15	
tinamyl-3,4-dihydroxy-alpha-cyanobiphenyl	chemical reagent		4.11E-03	bias	4.11E-03	Cc2, MRC1	
retinaldehyde	chemical - endogenous mammal		4.11E-03	bias	4.11E-03	CASP3, ICAM1	
Sta3-Stat3	complex	Activated	2.000	bias	4.14E-03	BMP2, CD44, CYBA, ICAM1, JAG1, JUN, SERPINE1	144 (7)
HGX68	transcription regulator		-1.000	bias	4.14E-03	ADAM19, Cc2, KRT19, NQO1	
SHH	peptidase		1.133	bias	4.28E-03	BMP2, BMP4, HK2, JHMSA1, ID1, LAMP1, MCM3, RUNX2, SERPINE1, YAP1	213 (26)
miR-199a-5p (and other miRNAs)	mature miRNA	Inhibited	2.407	bias	4.33E-03	CD3, JAG1, KLF4, LAMC2, RND1, ZBTB16	
methylphenanthramine	chemical drug		4.35E-03	bias	4.35E-03	Cc2, FAS, HOMER2, ICAM1, IL1B, JUN	200 (18)
PELP1	G-protein coupled receptor	Activated	2.236	bias	4.35E-03	AHNAK2, BMP2, CSF3, GJB2, IL1B, KLF3, MAPK4, MRC1	121 (7)
GPER1	G-protein coupled receptor	Activated	2.236	bias	4.37E-03	CEBPD, JUN, NFKBIA, RND1, TNFAIP3	259 (21)
enalapril	biologic drug		4.477	bias	4.37E-03	CD44, Cc2, SERPINE1, SLC3A2, TNFRSF12A	
RB1	transcription regulator		-0.473	bias	4.41E-03	BTG3, CASP3, CCA2, CEBA, DONSON, FAS, FOSL1, GPR179, GPRCSC1D1	215 (20)
Pdgfr (complex)	complex		1.424	bias	4.55E-03	Cc2, CD44, CYBA, ICAM1, JAG1, JUN, SERPINE1	197 (20)
NTRK2	kinase		1.964	bias	4.63E-03	BMP2, CCA2, JAG1, Muc1, SERPINE1, SYT1	97 (7)
KDM5A	transcription regulator		1.962	bias	4.63E-03	ALCAM, Cc2, GDF15, SERPINE1	
ARRHGAP31	other		4.63E-03	bias	4.63E-03	BMP2, GADD45B, GDF15, JUN	
SOST	other		1.980	bias	4.63E-03	Cc2, CEBA, IL1B, SOD2	129 (12)
CYBB	enzyme	Activated	2.000	bias	4.63E-03	Cc2, CYBA, ICAM1, IL1B	195 (17)
IL17RA	transmembrane receptor		1.992	bias	4.63E-03	Cc2, CSF3, CXCL12, IL1B	153 (15)
SIRP1	transmembrane receptor		1.413	bias	4.74E-03	CASP3, GATA3, RUNX2, SERPINE1, Tc7	189 (16)
MMP1	peptidase		1.432	bias	4.74E-03	CXCL12, JUN, NFKBIA, RUNX2, SERPINE1	152 (15)
DCN	other		-0.836	bias	4.74E-03	CASP3, ICAM1, IL1B, SDC1, SERPINE1	167 (23)
IL12 (family)	group	Activated	2.813	bias	4.79E-03	ADAM19, CD44, CD86, GATA3, IL1B, NFKB1Z, SERPINE1, SLC2A3	185 (20)
FZD9	G-protein coupled receptor		4.85E-03	bias	4.85E-03	Cc2, CXCL14, IFF1B	
fentazumab	biologic drug		4.85E-03	bias	4.85E-03	FAS, LAG3, TGM5	
GIP	other		4.85E-03	bias	4.85E-03	Cc2, Cc8, Tc7	
CD70	cytokine		4.85E-03	bias	4.85E-03	BCL2A1, CD44, FAS	140 (19)
IL1RAP	transmembrane receptor		4.85E-03	bias	4.85E-03	CD14, CD40, IL1RL1	134 (10)
SIRP2	G-protein coupled receptor		4.85E-03	bias	4.85E-03	Cc2, ICAM1, JUN	197 (20)
KLK5	peptidase		4.85E-03	bias	4.85E-03	Cc8, ICAM1, IL1B	
7-nitroindazole	chemical reagent		4.85E-03	bias	4.85E-03	GSTP1, NFKBIA, PRKG1	
phenyl-N-tert-butylurea	chemical reagent		4.85E-03	bias	4.85E-03	CD40, CD83, CD86	169 (14)
glutaryl-Sa-methylselenocysteine	chemical - endogenous mammal		4.85E-03	bias	4.85E-03	GSTP1, ID1, JUN	
IB	cytokine		4.94E-03	bias	4.94E-03	ADAM19, CD14, CD88, CSF1, CSF3, FAS	165 (19)
MAP2K6	kinase		-0.763	bias	4.94E-03	Cc2, CD40, CD83, CD86, JUN, RELB	138 (17)
doxycycline	chemical drug		1.000	bias	4.94E-03	BMP2, CD86, CXCL12, SDC1, SOD2, XDH	127 (13)
ESRRB	ligand-dependent nuclear receptor	Activated	1.562	bias	4.99E-03	ALAS1, CCR7, CEBA, CSF3, HK1, HK2, KRT19, KRT20, KRT23, RUNX2	80 (5)
acetaminophen	chemical drug		2.394	bias	4.99E-03	CASP3, Cc2, CXCR3, FAS, GSTP1, HMGCS2, ICAM1, IL1B, JUN, NQO1	187 (19)
dibethylrosamine	chemical toxicant		0.555	bias	5.07E-03	CASP3, CXCL12, GSTP1, Hspa1b, KRT8, OAT, Vnn3	136 (7)
L-methionine	chemical - endogenous mammal		5.14E-03	bias	5.14E-03	BUB1, GADD45B, IFF1B, NFKBIA, SOD2	143 (7)
CASP8	peptidase		5.14E-03	bias	5.14E-03	CD14, CD44, CSF1, FAS, IL1B	139 (14)
LPL	enzyme		1.792	bias	5.14E-03	APOA1, CASP3, CSF1, ICAM1, IL1B	208 (20)
MAP3K1	kinase		2.178	bias	5.14E-03	BIRC3, FAS, HSPB1, JUN, SERPINE1	146 (18)
RGS10	other		5.14E-03	bias	5.14E-03	Cc8, CXCR3, FAS, IL1B, IL6ST	121 (10)
DETA-NONOate	chemical reagent		0.365	bias	5.14E-03	BIRC3, FAS, ICAM1, PRKG1, SERPINE1	202 (23)
ARRB2	other		-1.987	bias	5.16E-03	Cc2, IL1B, NFKB1Z, SERPINE1	182 (18)
MARK2	kinase		1.000	bias	5.16E-03	BATE, CD44, NFKB1Z, Vnn3	
green tea polyphenol	chemical drug		-1.067	bias	5.16E-03	CASP3, ICAM1, IL1B, JUN	139 (15)
bardoxolone	chemical drug		1.067	bias	5.16E-03	CEBA, FTH1, NFKBIA, NQO1	
PD173074	chemical reagent	Activated	2.449	bias	5.27E-03	CCR7, CEBA, DEFP1, GATA3, KRT23, PRR5	
kainic acid	chemical toxicant	Activated	2.919	bias	5.35E-03	CASP3, Cc2, FOSL1, GADD45B, GAP43, IL1B, JUN, SDC1, SLC39A4	169 (18)
IL1RN	cytokine	Inhibited	-2.179	bias	5.52E-03	CD44, HSPD, ICAM1, IL1B, KLF6, OASL, RHP2, SERPINE1	175 (19)
MOG	other		5.56E-03	bias	5.56E-03	Cc2, CD40, CD44, CD86, ICAM1	156 (16)
miR-34a-5p (and other miRNAs)	mature miRNA	Inhibited	-2.215	bias	5.56E-03	ICAM1, JAG1, KLF4, MCM3, NOTCH2	
BNIP3L	other		0.000	bias	5.56E-03	BLNK, Cc2, CCA2, NFKBIA, PTK2B	110 (11)
bucouline	chemical - endogenous non-mammal	Activated	2.191	bias	5.56E-03	GADD45B, HK2, JUN, KLF4, SLC2A3	152 (12)
PRKCE	kinase		1.633	bias	5.61E-03	AMIGO2, BIRC3, CSF3, IL1B, LLES1, JUN	164 (17)
CCL5	cytokine	Activated	2.416	bias	5.61E-03	ALCAM, Cc2, CD40, CD44, HMG1, IL1B	166 (18)
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin	chemical toxicant	Activated	2.180	bias	5.61E-03	CASP3, Cc2, HSPB1, IL1B, JUN, SOD2	171 (15)
rotitrem	chemical toxicant	Inhibited	-2.415	bias	5.61E-03	APOBEC3B, BIRC3, Cc2, CLDN, ICAM1, JUN	195 (18)
Ctbp	group		5.73E-03	bias	5.73E-03	GATA3, JUN, PRR	

NUPR1		transcription regulator		0.688	bias	9.57E-03	AP0REC3B, BUB1, CCNA2, CD68, FCHSD2, GDF15, HK2, KL4, KL6, LHFPL2
PP1		chemical - kinase inhibitor		-1.353	bias	1.01E-02	CXCL15, IL1B, JUN, SERPINE1
HOTAIR		other		0.819		1.01E-02	GDF15, ICAM1, LAMB3, LAMC2
LGR4		transmembrane receptor		-1.091	bias	1.01E-02	GD14, HSD17B13, IL1B, OAT
RCE1		peptidase				1.01E-02	Cd2, CXCL12, FLT3, RON
SRG		kinase	Activated	2.547	bias	1.01E-02	CAVIN1, CSF3, FOSL1, ICAM1, ID1, JUN, KLF3
PARPBP		other				1.02E-02	KRT8, TIAM1, TST
CaMKII		complex				1.02E-02	BIRC3, CD44, IL1B
IKK (complex)		complex				1.02E-02	BIRC3, ICAM1, IL1B
SALL4		transcription regulator				1.02E-02	CD44, CEBPA, KRT19
IGT1		complex				1.02E-02	CD14, CD40, CD86
IL2RA		transmembrane receptor				1.02E-02	CD86, GZMA, JUN
mR-218-Sp (and other miRNAs)		mature microRNA				1.02E-02	CASP3, LAMB3, RUNX2
STK4		kinase				1.02E-02	FAS, IL7R, YAP1
IGFBP5		other				1.02E-02	RUNX2, SERPINE1, SFN
PLA2G6		enzyme				1.02E-02	Cd2, MRC1, RUNX2
SFTPD		other				1.02E-02	Cd2, CD14, IL1B
GADD45A		other				1.02E-02	IL1B, JUN, NFKB2
CCNA2		growth factor				1.02E-02	BMP4, RUNX2, SERPINE1
DYRK1A		kinase				1.02E-02	ARPA1, MCM3, SERPINE1
ELF5		transcription regulator				1.02E-02	GATA3, KLF3, KRT8
Gm21596/Himgb1		transcription regulator				1.02E-02	CXCL12, IL1B, IL1RL1
probuticol		chemical drug				1.02E-02	BMP2, CYBA, SERPINE1
guanine		chemical - endogenous mamma				1.02E-02	BMP2, BMP4, ICAM1
fulicason propionate		chemical drug	0.000			1.02E-02	CD83, CD86, GADD45B, GJB2, IL1B, ITGB7, OLFML2B, SDC4, SERPINE1
WT1		transcription regulator	0.734			1.03E-02	BCL2A1, CSF1, IL1B, JUP, KLF4, LRP1, PIR, SDC1, SERPINE1, SLC2A3
MMP2		peptidase				1.05E-02	CD8, IL6ST, NFKBIA, PL, S3, VCL
gemfibrozil		chemical drug				1.05E-02	Cd2, CXCL12, FAS, FOSL1, IL1B
4-hydroxybutyric acid		chemical - endogenous mamma	-0.816			1.05E-02	CASP3, CCL2, CXCL12, IL1A, PADI2, SOD2
TO-901317		chemical reagent	-1.755	bias		1.09E-02	ALAS1, ALDH2, Cc2, FABP5, FBP1, GSTP1, HK2, HMGCS2, IL1B, MGLL
Laminin (complex)		complex				1.10E-02	BIRC3, RUNX2, SDC4, SERPINE1
SUMO2		enzyme	1.067			1.10E-02	CAV2, CXCL16, HMGA1, RNASE4
ATF1		transcription regulator				1.10E-02	FOSL1, FTH1, JUN, SOD2
SAHM1		chemical reagent	-2.000	bias		1.10E-02	CD44, HK2, ID1, RHOU
UDP		chemical - endogenous mamma				1.11E-02	Cd2, SERPINE1
L-phenylalanine		chemical - endogenous mamma				1.11E-02	FAS, SOD2
salsalazin A		chemical reagent				1.11E-02	BMP4, JUN
ganglioside GM3		chemical - endogenous mamma				1.11E-02	CD40, ICAM1
Calcineurin B		group				1.11E-02	B3GAT1, CXCR3
Cyp4a14		enzyme				1.11E-02	Cd2, IL1B
budilast		chemical drug				1.11E-02	IL1B, NCS1
foslogenin		chemical - endogenous non-mar				1.11E-02	ICAM1, IL1B
GPR84		G-protein coupled receptor				1.11E-02	Cd2, IL1B
GSTK1		enzyme				1.11E-02	Cd2, TMEM73
ADGRF5		G-protein coupled receptor				1.11E-02	Cd2, CSF1
TBP4		growth factor				1.11E-02	BMP4, ID1
SMAD1/5		group				1.11E-02	ID1, ID3
IL26		cytokine				1.11E-02	ICAM1, IL1B
ABCC1		transporter				1.11E-02	CYBA, NQO1
PDLIM7		other				1.11E-02	BMP2, RUNX2
CD8A	8,241	other				1.11E-02	CASP3, IL1B
SLC25A4		transporter				1.11E-02	BIRC3, SOD2
MAP3K12		kinase				1.11E-02	CASP3, JUN
CAV3		enzyme				1.11E-02	CAV2, DMD
mR-326		microRNA				1.11E-02	NOTCH2, SMO
levetacetam		chemical drug				1.11E-02	GAP43, IL1B
SMN1/SMN2		other				1.11E-02	Cd2, DMD
LPA		other				1.11E-02	ICAM1, SERPINE1
RASSF10		other				1.11E-02	CASP3, JUN
LY86		other				1.11E-02	CD14, CD86
CCX771		chemical reagent				1.11E-02	CD44, CXCL12
RBCK1		transcription regulator				1.11E-02	ICAM1, TNFAIP3
Pla2os2		other				1.11E-02	Cd2, Saa3
ULBP1		transmembrane receptor				1.11E-02	CD83, HLA-A
influnac acid		chemical drug				1.11E-02	CD83, FAS
NCX-4040		chemical drug				1.11E-02	GSTP1, NQO1
mechlorethamine		chemical drug				1.11E-02	CD40, IL1B
benzoic acid		chemical - endogenous mamma				1.11E-02	CD83, IL1B
SC-58125		chemical drug				1.11E-02	FAS, GDF15
acetic acid		chemical - endogenous mamma				1.11E-02	CASP3, JUN
apidine		biologic drug				1.11E-02	FOSL1, JUN
N,N-dimethylarginine		chemical - endogenous mamma				1.11E-02	ICAM1, SERPINE1
SOC35		phosphatase	-1.887	bias		1.11E-02	Cd2, CD40, CD86, ICAM1, IL1B, JUN
lunizamylin		chemical - endogenous non-mar	1.553	bias		1.11E-02	BIRC3, CD2, CEBP, GADD45B, Hamp/Hamp2, ICAM1, IL1B, KLF4, NFKBIA, Nrg1
12-(3-adamantan-1-ylureido) d		chemical reagent	0.000			1.12E-02	BIRC3, CASP3, CD40, FAS, RPK2
BSCL2		other				1.12E-02	Cd2, CEBPA, HMGA1, IL1RL1, MGLL
NEUROG1		transcription regulator	-1.342			1.12E-02	AMISQ2, MST1, PPRC, PXDN, SLC43A3
methotrexate		chemical reagent	3.360	bias		1.13E-02	CAV1, CAV2, CCNA2, FGFR1, GDF15, HK1, HK2, HOMER2, KLF3, MGLL
NRB-ReIA		complex				1.15E-02	ICAM1, IL1B, NFKBIA
PDGF-DD		complex				1.15E-02	CASP3, Cc2, TNFRSF12A
MGP		other				1.15E-02	JAG1, Prrs1 (includes others), RUNX2
resolvin D2		chemical - endogenous mamma				1.15E-02	Cd2, IL1B, JUN
RNKL		cytokine				1.15E-02	CD40, CD83, CD86
LTB		cytokine				1.15E-02	Cd2, GlycA1, IL1B
hydrochloric acid		chemical - endogenous mamma				1.15E-02	ICAM1, IL1B, JUN
lipoarabinomannan		chemical - endogenous non-mar				1.15E-02	CD14, ICAM1, IL1B
diallyl trisulfide		chemical - endogenous non-mar				1.15E-02	FAS, JUN, NQO1
Ionomstat		chemical drug				1.15E-02	Cd2, F11R, IL1B
NCOR1		transcription regulator				1.16E-02	CCNA2, CEBPA, HK1, IL1B, KLF3, PDE9A
mR-10		microRNA	-1.166	bias		1.16E-02	BMP, CD40, CD44, CD86, KLF4, SMO
phosphate		chemical - endogenous mamma	2.449	bias		1.16E-02	BMP2, ENRP1, FOSL1, HK2, SLC34A2, STC2
UMK2		kinase	2.193	bias		1.17E-02	IL1B, Cc2, GlycA1, ICAM1, IL1B, LYN, Saa3, SDC4
JQ1		chemical reagent	-2.213	bias		1.19E-02	BIRC3, Cd2, CCNA2, MCM3, TNFAIP3
ACVR1		kinase				1.19E-02	C1R, Hamp/Hamp2, ICAM1, ID1
mR-2006-3p (and other miRNA)		mature microRNA	-1.944	bias		1.19E-02	BST1, JAG1, PERP, PTPN13
EED		transcription regulator				1.19E-02	GATA3, KLF4, RUNX2, SCN1
SELPLG		other	2.000	bias		1.19E-02	BCL2A1, BST1, IL1B, LAG3
CALR		transcription regulator				1.19E-02	Cd2, CEBPA, ICAM1, VCL
GABPA		transcription regulator				1.19E-02	FAS, IL7R, NQO1, RRAS
4-hydroxyxanoneal		chemical toxicant	1.001	bias		1.19E-02	ICAM1, IL1B, JUN, SERPINE1
N,N-bis-(4-fluorophenyl)acetamide		chemical - protease inhibitor	Inhibited			1.19E-02	IL1B, IL1B, RELB, RNF3
NCOA1		transcription regulator	1.331	bias		1.22E-02	CEBPA, CHD9, GJB2, KLF3, Muc1, NFKBIA, NFKBIZ, SERPINE1
CDX2		transcription regulator	1.032	bias		1.22E-02	CD9, JUN, KLF4, KRT23, LAMC2, Muc1, SCIN, UGT1A7 (includes others)
EPZF		transcription regulator	0.478	bias		1.22E-02	CAV2, CCNA2, CD9, CXCR3, ID3, MCM3, PLEC4, Raet1d, Raet1e, SERPINE1
HXA9		transcription regulator	1.949	bias		1.22E-02	CD83, F11R, HMGA1A, IL7R, JUN, LYN, PRKQ3, SDC4, SERVINC
FGF8		growth factor	0.747	bias		1.22E-02	BMP2, BMP4, CSF3, LAMB3, RUNX2, TRIP6
CIP2A		other	-0.600	bias		1.26E-02	HK2, LASP1, S100A16, SCIN, SERPINE2
mR-29b-3p (and other miRNAs)		mature microRNA	-2.182	bias		1.26E-02	CAV2, KLF4, PPIC, TNFAIP3, Tpm1
TBP		transcription regulator				1.26E-02	BCL2A1, HLA-A, NFKBIA, TNFAIP3, XDH
Wnt1		group				1.29E-02	CD44, CEBPA, GATA3, RUNX2
ALB		transporter	1.982	bias		1.29E-02	CASP3, Cc2, CYBA, IL1B
RAC2		enzyme				1.29E-02	Cd24a, IL1B, RUNX2, ZYX
TNC		other				1.29E-02	Cd2, CD8A, CXCL12, IL1B
OGT		enzyme	-0.928			1.29E-02	DTNA, GAP43, HMGA1, JUN, JUP, NFKB2
leukotriene B4		chemical - endogenous mamma				1.30E-02	Cd2, IL1B, JUN
dexamethasone phosphate		chemical drug				1.30E-02	ID3, IL1B, NFKBIA
deoxy corticosterone acetate		chemical drug				1.30E-02	Gald1, CD86, CYBA
Cbp		group				1.30E-02	Cd2, CSF3, IL1B
dapsinad		chemical drug				1.30E-02	ID1, SERPINE1, TRIP13
GRHL2		transcription regulator				1.30E-02	BMP2, CLDN4, SEMA3B
CD81	0.944	other				1.30E-02	CD86, ICAM1, ID1
IL36G	6.581	cytokine				1.30E-02	CD83, CSF3, MRC1
Coln1c		other				1.30E-02	CCNA2, MAL, MCM3
AZGP1		transporter				1.30E-02	BMP4, HK2, KRT19
carvedilol		chemical drug				1.30E-02	CYBA, GAP43, IL1B
N2+		chemical reagent				1.30E-02	BIRC3, CSF1, ICAM1
RUNX2		transcription regulator	1.726	bias		1.31E-02	BMP2, CEBPA, CEBP, GADD45B, GALNT3, RUNX2, SERPINE1
TEAD1	2.637	transcription regulator	2.226	bias		1.34E-02	ARID3B, F3, LATS2, NFKBIZ, TRNP1
F3		transmembrane receptor	1.951	bias		1.34E-02	Cd2, DOCK4, ICAM1, IL1B, SERPINE1
uric acid		chemical - endogenous mamma	1.178	bias		1.35E-02	Cd2, CD86, CSF3, ICAM1, IL1B, RELB
sodium bisulfide		chemical reagent	0.152			1.39E-02	CASP3, FAS, ICAM1, SOD2
ZMPSTE24		peptidase	1.964	bias		1.39E-02	Cc2, CXCL14, GADD45B, ICAM1
PPP2CA		phosphatase	2.000	bias		1.39E-02	Cd2, GZMA, Saa3, UPP1
PRKACA		kinase	1.951	bias		1.39E-02	ALAS1, ANTXR1, ANTXR2, SDC1
dimethylnitrosamine		chemical toxicant				1.39E-02	ICAM1, IL1B, NQO1, SOD2
RS1-8220		chemical - kinase inhibitor	-1.987	bias		1.39E-02	ICAM1, IL1B, KLF3, SERPINE1
K1		chemical - endogenous mamma	-1.264	bias		1.39E-02	CASP3, IL1B, JUN, SLC12A4
ganglioside		chemical - endogenous mamma				1.40E-02	Cd2, ICAM1
16,16-dimethylprostaglandin E2		chemical - endogenous mamma				1.40E-02	CD44, IL1B
TEAD		group				1.40E-02	CAV2, CD44
bandoside GD3		chemical - endogenous mamma				1.40E-02	CD40, ICAM1
desoxy corticosterone		chemical - endogenous mamma				1.40E-02	CYBA, SERPINE1
SLC11A1		transporter				1.40E-02	Hamp/Hamp2, SLC11A2
(-)-epigallocatechin gallate		chemical - endogenous non-mar				1.40E-02	GDF15, RUNX2
APC/APC2		group				1.40E-02	JAG1, JUP
glydyl-5'-2'-guanosine		chemical reagent				1.40E-02	CD86, IL1B
bacterial lipopolysaccharides		chemical - other				1.40E-02	IL1B, Saa3
OLFM4		other				1.40E-02	Cd2, IL1B
FBXO42		other				1.40E-02	CSF1, ICAM1
FAT1		other				1.40E-02	IL1B, JUN

PHF9					1.40E-02				ID1, IRAK3
MEMO1					1.40E-02				JUN, STC2
STK17A					1.40E-02				GSTO1, SOD2
nicotiflorin					1.40E-02				ICAM1, IL1B
UNC5B					1.40E-02				Cd2, YAP1
SERPINE2					1.40E-02				CN2A2, CD14
THBD					1.40E-02				Cd2, IL1B
TRG					1.40E-02				CAV2, IL1B
DLX1					1.40E-02				ARX, SERPINE1
CTSZ	0.893				1.40E-02				CD86, CD86
PTGDR					1.40E-02				Cd2, IL1B
HAS2					1.40E-02				Cd2, CD44
CDKN2B					1.40E-02				CD86, SERPINE1
INCA4					1.40E-02				Cd2, NFKBIA
FKBP5					1.40E-02				ICAM1, KLK3
USP37					1.40E-02				CEBPA, ZBTB16
ST6GAL1					1.40E-02				BIRC3, SLCA2A3
COCH					1.40E-02				Cd2, IL1B
IL22RA1					1.40E-02				Hamp/Hamp2, SOD2
cyto d guanosine monophosph					1.40E-02				CD86, IL1B
asbestos					1.40E-02				FOSL1, JUN
6-aminocaprolactamide					1.40E-02				Cd2, Saa3
sulindac sulfone					1.40E-02				NOO1, PRKG1
bupivacaine					1.40E-02				FOSL1, HPGDS
ketorolac					1.40E-02				Cd2, NFKBIA
SR1078					1.40E-02				Cd2, PAD2
mR-182 inhbtor					1.40E-02				CASP3, NFKBIA
2,4-dinitrobenzenesulfonic acid					1.40E-02				CD86, ICAM1
YBX1			1.982	bias	1.42E-02				Cd2, ID1, IRF5, KLK4, SLC2A3, STC2
ITGB3			0.200	bias	1.42E-02				CD40, CSF1, IL1B, RUNX2, SERPINE1
CHD7					1.45E-02				JAG1, PERP, PLE4
Smad					1.45E-02				ID1, ID3, SERPINE1
BCL2L11					1.45E-02				CASP3, Cc2, IL1B
miR-124					1.45E-02				CASP3, Cc2, RUNX2
BTG2					1.45E-02				IL1B, NQO1, SOD2
BAG1					1.45E-02				Hspa1b, JUN, KLK3
hemocyanin					1.45E-02				CD14, CD83, CD88
amitriptyline					1.45E-02				DEP1, HPN, SLC2A3
piceatannol					1.45E-02				FAS, ICAM1, IL1B
camptofol					1.45E-02				ICAM1, JUN, RUNX2
rescovitrol					1.50E-02				CD4, CEBPA, Rael1d/Rael1e, RALA
EGFR			-1.954	bias	1.50E-02				ESD, ID3, JUN, PLYND1
TEAD3			2.000	bias	1.50E-02				ARID5B, FJX1, NFKB2, TRNP1
ABCA1			-1.009	bias	1.50E-02				APOA1, Cc2, CSF3, IL1B
Naacetylspingosine			1.969	bias	1.50E-02				Cd2, JUN, SERPINE1, SOD2
dopipogrel			-1.342	bias	1.50E-02				ATO4B, BME, CXCL12, DHRS3, STC2
Ibuprofen			-1.342	bias	1.53E-02				CANX4, CN2A2, CD2, ID1, OAT1, PGD, RTN1, SERPINE2, TCEA3
DMD	1.365				1.55E-02				BLNK, DMD, FTH1, Marks, PAD2, PTGFRN, SCIN, SERPINE1, SYNC, WWC1
PC-SPE5					1.56E-02				CN2A2, CD9, FTL, ID1, IL1B, KLK3
LCK	1.108				1.59E-02				CN2A2, CD2, GADD45B, JUN, NOTCH2
ID1	1.349		1.380	bias	1.59E-02				DTX4, GATA3, ICAM1, IT1B, RUNX2
sulindac sulfide			1.480	bias	1.61E-02				ESD, GDF15, KRT19, NQO1, STC2
ADRA1D					1.61E-02				CEBP, FABP5, IL6ST, JUN
herbimycin			-1.118	bias	1.61E-02				ICAM1, IL1B, SERPINE1, SOD2
Sb202190			-1.980	bias	1.61E-02				Cd2, CD86, ICAM1, IL1B, MAPK6, SERPINE1, XDH
Tms30c1					1.61E-02				Cd2, IL1B, FERP
CXCL10					1.61E-02				Cd2, CXCR3, IL1B
LTBP1					1.61E-02				BMP, GATA3, SERPINE1
FGF9					1.61E-02				BMP4, CSF3, RUNX2
HMGCS2					1.61E-02				CSF3, IL1B, RUNX2
K-252					1.61E-02				CD14, JUN, SOD2
geranylgeranyl pyrophosphate					1.61E-02				BMP2, ICAM1, IL1B
Inoic acid					1.61E-02				ICAM1, NFKBIA, SERPINE1
CEBPD	0.429		0.447	bias	1.63E-02				BCL2A1, Cc2, CD14, CEBPD, IL1B, Saa3
Inoic acid			0.468	bias	1.68E-02				APOA1, Cc2, ICAM1, IL1B, NFKBIA
ATM					1.68E-02				FAS, GADD45B, JUN, SERPINE1, TNFAIP3
ETS2			2.236	bias	1.68E-02				BMP4, CSF3, ICAM1, JUN, PLA2G16
TL6-hydroxymethyl-chiro-inositol					1.73E-02				CXCL1b, GDF15
THOCS					1.73E-02				APOA1, CEBPA
DPY30					1.73E-02				ID1, ID3
ADCY7					1.73E-02				IL1RL1, IRAK2
FOXN1					1.73E-02				GZMA, SERPINE1
SEMA4D					1.73E-02				CD40, RRS4
ITGA4					1.73E-02				IL1B, TNFAIP3
AMBP					1.73E-02				Cd2, IL1B
SPRY4-IT1					1.73E-02				F11R, ZNF703
FRM6					1.73E-02				BMP2, RASSF4
HLA-G					1.73E-02				CD8A, FAS
LUM					1.73E-02				FAS, IL1B
LY9	2.405				1.73E-02				CD81, ZBTB16
lckv1-117					1.73E-02				JUN, RELB
Snv					1.73E-02				IL1B, SOD2
NFKBIE					1.73E-02				CSF3, ICAM1
PA2G4					1.73E-02				GDF15, KLK3
HBB					1.73E-02				ICAM1, SERPINE1
CDP1					1.73E-02				FAS, ICAM1
S100P					1.73E-02				KRT19, KRT8
CYBA	1.652				1.73E-02				SERPINE1, SOD2
zileuton					1.73E-02				Cd2, ICAM1
astressin 2B					1.73E-02				Cd2, SLC2A3
polyoxin B					1.73E-02				APOBEC3B, IL1B
S-equal					1.73E-02				CD86, SERPINE1
formononetin					1.73E-02				BMP2, CD86
lysophosphatidylinositol			2.000	bias	1.73E-02				CSF3, ICAM1, IL1B, SOD2
JAK3					1.78E-02				CSF3, GATA3, IL7R, LAG3
EZF2					1.78E-02				CN2A2, ID1, MC3J, Rael1d/Rael1e, SERPINE1
PSEN1			-0.762	bias	1.78E-02				AMY2A, BASP1, C1R, CASP3, CD9, CTZS, GADD45B, GSTP1, HK1, IL1B
glutamine			-2.000	bias	1.79E-02				FABP5, HK1, ICAM1, JUN, KLK4, NFKBIA
tetradotoxin					1.79E-02				AMIGO2, FAS, ID1
PRKDC					1.79E-02				BIRC3, ALK3, PEXE1
CTSS					1.79E-02				CASP3, FAS, IL1B
miR-23					1.79E-02				PTK2B, RUNX2, SOD2
ICOSLGL/LOC10273996					1.79E-02				CD28, IL1B, IL1RL1
PITPN2					1.79E-02				IL1B, LAG3, MRCl
ESRRA					1.79E-02				HK2, Hspa1b, PLE4
ozon					1.79E-02				Cd2, IL1B, JUN
PML			-1.066	bias	1.81E-02				APOA1, FAS, FTL, HSPB1, IL1B, JUP, NQO1, TNFAIP3
isoprotorenol			1.860	bias	1.81E-02				ALDH3B1, CSF3, DHRS3, FOSL1, IL1B, JUN, PRKD3, SOD2
GFR2					1.81E-02				BMP4, FAS, ICAM1, IL1B, MEST, RUNX2, TSPAN8
EPA51			2.404	bias	1.84E-02				BIRC3, CEBPA, GADD45B, SERPINE1, SLC11A2, SLC2A3, SOD2, STC2, TNFAIP3, YAP1
SCARB1			-1.387	bias	1.85E-02				APOA1, CD86, ICAM1, IL1B
ITGA5					1.85E-02				CD40, CD44, IL1B, JUN
RETN			1.067	bias	1.85E-02				APOA1, FABP5, ICAM1, SERPINE1
TEAD2			2.000	bias	1.85E-02				ARID5B, FJX1, NFKB2, TRNP1
ATF4			Activated		1.93E-02				GDF15, JAG1, JUN, KLK4, SOD2, STC2, TNFRSF12A, XDH
STAT4			Activated	2.800	bias	1.94E-02			GATA3, Hspa1b, LRP1, M5a4b (includes others), RCN3, SERPINE1, SLC2A3, STC2, TGF
N-corr					1.95E-02				Cd8, CXCL14, DHRS3, GSTP1, IL1B, ZNF703
Mir122a.b					1.97E-02				Cd2, CD86, IL1B
CDH11					1.97E-02				CD9, JUP, PTK2B
USP7					1.97E-02				BMP, KLK3, PDE9A
PLA2R1					1.97E-02				ALDH2, BDH2, SOD2
FABP4					1.97E-02				Cd2, FABP5, IL1B
CD47					1.97E-02				CSF1, FTL, IL1B
mipramine					1.97E-02				DEP1, HPN, SLC2A3
BTNL2			1.342	bias	1.97E-02				GJb2, Hspa1b, IL1RL1, SPECC1, XDH
tridamfon			1.000	bias	1.98E-02				ALAS1, CYP3A7, GSTA3, TST
fish oils					1.98E-02				APOA1, Cc2, CEBPA, IL1B
SGS1M1					1.98E-02				IL1B, JUN, NFKBIA, NQO1
CUL3			-0.849	bias	1.98E-02				NOO1, PLS3, Prss1 (includes others), TCEA3
ADRA1A					1.98E-02				CEBP, FABP5, IL6ST, JUN
FOXO3			1.597	bias	2.04E-02				ANKK3, BMP2, FABP5, GADD45B, HMGCS2, ICAM1, JAG1, LCP2, NFKBIA, NTN4
9-hydroxy(S)-10,12-octadecadi					2.07E-02				SERPINE1
acetylacetylcoenzyme A					2.07E-02				IL1B
endocannabinoid					2.07E-02				APOA1
GPSM3					2.07E-02				IL1B
COMMD5					2.07E-02				NOTCH2
nabutinase					2.07E-02				Cd2
BDNF-AS					2.07E-02				CASP3
BMP2/4					2.07E-02				Hamp/Hamp2
Palthead					2.07E-02				SMO
IRAK14					2.07E-02				IL1B
glutathimide					2.07E-02				ALAS1
G-Actin					2.07E-02				JUN
acridine half-mustard					2.07E-02				ANTXR2
WSX1-sp130					2.07E-02				GATA3
bovine testicular hyaluronidase					2.07E-02				CD44
PMM2					2.07E-02				ICAM1
NLRP2					2.07E-02				ICAM1
II3 bos					2.07E-02				IL1B
REL3					2.07E-02				IL1B

WFDC1		other				2,07E-02	ICAM1
CMPK2		kinase				2,07E-02	IL1B
PP1P5K1		phosphatase				2,07E-02	RUNX2
SV2B		transporter				2,07E-02	SYT1
SNORD21		other				2,07E-02	HLA-A
ID22		enzyme				2,07E-02	G2M4
FNDC3B		other				2,07E-02	RUNX2
CLPX		enzyme				2,07E-02	ALAS1
DAGLA		enzyme				2,07E-02	IL1B
UBN1		transcription regulator				2,07E-02	CDNA2
canakinumab		biologic drug				2,07E-02	IL1B
DEPDC1		transcription regulator				2,07E-02	TNFAIP3
SGMS2		enzyme				2,07E-02	APOA1
MYADM		other				2,07E-02	ICAM1
MACROD1		enzyme				2,07E-02	NFKBIA
CCDC22		other				2,07E-02	BIRC3
MLLT11		other				2,07E-02	CD44
COMMD9		other				2,07E-02	NOTCH2
KIF26B		other				2,07E-02	NGO1
CLIC1		ion channel				2,07E-02	IL1B
TCFL5		transcription regulator				2,07E-02	CD2
PHF10		other				2,07E-02	CASP3
DSC2		other				2,07E-02	CD44
THUM23	0,505	other				2,07E-02	CD40
DPP3		peptidase				2,07E-02	NGO1
FANK1		transcription regulator				2,07E-02	JUN
Testosterone-AR dimer		complex				2,07E-02	KLK3
CEL3R3		G-protein coupled receptor				2,07E-02	Nrg1
gattaparan		biologic drug				2,07E-02	CASP3
landutinib		chemical drug				2,07E-02	ID1
FAS-AS1		other				2,07E-02	FAS
Ox-4503		chemical drug				2,07E-02	CXCL12
black cohosh extract		chemical drug				2,07E-02	SERPINE1
GTPase		group				2,07E-02	BMP2
EIF3i		translation regulator				2,07E-02	SERPINE1
ACBD3		other				2,07E-02	SLC11A2
PRCC		other				2,07E-02	SERPINE1
cabazitaxel		chemical drug				2,07E-02	KLK3
DYNLRB1		other				2,07E-02	SERPINE1
NFE2L3		transcription regulator				2,07E-02	NGO1
GF6F		growth factor				2,07E-02	CSF3
COL5A3		other				2,07E-02	WWC1
RAB27A		enzyme				2,07E-02	CD44
MED7		transcription regulator				2,07E-02	TNFAIP3
LINC00872		other				2,07E-02	LASP1
SLC22A1		transporter				2,07E-02	ICAM1
miR-615-5p (and other miRNAs)		mature microRNA				2,07E-02	KRT18
miR-690 (miRNAs wisned AAG)		mature microRNA				2,07E-02	CEBPA
miR690		microRNA				2,07E-02	CEBPA
mi-1301		microRNA				2,07E-02	KLF6
mi-613		microRNA				2,07E-02	RTKN
AQUAPORIN		group				2,07E-02	IL1B
CAMK2		group				2,07E-02	BIRC3
EPST11		other				2,07E-02	NFKBIA
Raet1d/Raet1e	3,853	other				2,07E-02	HLA-A
RNF14		transcription regulator				2,07E-02	KLK3
PLXNB1		transmembrane receptor				2,07E-02	KLK3
COL4A2		other				2,07E-02	FAS
AXIN2		other				2,07E-02	BMP4
FSM1		peptidase				2,07E-02	GSTP1
RNF7		enzyme				2,07E-02	JUN
CTNNA1		other				2,07E-02	VCL
SART3		other				2,07E-02	KLK3
WED21		transcription regulator				2,07E-02	TNFAIP3
Ulox		enzyme				2,07E-02	IL1B
B3GAT2		enzyme				2,07E-02	B3GAT1
PRDM14		transcription regulator				2,07E-02	POLE4
PPDP		other				2,07E-02	CD44
UM2		other				2,07E-02	CXCL12
RPN2		enzyme				2,07E-02	GSTP1
FAP		peptidase				2,07E-02	Cd2
VPS4B		transporter				2,07E-02	CASP3
ZC3H8		transcription regulator				2,07E-02	GATA3
gularabine/daunubicin		chemical drug				2,07E-02	CEBPA
GDF10		growth factor				2,07E-02	SERPINE1
FI2		peptidase				2,07E-02	IL1B
binapant		biologic drug				2,07E-02	MLKL
quercetin-3-methyl ether		chemical reagent				2,07E-02	IL1B
quercetin-3,4'-dimethyl ether		chemical reagent				2,07E-02	IL1B
CDKL2		kinase				2,07E-02	CD44
SRRM1		other				2,07E-02	CD44
HIST1H4B		other				2,07E-02	Hsp91b
inositol free base		chemical reagent				2,07E-02	IL1B
IGHMIP2		enzyme				2,07E-02	APOA1
Rhodobacter sphaeroides lipote		chemical - endogenous non-mar				2,07E-02	IL1B
3MA052		chemical drug				2,07E-02	G2g
ETP-46464		chemical reagent				2,07E-02	OASL
ISCU		other				2,07E-02	FTH1
sintokamide A		chemical reagent				2,07E-02	KLK3
erlebene		chemical drug				2,07E-02	IL1B
mebabole		chemical - endogenous mamma				2,07E-02	NGO1
1beta-phosphonoglycan		chemical - endogenous non-mar				2,07E-02	IL1B
3-hydroxybutyric acid		chemical - endogenous mamma				2,07E-02	IL1B
SC-19220		chemical reagent				2,07E-02	ICAM1
bathophenanthroline		chemical reagent				2,07E-02	G2
RC31-9790		chemical - protease inhibitor				2,07E-02	GAF3
AZ10606120		chemical reagent				2,07E-02	CD86
fluorescein		chemical drug				2,07E-02	CASP3
1-(3-(1,4-dihydroimidazo[4,5-c]		chemical - kinase inhibitor				2,07E-02	Cd2
pentachlorophenol		chemical toxicant				2,07E-02	NGO1
SiM2N		chemical reagent				2,07E-02	CD86
L18-muramyl dipeptide		chemical reagent				2,07E-02	ACOD1
anti-miR-32 inhibitor		chemical reagent				2,07E-02	KLF4
1-methylspemidine		chemical reagent				2,07E-02	AMY2A
hecyl leucine-methyl ester		biologic drug				2,07E-02	IL1B
2-methoxy-5-(2,3,4'-trimethoxy		chemical reagent				2,07E-02	JUN
carbon		chemical reagent				2,07E-02	GSTP1
17S-hydroperoxy-docosahexae		chemical - endogenous mamma				2,07E-02	IL1B
UMP		chemical - endogenous mamma				2,07E-02	IL1B
eladipine		chemical drug				2,07E-02	IL1B
2'-fucosylactose		chemical - endogenous mamma				2,07E-02	ICAM1
P2y Receptor		group				2,07E-02	SLC2A3
ferric citrate		chemical drug				2,07E-02	FTH1
tetracycline		chemical drug	Activated	2,000	bias	2,08E-02	CSF1,JAG1,MAL,SERPINE1,SOD2
triploleide		chemical drug		-9,277	bias	2,08E-02	CASP3,CXCL12,FAS,ICAM1,JUN
coal tar		chemical drug				2,08E-02	GSTP1,NGO1
METT13		enzyme				2,08E-02	CD9,SERPINE2
APOL1		transporter				2,08E-02	IFNGR2,IL1B
Adaptor protein 1		complex				2,08E-02	CD44,SOD2
T0070907		chemical reagent				2,08E-02	Cd2,CEBPA
PLCL2		enzyme				2,08E-02	ID1,RUNX2
Anal Natriuretic Peptide		group				2,08E-02	NPR2,SERPINE1
Kaikarin		group				2,08E-02	Cd2,ICAM1
astragaln		chemical - endogenous non-mar				2,08E-02	ICAM1,IL1B
Mcp4		peptidase				2,08E-02	Cd2,CLDN4
TXK		kinase				2,08E-02	CD44,ZB1B16
DYRK1B		kinase				2,08E-02	G2,SOD2
miR-208a-3p (and other miRNA)		mature microRNA				2,08E-02	CD14,RUNX2
MAFF		transcription regulator				2,08E-02	GSTP1,NGO1
IL17RB		transmembrane receptor				2,08E-02	Cd2,CSF3
VLDR		transporter				2,08E-02	SERPINE1,TNFAIP3
ENTPD1		enzyme				2,08E-02	CD6,SERPINE1
CHRNA3		transmembrane receptor				2,08E-02	CASP3,GATA3
HIST2H3C		other				2,08E-02	IL1B,RND3
sevolunam		chemical drug				2,08E-02	CASP3,IL1B
ferric ammonium citrate		chemical drug				2,08E-02	FTH1,FTL
8-chlorophenylthio-adenosine 3		chemical - kinase inhibitor		1,982	bias	2,12E-02	BIRC3,CASP3,CEBP,LPIN2
IFN type 1		group		1,969	bias	2,12E-02	Cd2,IF16,OASL,XDH
EPH4		kinase		1,000	bias	2,12E-02	BMP2,BMP4,GATA3,Nes
IGFBP2		other				2,12E-02	CASP3,CHD9,GDF15,PTGFRN
ARNTL		transcription regulator		0,591	bias	2,12E-02	CEBPA,HMSCS2,IL1B,NGO1
LMNB1		other				2,12E-02	Cd2,CXCL12,FLT3,RCN1
benefitin A		chemical - endogenous non-mar		-0,130		2,12E-02	CD44,GADD45B,HLA-A,KLF4
GRP		growth factor				2,17E-02	CTR2B,JUN,KLK3
ACTL6A		other				2,17E-02	CDNA2,FAS,SFN
DLL1		enzyme				2,17E-02	CD86,GATA3,JAG1
CHADL		other				2,17E-02	Cd2,FAS,S,STEAP4
CFLAR		other				2,17E-02	CSF3,GATA3,IL1B
PD 123319		chemical drug				2,17E-02	Cd2,CY8A,SERPINE1
chrysotile asbestos		chemical toxicant				2,17E-02	CLCA1,CTS2,IL1B

6-bromovirulenol		chemical toxicant			2.17E-02	CLDN4, ICAM1, IL1B	
glucic acid		chemical - endogenous mammal			2.17E-02	ICAM1, IL1B, NFKBIA	
GnRH analog		biologic drug	0.577		2.18E-02	ACOT7, BCL2A1, CASP3, CD40, FAS, GAB1, GSTO1, JUN, NFKBIA, PLA2G1B	
GNA12		enzyme	0.447	bias	2.19E-02	GCNA2, GSTA3, GSTP1, LAMB3, VCL	
PAX3		transcription regulator			2.21E-02	BMP4, FLT3, IIG3, IL7R, LAMB3, MEST, PTPN14, PXDN, SFN	
FOXP3		transcription regulator	0.447	bias	2.21E-02	HLA-A, IIGF3, IL11R1, IL7R, LATS2, TNFAIP3	
SRC (family)		group	1.969	bias	2.26E-02	BMP2, Ccl2, ICAM1, ID1	
RTN4		other			2.26E-02	GAP43, JUN, NQO1, Tpm1	
CCN2		growth factor	1.148	bias	2.31E-02	BCL2A1, CD44, JUN, SDC4, SERPINE1, Tpm1	
ROXRA		ligand-dependent nuclear recep	0.000		2.33E-02	APOA1, CCR6, CCR2, CE2PA, CEPD, CLMN, FABP5, FTL, HMGCS2, IL1B	
elastin		biologic drug			2.37E-02	CD53, ICAM1, IL1B	
LPIN1		phosphatase			2.37E-02	CE2PA, IL1B, LPIN2	
indican		chemical - endogenous mamma			2.37E-02	GATA3, ICAM1, IL1B	
LLGL2		other			2.37E-02	CRM1, SERPINE1, SH2D4A	
Focal adhesion kinase		group			2.37E-02	ICAM1, KLF3, KR78	
CASP3	0.801	peptidase			2.37E-02	CAMK4, CASP3, RUNX2	
ROCK1		kinase			2.37E-02	CD44, ICAM1, LAMA2	
PRKC1		kinase			2.37E-02	CLDN4, HK1, HK2	
NG2A4		transcription regulator			2.37E-02	FABP5, JAG1, KLF3	
benzoic acid		chemical - endogenous non-mar			2.37E-02	CASP3, CSF3, IL1B	
R-WIN_55_212		chemical reagent			2.37E-02	CASP3, ICAM1, IL1B	
glyoxylic acid		chemical drug			2.37E-02	APOA1, CASP3, CD40	
baradoxolone methyl		chemical drug			2.37E-02	BIRC3, Ccl2, IL1B	
fucoxanthin		chemical reagent			2.37E-02	CASP3, CXCL12, IL1B	
CD5		transmembrane receptor	0.762	bias	2.40E-02	CCR7, CD86, ICAM1, RELB	
ADM		other	-1.067		2.40E-02	Ccl2, ICAM1, IL1B, PRKG1	
phenethyl isothiocyanate		chemical drug			2.40E-02	BUB1, CYP3A7, GSTA3, KRT20, MAPK6, PL33	
budesonide		chemical drug	1.342		2.41E-02	BTG3, Ccl2, CSF3, JUN, PDLIM1	
ascorbic acid		chemical - endogenous mamma	-0.277		2.41E-02	APOA1, BME, FAS, RUNX2, SERPINE1	
FOXO1		transcription regulator	Activated	2.582	bias	2.43E-02	CCNA2, CXCL12, CXCR3, JUN, NEK2, Nes, SOD2
halofuginone		chemical drug			2.43E-02	Ccl24a, CD44, CP, HK1, PL, CB4, PTGFRN, PTK2B	
movaltinostat		chemical drug			2.47E-02	CASP3, IL1B	
WIF106		chemical drug			2.47E-02	CD86, IL1B	
TCIRG1	1.150	enzyme			2.47E-02	CD44, CD86	
CLEC1B		transmembrane receptor			2.47E-02	CXCL12, LCP2	
ROG2		other			2.47E-02	CEBP2, Vmn3	
ALOX12		enzyme			2.47E-02	FOSL1, JUN	
CST3		other			2.47E-02	IL1B, NFKBIA	
PLTP		enzyme			2.47E-02	APOA1, IL1B	
DD2		other			2.47E-02	NFKBIA, SOD2	
BAP1		peptidase			2.47E-02	Ccl2, MCM3	
ETV6		transcription regulator			2.47E-02	CASP3, ID1	
NUMBL		other			2.47E-02	CASP3, KLF4	
ZBTB32		transcription regulator			2.47E-02	CSF2RB, GATA3	
HSPB8		kinase			2.47E-02	BMP4, ICAM1	
RIFK3		kinase			2.47E-02	Ccl2, IL1B	
PAK4		transcription regulator			2.47E-02	ARK, Nes	
AJUBA		transcription regulator			2.47E-02	BUB1, DOCK1	
ITGA3		other			2.47E-02	SERPINE1, VCL	
CDH5		other			2.47E-02	ICAM1, TIMM1	
IRRS2		translocation regulator			2.47E-02	FTH1, FTL	
ELN		other			2.47E-02	CD86, IL1B	
PLCL1		enzyme			2.47E-02	ID1, RUNX2	
ACO1		enzyme			2.47E-02	FTH1, FTL	
pentylselenotetrazol		chemical drug			2.47E-02	IL1B, JUN	
tonifenans		chemical drug			2.47E-02	CD86, KLF3	
D-sphingosine		chemical - endogenous mamma			2.47E-02	Ccl2, SERPINE1	
KT5720		chemical - kinase inhibitor			2.47E-02	NFKBIA, PRKG1	
tin protoporphyrin IX		chemical reagent			2.47E-02	CD86, Hamp/Hamp2	
curcubidin B		chemical - endogenous non-mar			2.47E-02	CASP3, CCR2	
fatty acid		chemical - endogenous mamma	1.519	bias	2.50E-02	APOA1, Ccl2, IL1B, LPIN2, NFKBIA, SERPINE1	
TET2		enzyme	-0.378	bias	2.51E-02	Ccl2, CLEC4D, IFI16, IL1B, PL33, RND3, ZBTB16	
NRA1		ligand-dependent nuclear recep	-1.615	bias	2.53E-02	CE2PA, CSF1, CXCL12, FBP1, HK2, ICAM1, IL1B, JUP, KR78, NFKBIA	
RSO20		chemical reagent	1.969	bias	2.53E-02	BIRC3, CE2PA, LAMC2, NFKBIA, ZBTB16	
CK39		kinase			2.55E-02	ALAS1, NFKBIA, STC2, TNFAIP3	
ZEB2		transcription regulator	-1.000	bias	2.55E-02	GZMA, IL7R, KRT19, Tcf7	
AKT2		kinase			2.55E-02	BUB1, Ccl2, IRAK3, NQO1	
VAV1		transcription regulator			2.59E-02	BCL2A1, JUN, RALA	
HRD1		other			2.59E-02	CTSC, HK1, LAMA2	
THBS4		other			2.59E-02	Ccl2, CD40, ICAM1	
fluvoxamine		chemical drug			2.59E-02	CCR7, HTR7, RACK1	
ERN1		kinase	1.404	bias	2.60E-02	ANG, Ccl2, CE2PD, FAS, IL1B, JUN, TINAGL1	
SPARC		other	-1.353		2.60E-02	CE2PD, CLDN4, NOTCH2, PLE1, SERPINE1, SLC34A2	
GAS1		other	1.342	bias	2.65E-02	Hamp/Hamp2, JAG1, JUN, MCM3, NFKBIA	
berberine		chemical drug	0.686	bias	2.71E-02	BIRC3, CASP3, CD40, CD86, ICAM1, IL1B	
alefacept		biologic drug	-1.982	bias	2.71E-02	CD2, CD8A, CYBA, IL7R	
oblimersen		biologic drug	2.000	bias	2.71E-02	CE2PD, GADD45B, IFI16, OASL	
GAT		enzyme	1.087	bias	2.71E-02	BCL2A1, Ccl2, CLG1, SERPINE1	
PLAG1		transcription regulator	0.000	bias	2.71E-02	KRT19, LILRB3, PIR, PPIP	
mi-24		microRNA	-0.404		2.71E-02	CXCR3, GATA3, SERPINE1, Tcf7	
CLEC11A		growth factor			2.71E-02	CXCL12, IL1B, RUNX2, ZYX	
anisomycin		chemical - endogenous non-mar	1.966	bias	2.71E-02	IL1R1, JUN, SDC1, SERPINE1	
SP110	2.929	transcription regulator	-0.378		2.78E-02	BMP4, DND1, PANK1, PERP, RPK2, TAB3, YAP1	
CARD9		other			2.81E-02	Ccl2, CSF3, IL1B	
IHH		enzyme			2.81E-02	BMP4, RUNX2, SMO	
PRKC2		kinase			2.81E-02	CASP3, JUN, NFKBIA	
BECN1		other			2.81E-02	BME, IL1B, SOD2	
CORT		other			2.81E-02	Ccl2, CCR7, IL1B	
N-3-(aminomethyl)benzylacetate		chemical reagent			2.81E-02	CASP3, FAS, RPK2	
hymecromone		chemical drug			2.81E-02	CASP3, CD44, FAS	
IFN17/FN13		cytokine	1.131	bias	2.87E-02	CD80, CD83, CD86, IL1B	
FN3		cytokine	1.982	bias	2.87E-02	CD86, HLA-A, ICAM1, LAG3	
MDG2A2		other			2.88E-02	BCL2A1, FAS	
FH		enzyme			2.88E-02	LTBP2, NQO1	
CRBN		enzyme			2.88E-02	IL1B, JUN	
humaine		chemical - endogenous non-mar			2.88E-02	BMP7, RUNX2	
SOX5		transcription regulator			2.88E-02	BMP6, RUNX2	
miR-210-3p (mRNAs w/seed U)		mature microRNA			2.88E-02	FGFRL1, RAD52	
mi-127		microRNA			2.88E-02	IL1B, MRC1	
HLA-A	1.061	other			2.88E-02	HLA-A, LAG3	
XRCC5		enzyme			2.88E-02	KLK3, XOH	
CD180		other			2.88E-02	BCL2A1, CD86	
NLR4		other			2.88E-02	CD86, IL1B	
FRS2		other			2.88E-02	BMP4, CD44	
PLA2G2E		enzyme			2.88E-02	IL1B, SERPINE1	
UGGQ		enzyme			2.88E-02	CASP3, ICAM1	
PONI		phosphatase			2.88E-02	CD86, ICAM1	
SDC1	1.625	enzyme			2.88E-02	Ccl2, GALNT3	
CRV1		enzyme			2.88E-02	CE2PA, IL1B	
CRK7		kinase			2.88E-02	STC2, TNFAIP3	
DUSP14		phosphatase			2.88E-02	NFKBIZ, Vmn3	
BHLHE41		transcription regulator			2.88E-02	GATA3, HK2	
HSPA1A/HSPA1B		enzyme			2.88E-02	Hspa1b, IL1B	
2'-3'-cyclic quanosine monophosphate		chemical - endogenous mamma			2.88E-02	CD86, IL1B	
bisphenol A diglycidyl ether		chemical reagent			2.88E-02	ICAM1, SERPINE1	
RV 538		chemical reagent			2.88E-02	ICAM1, IL1B	
ethylene diaminetetraacetic acid		chemical drug			2.88E-02	BCL2A1, IL1B	
imnomican		chemical drug			2.88E-02	FAS, IL1B	
isatorone		chemical reagent			2.88E-02	CD40, CD86	
cyclo maltodextrin		chemical drug			2.88E-02	CSF3, IL1B	
topiramate		chemical drug			2.88E-02	CASP3, IL1B	
CNR1		G-protein coupled receptor	0.420	bias	2.88E-02	BMP2, BMP4, Ccl2, Ccl8, CORO2A, NOD2, PTK2B	
ZAP70		kinase	1.992	bias	3.04E-02	ALAS1, ANG, CCR7, CYBA	
ELK1		transcription regulator	1.951	bias	3.04E-02	BMP2, FOSL1, JUN, RUNX2	
Pin		other			3.04E-02	APOA1, RACK1, RALA, RRAS	
FBXO32		enzyme	1.109		3.04E-02	IL1B, KRT19, OAT, SOD2, Tcf7	
SMO11		chemical reagent			3.05E-02	CD40, CD83, CD86	
MALAT1		other			3.05E-02	Ccl2, FRMD8, Glicem1	
KEAP1		transcription regulator			3.05E-02	GSTP1, IL1B, NQO1	
PDPK1		kinase			3.05E-02	CCR7, IL1B, SERPINE1	
TMPP1		cytokine			3.05E-02	IL1B, JUN, NQO1, SERPINE1	
lactic acid		chemical - endogenous mamma			3.05E-02	CXCL12, IL1B, MRC1	
batifomycin A1		chemical drug			3.05E-02	CD40, CD86, NFKBIA	
TGF3		growth factor	1.709	bias	3.15E-02	ADAM19, GATA3, JUN, LTBP2, SERPINE1, SERPINE2	
Whim		chemical drug	-0.447	bias	3.16E-02	CAMK4, CASP3, FAS, JUN, NCS1	
FBXW7		enzyme			3.21E-02	HSPB1, JUN, NQO1, SERPINE1	
POU2AF1		transcription regulator	-0.577	bias	3.21E-02	BAGALT1, CD86, IIG3, LK	
cadmium chloride		chemical toxicant			3.21E-02	CXCL12, HSPB1, JUN, KLF3	
Secretase gamma		complex			3.29E-02	BATF, CD83, CD86	
ZBED6		transcription regulator			3.29E-02	CRM1, UPP1, WWC1	
GHRNA7		transmembrane receptor			3.29E-02	Ccl2, ID1, IL1B	
ANXA2		other			3.29E-02	ANG-FAS, JUN	
DNASE2		enzyme			3.29E-02	CP, Hamp/Hamp2, Mef44b (includes others)	
SELP		transmembrane receptor			3.29E-02	BCL2A1, BST1, IL1B	
PRMT1		enzyme			3.29E-02	FTH1, FTL, MRC1	
ZBTB7B		transcription regulator			3.29E-02	CD8A, GATA3, KLF4	
PLAT		peptidase			3.29E-02	IL1B, JUN, SERPINE1	
TYK2		kinase			3.29E-02	CSF3, Hamp/Hamp2, IL1B	
CDC42		enzyme			3.29E-02	CASP3, CD86, JUN	
MEIS1		transcription regulator			3.29E-02	CHD9, FLT3, RUNX2	

S-nitroso-N-acetylpenicillamine		chemical reagent		3.29E-02		CXCL12,FAS,PRKG1
glycochenodeoxycholate		chemical - endogenous mamma		3.31E-02		BCL2A1,BIRC3
MEG3		other		3.31E-02		GDF15,JUN
Rac		group		3.31E-02		BMP2,CD9
belnacasan		chemical drug		3.31E-02		Cd2,IL1B
SGRP1		phosphatase		3.31E-02		IL1B,TGFB
NFKB1D		transcription regulator		3.31E-02		CD86,CD9
TNFAIP6L2		other		3.31E-02		Cd2,IL1B
CBS/CBSL		enzyme		3.31E-02		APOA1,CASP3
TACA		other		3.31E-02		CD86,IL1B
COX4I1		enzyme		3.31E-02		SLC20A3,SPAN8
SRSF3		other		3.31E-02		CD44,JUN
PIAS4		transcription regulator		3.31E-02		IL1B,SERPINE1
ATXN7		other		3.31E-02		BASP1,Marco6
CSF3R		transmembrane receptor		3.31E-02		CD44,CXCL12
ACVR1B		kinase		3.31E-02		KLF4,SERPINE1
CSAR2		G-protein coupled receptor		3.31E-02		Cd2,CSF3
NFFF		other		3.31E-02		CEBPA,ID3
STT4		peptidase		3.31E-02		ICAM1,IL1B
elbaslen		chemical drug		3.31E-02		ICAM1,IL1B
clasto-lactacycin beta-lactone		chemical - protease inhibitor		3.31E-02		GSTP1,MAPK6
N-(3-oxododecanoyl)-homoserine		chemical reagent		3.31E-02		CSF1,IL1B
dimethyl fumarate		chemical drug		3.31E-02		CD37,JUN
polyamines		chempal - other		3.31E-02		CD44,CEBPA
nickel chloride		chemical toxicant		3.31E-02		IL1B,JUN
spemine		chemical - endogenous mamma		3.31E-02		IL1B,RUNX2
anti-benzo(a)pyrene-diol-epoxide		chemical toxicant		3.31E-02		GADD45B,JUN
bochannin A		chemical toxicant		3.31E-02		CD86,RUNX2
nosipagin		chemical drug		3.31E-02		BIRC3,ICAM1
cyproterone acetate		chemical drug		3.31E-02		GAP43,CLK3
MAPK3		kinase	0.000	3.32E-02	bias	B4GAL1,BMP4,CD86,FOSL1,JUN
HNRNP2B1		other		3.38E-02		GP,GDF15,JUP,MEST,PLCB4,SEMA3B,SYT1
5-hydroxytryptamine		chemical - endogenous mamma	1.954	3.39E-02	bias	APBB1P,ICAM1,IL1B,PLIN3,RUNX2,SERPINE1
oxalalatin		chemical drug		3.39E-02		CASP3,FAS,GAP43,GDF15
ISL1		transcription regulator	1.387	3.47E-02		BMP4,CCKAR,IL1B,LILRB3,PIRT
NFYA		transcription regulator	2.000	3.47E-02	bias	CCNA2,FTH1,GADD45B,ICAM1,JUN
MAPK1		kinase	-0.163	3.48E-02		BCL11A,CentH4,Om7094,GATAs,IF16,IL1B,JUN,LAG3,OASL,PRKG1,PTRPK
USP22		peptidase		3.55E-02		BCL2A1,CSF2RB,MRC1
SETD2		enzyme		3.55E-02		ANG,JUN,SERPINE1
ABCG1		transporter		3.55E-02		Cd2,CSF3,IL1B
PRKCO		kinase		3.55E-02		CD44,FOSL1,GATA3
formaldehyde		chemical - endogenous mamma		3.55E-02		FOSL1,IL1B,JUN
methylvinlosourea		chemical toxicant		3.55E-02		GSTP1,IDI1,JUN
phorbol 12,13-dibutyrate		chemical - endogenous non-mar		3.55E-02		APOA1,Cd2,SERPINE1
AIRE		transcription regulator		3.58E-02		AKR1B10,BMP2,BMP4,CLK3
ursolic acid		chemical drug		3.58E-02		CASP3,GDF15,IL1B,SOD2
SRD5		other		3.62E-02		GADD45B,GAP43,IDI1,IFI16,ZNRF1
MAP1		other		3.62E-02		ANXA6,BASP1,C1R,CASP3,GSTP1,HK1,IL1B,JUN,Ptss1 (includes others),SERPINE1
MAPK4		kinase	Inhibited	-2.449	bias	ALDH3B1,CEBPA,H6PD,MGLL,PLCB4,ST3GAL4
BDNF		growth factor	1.779	3.64E-02	bias	AC077,BMP2,CASP3,CAV2,GP,FTL,GAP43,JUN,SEMA3E,SOD2
SIRT5		transcription regulator	0.302	3.72E-02	bias	CD86,CD9,CD11A,CD11B,CD11C,CD11D,CD11E,CD11F,CD11G,CD11H,CD11I,CD11J,CD11K,CD11L,CD11M,CD11N,CD11O,CD11P,CD11Q,CD11R,CD11S,CD11T,CD11U,CD11V,CD11W,CD11X,CD11Y,CD11Z,CD120,CD121,CD122,CD123,CD124,CD125,CD126,CD127,CD128,CD129,CD130,CD131,CD132,CD133,CD134,CD135,CD136,CD137,CD138,CD139,CD140,CD141,CD142,CD143,CD144,CD145,CD146,CD147,CD148,CD149,CD150,CD151,CD152,CD153,CD154,CD155,CD156,CD157,CD158,CD159,CD160,CD161,CD162,CD163,CD164,CD165,CD166,CD167,CD168,CD169,CD170,CD171,CD172,CD173,CD174,CD175,CD176,CD177,CD178,CD179,CD180,CD181,CD182,CD183,CD184,CD185,CD186,CD187,CD188,CD189,CD190,CD191,CD192,CD193,CD194,CD195,CD196,CD197,CD198,CD199,CD200,CD201,CD202,CD203,CD204,CD205,CD206,CD207,CD208,CD209,CD210,CD211,CD212,CD213,CD214,CD215,CD216,CD217,CD218,CD219,CD220,CD221,CD222,CD223,CD224,CD225,CD226,CD227,CD228,CD229,CD230,CD231,CD232,CD233,CD234,CD235,CD236,CD237,CD238,CD239,CD240,CD241,CD242,CD243,CD244,CD245,CD246,CD247,CD248,CD249,CD250,CD251,CD252,CD253,CD254,CD255,CD256,CD257,CD258,CD259,CD260,CD261,CD262,CD263,CD264,CD265,CD266,CD267,CD268,CD269,CD270,CD271,CD272,CD273,CD274,CD275,CD276,CD277,CD278,CD279,CD280,CD281,CD282,CD283,CD284,CD285,CD286,CD287,CD288,CD289,CD290,CD291,CD292,CD293,CD294,CD295,CD296,CD297,CD298,CD299,CD300,CD301,CD302,CD303,CD304,CD305,CD306,CD307,CD308,CD309,CD310,CD311,CD312,CD313,CD314,CD315,CD316,CD317,CD318,CD319,CD320,CD321,CD322,CD323,CD324,CD325,CD326,CD327,CD328,CD329,CD330,CD331,CD332,CD333,CD334,CD335,CD336,CD337,CD338,CD339,CD340,CD341,CD342,CD343,CD344,CD345,CD346,CD347,CD348,CD349,CD350,CD351,CD352,CD353,CD354,CD355,CD356,CD357,CD358,CD359,CD360,CD361,CD362,CD363,CD364,CD365,CD366,CD367,CD368,CD369,CD370,CD371,CD372,CD373,CD374,CD375,CD376,CD377,CD378,CD379,CD380,CD381,CD382,CD383,CD384,CD385,CD386,CD387,CD388,CD389,CD390,CD391,CD392,CD393,CD394,CD395,CD396,CD397,CD398,CD399,CD400,CD401,CD402,CD403,CD404,CD405,CD406,CD407,CD408,CD409,CD410,CD411,CD412,CD413,CD414,CD415,CD416,CD417,CD418,CD419,CD420,CD421,CD422,CD423,CD424,CD425,CD426,CD427,CD428,CD429,CD430,CD431,CD432,CD433,CD434,CD435,CD436,CD437,CD438,CD439,CD440,CD441,CD442,CD443,CD444,CD445,CD446,CD447,CD448,CD449,CD450,CD451,CD452,CD453,CD454,CD455,CD456,CD457,CD458,CD459,CD460,CD461,CD462,CD463,CD464,CD465,CD466,CD467,CD468,CD469,CD470,CD471,CD472,CD473,CD474,CD475,CD476,CD477,CD478,CD479,CD480,CD481,CD482,CD483,CD484,CD485,CD486,CD487,CD488,CD489,CD490,CD491,CD492,CD493,CD494,CD495,CD496,CD497,CD498,CD499,CD500,CD501,CD502,CD503,CD504,CD505,CD506,CD507,CD508,CD509,CD510,CD511,CD512,CD513,CD514,CD515,CD516,CD517,CD518,CD519,CD520,CD521,CD522,CD523,CD524,CD525,CD526,CD527,CD528,CD529,CD530,CD531,CD532,CD533,CD534,CD535,CD536,CD537,CD538,CD539,CD540,CD541,CD542,CD543,CD544,CD545,CD546,CD547,CD548,CD549,CD550,CD551,CD552,CD553,CD554,CD555,CD556,CD557,CD558,CD559,CD560,CD561,CD562,CD563,CD564,CD565,CD566,CD567,CD568,CD569,CD570,CD571,CD572,CD573,CD574,CD575,CD576,CD577,CD578,CD579,CD580,CD581,CD582,CD583,CD584,CD585,CD586,CD587,CD588,CD589,CD590,CD591,CD592,CD593,CD594,CD595,CD596,CD597,CD598,CD599,CD600,CD601,CD602,CD603,CD604,CD605,CD606,CD607,CD608,CD609,CD610,CD611,CD612,CD613,CD614,CD615,CD616,CD617,CD618,CD619,CD620,CD621,CD622,CD623,CD624,CD625,CD626,CD627,CD628,CD629,CD630,CD631,CD632,CD633,CD634,CD635,CD636,CD637,CD638,CD639,CD640,CD641,CD642,CD643,CD644,CD645,CD646,CD647,CD648,CD649,CD650,CD651,CD652,CD653,CD654,CD655,CD656,CD657,CD658,CD659,CD660,CD661,CD662,CD663,CD664,CD665,CD666,CD667,CD668,CD669,CD670,CD671,CD672,CD673,CD674,CD675,CD676,CD677,CD678,CD679,CD680,CD681,CD682,CD683,CD684,CD685,CD686,CD687,CD688,CD689,CD690,CD691,CD692,CD693,CD694,CD695,CD696,CD697,CD698,CD699,CD700,CD701,CD702,CD703,CD704,CD705,CD706,CD707,CD708,CD709,CD710,CD711,CD712,CD713,CD714,CD715,CD716,CD717,CD718,CD719,CD720,CD721,CD722,CD723,CD724,CD725,CD726,CD727,CD728,CD729,CD730,CD731,CD732,CD733,CD734,CD735,CD736,CD737,CD738,CD739,CD740,CD741,CD742,CD743,CD744,CD745,CD746,CD747,CD748,CD749,CD750,CD751,CD752,CD753,CD754,CD755,CD756,CD757,CD758,CD759,CD760,CD761,CD762,CD763,CD764,CD765,CD766,CD767,CD768,CD769,CD770,CD771,CD772,CD773,CD774,CD775,CD776,CD777,CD778,CD779,CD780,CD781,CD782,CD783,CD784,CD785,CD786,CD787,CD788,CD789,CD790,CD791,CD792,CD793,CD794,CD795,CD796,CD797,CD798,CD799,CD800,CD801,CD802,CD803,CD804,CD805,CD806,CD807,CD808,CD809,CD810,CD811,CD812,CD813,CD814,CD815,CD816,CD817,CD818,CD819,CD820,CD821,CD822,CD823,CD824,CD825,CD826,CD827,CD828,CD829,CD830,CD831,CD832,CD833,CD834,CD835,CD836,CD837,CD838,CD839,CD840,CD841,CD842,CD843,CD844,CD845,CD846,CD847,CD848,CD849,CD850,CD851,CD852,CD853,CD854,CD855,CD856,CD857,CD858,CD859,CD860,CD861,CD862,CD863,CD864,CD865,CD866,CD867,CD868,CD869,CD870,CD871,CD872,CD873,CD874,CD875,CD876,CD877,CD878,CD879,CD880,CD881,CD882,CD883,CD884,CD885,CD886,CD887,CD888,CD889,CD890,CD891,CD892,CD893,CD894,CD895,CD896,CD897,CD898,CD899,CD900,CD901,CD902,CD903,CD904,CD905,CD906,CD907,CD908,CD909,CD910,CD911,CD912,CD913,CD914,CD915,CD916,CD917,CD918,CD919,CD920,CD921,CD922,CD923,CD924,CD925,CD926,CD927,CD928,CD929,CD930,CD931,CD932,CD933,CD934,CD935,CD936,CD937,CD938,CD939,CD940,CD941,CD942,CD943,CD944,CD945,CD946,CD947,CD948,CD949,CD950,CD951,CD952,CD953,CD954,CD955,CD956,CD957,CD958,CD959,CD960,CD961,CD962,CD963,CD964,CD965,CD966,CD967,CD968,CD969,CD970,CD971,CD972,CD973,CD974,CD975,CD976,CD977,CD978,CD979,CD980,CD981,CD982,CD983,CD984,CD985,CD986,CD987,CD988,CD989,CD990,CD991,CD992,CD993,CD994,CD995,CD996,CD997,CD998,CD999,CD1000

N-acetylcysteine		chemical - endogenous mamma			4,10E-02	IL1B
BORCS-MEF2B		transcription regulator			4,10E-02	JUN
STK38L		kinase			4,10E-02	YAP1
NBR1		other			4,10E-02	GATA3
abiraterone		chemical drug			4,10E-02	KLK3
NOXO1		other			4,10E-02	SOD2
IFI30		enzyme			4,10E-02	HLA-A
SIGLEC11		other			4,10E-02	IL1B
OSTF1		transcription regulator			4,10E-02	RUNX2
FSB		other			4,10E-02	ICAM1
poly-L-glutamic acid-peptid 1		chemical reagent			4,10E-02	Cd2
cyclo(iso-Asp-GR-L-IUKLAKLA)		chemical reagent			4,10E-02	CASP3
SLC7A11		transporter			4,10E-02	IL1B
VANGL1		other			4,10E-02	JUN
PLEKHA1		other			4,10E-02	CD86
ING2		transcription regulator			4,10E-02	SERPINE1
RBM3		other			4,10E-02	CD44
MYBPC1		other			4,10E-02	Cd2
CD86		other			4,10E-02	IL1B
PLEKHA2		other			4,10E-02	CD86
PATZ1		transcription regulator			4,10E-02	KLK3
ENC1		peptidase			4,10E-02	NOO1
FOXL1		transcription regulator			4,10E-02	SDC1
DRP2		other			4,10E-02	DM3
FGF5		growth factor			4,10E-02	CSF3
SMC1A		transporter			4,10E-02	POLE4
FRAT1		other			4,10E-02	JUN
14,15-epoxyicoso-5(Z)-enoic a		chemical reagent			4,10E-02	Cd2
IPD9		transporter			4,10E-02	PTK2B
nitrosonifedipine		chemical reagent			4,10E-02	ICAM1
CRTAP		other			4,10E-02	SERPINE1
Acp5		phosphatase			4,10E-02	IL1B
SI1		other			4,10E-02	Cd2
APOC1		transporter			4,10E-02	CASP3
CDK11B		kinase			4,10E-02	KLK3
NLRP1		other			4,10E-02	IL1B
RNF11		enzyme			4,10E-02	SERPINE1
CLEC2D		transmembrane receptor			4,10E-02	CD3
COP6		other			4,10E-02	SFN
ZFYVE16		transporter			4,10E-02	SERPINE1
N-acetylcysteyltyrosylcysteine-am		chemical reagent			4,10E-02	XDH
ATB-348		chemical drug			4,10E-02	IL1B
E-c-HMAPP		chemical reagent			4,10E-02	BCL2A1
verticillin A		chemical reagent			4,10E-02	FAS
hydroxyl radical		chemical radical			4,10E-02	KLK4
trimellitic anhydride		chemical toxicant			4,10E-02	IL1B
emsamine		chemical drug			4,10E-02	JUN
sarpogrelate		chemical drug			4,10E-02	SERPINE1
meliothepin		chemical drug			4,10E-02	SERPINE1
albutamne		chemical drug			4,10E-02	SERPINE1
2,5-hexamidone		chemical toxicant			4,10E-02	FAS
hexaarginine-neomycin B conju		chemical reagent			4,10E-02	CD8A
oxazepam		chemical drug			4,10E-02	GADD45B
3,3'-aminodipropionitrile		chemical toxicant			4,10E-02	Cd2
glicazone		chemical drug			4,10E-02	SLC2A3
chalcone-24		chemical reagent			4,10E-02	BIRC3
trichosanthin		chemical drug			4,10E-02	JAG1
terpenoid		chemical - endogenous mamma			4,10E-02	LRP1
unushiol		chemical - endogenous non-mar			4,10E-02	IL1B
phenol		chemical - endogenous mamma			4,10E-02	IL1B
sodium fluoride		chemical drug			4,10E-02	ICAM1
cation		chemical - other			4,10E-02	GSTP1
echium oil		chemical drug			4,10E-02	IL1B
procotanol		chemical drug			4,10E-02	ICAM1
ZYYAD-FMK		chemical reagent			4,10E-02	IL1B
verteporfin		chemical drug			4,10E-02	YAP1
KT 5926		chemical - kinase inhibitor			4,10E-02	CD14
aluminum		chemical drug			4,10E-02	RUNX2
lyphostin B56		chemical - kinase inhibitor			4,10E-02	ICAM1
ibolone		chemical drug			4,10E-02	SERPINE1
flunilolide		chemical drug			4,10E-02	ICAM1
fluorocitric acid		chemical reagent			4,10E-02	IL1B
1-phenylacetic acid		chemical - endogenous non-mar			4,10E-02	ICAM1
HXXD10		transcription regulator	0,000		4,17E-02	CD4,ICAM1,NC51,SERPINE1
rotenone		chemical toxicant	0,832		4,17E-02	BIRC3,CASP3,IL1B,SOD2
interferon beta-1a		biologic drug			4,17E-02	GADD45B,GSTP1,LILRB3,MAL,NFKBIA,SERPINE1
CREM		transcription regulator	1,131		4,18E-02	CAMK4,CD86,CD8A,GADD45B,Marcks,MEF1,Tpm1
aldosterone		chemical - endogenous mamma	Activated	2,578 bias	4,18E-02	BMP2,Cd2,CYBA,ICAM1,NFKBIA,SERPINE1,ZBTB16
apotheline B		chemical drug			4,25E-02	FAS,SFN
selumetinib		chemical drug			4,25E-02	JUN,RUNX2
DPH5		enzyme			4,25E-02	IL1B,NFKBIA
NPK		growth factor			4,25E-02	Cd81,Cd2
NUP82		transporter			4,25E-02	PERP,WWC1
LY96		transmembrane receptor			4,25E-02	CD40,CD86
mi-204		microRNA			4,25E-02	IL1B,RUNX2
FCGR1A		transmembrane receptor			4,25E-02	CSF3,IL1B
HDA3		transcription regulator			4,25E-02	CEBPA,JUN
STIM1		ion channel			4,25E-02	GSTO1,NOO1
10-nitrooctate		chemical - endogenous mamma			4,25E-02	Cd2,ICAM1
CR2		transmembrane receptor			4,25E-02	FAS,IL1B
BCL10		transcription regulator			4,25E-02	CD44,TNFAIP3
CNR2		G-protein coupled receptor			4,25E-02	Cd2,IL1B
Cux1		transcription regulator			4,25E-02	Cd8,CD8A
101.10 peptide		chemical reagent			4,25E-02	Cd2,IL1B
3-aminobenamide		chemical toxicant			4,25E-02	ICAM1,IL1B
2-acetylaminofluorene		chemical toxicant			4,25E-02	JAG1,NOTCH2
allyl sulfide		chemical drug			4,25E-02	CASP3,GSTA3
concanamycin A		chemical drug			4,25E-02	ICAM1,NFKBIA
mevastatin		chemical drug			4,25E-02	BMP4,KLF4
indole		chemical - endogenous mamma			4,25E-02	CD4,IL1B
dimethyl pyrophosphate		chemical - endogenous mamma			4,25E-02	ICAM1,SERPINE1
tetrandrine		chemical drug			4,25E-02	CASP3,JUN
REST		transcription regulator	-1,400 bias		4,30E-02	B3GAT1,CEBPA,CXCL12,GAP43,Nes,OAT,SYT1
arsenic trioxide		chemical drug	1,672		4,34E-02	BCL2A1,CD44,FAS,FTTH,MAPK4,MAPK6,MCM3,NFKBIA,NOO1,PIR
CDX4A		kinase	-0,116 bias		4,37E-02	BMP2,CASP3,CXCA2,FAS,IL1B,JAG1,MCM3,SERPINE1,SOD2
saxagliin		chemical drug			4,37E-02	FAS,Marcks,RACK1
NSD2	0,462	enzyme			4,37E-02	ITGB7,JUN,RRAS
KRT14		other			4,37E-02	CXCL14,GJB2,KRT8
APR-246		chemical drug			4,37E-02	CD81,GADD45B,VCL
GID6C		other			4,37E-02	Cd2,SDC1,SERPINE1
ethylene glycol tetraacetic acid		chemical reagent			4,37E-02	BIRC3,CD3,CD86
NR4A3		ligand-dependent nuclear recep			4,37E-02	BIRC3,CEBPA,FBP1,NOO1
PLN		transporter			4,37E-02	APOA1,RACK1,RALA,RRAS
25-hydroxycholesterol		chemical reagent	1,000		4,37E-02	FOSL1,IL1B,JUN,NFKBIA
ATF2		transcription regulator	1,969 bias		4,42E-02	BCL2A1,CXCA2,IL1RL1,JUN,SOD2
LIF6		enzyme			4,46E-02	CEBPA,CP,IL1RL1,JUP,RUNX2,SDC4
BM1		transcription regulator			4,59E-02	FAS,HK2,MCM3,SFN
FOLR1		transporter			4,59E-02	BASP1,BIRC3,CD3,CD4,CLA1,ST3GAL4
KLF3		transcription regulator	-1,155 bias		4,59E-02	ALDH3B1,ANKK6,ARHGAP5,GSTP1,ITGB7,LILRB3,NEURL3,PARP3,PDLIM1,PTP4A2
phephenolone carbonitrile		chemical drug			4,67E-02	ALAS1,HMGS2,UGT1A7 (includes others)
INPP5D		phosphatase			4,67E-02	CD86,FAS,IRAK3
ATP7B		transporter			4,67E-02	CP,FABP5,TRIP13
SERPINE2	1,374	other			4,67E-02	Cd2,Cd8,IL1B
JAG2		growth factor			4,67E-02	BMP2,IL1B,JAG1
cyclopamine		chemical reagent			4,67E-02	CD14,FAS,SMO
RORC		ligand-dependent nuclear recep			4,69E-02	CD28,GADD45B,GSTP1,IL1B,L,PN2,SLC2A3,ZBTB16
3-deoxy-2-octulosonic acid(2)4		chemical - endogenous non-mar			4,75E-02	Cd2,IL1B
ICP7-cAMP		chemical - kinase inhibitor			4,75E-02	JUN,PRK1
Sod		group			4,75E-02	Cd2,ICAM1
trilosan		chemical drug			4,75E-02	JUN,NOO1
Angiotensin II receptor type 1		group			4,75E-02	GAP43,SERPINE1
ZC3H4		other			4,75E-02	BATF,Vmn3
PPP1R1B		phosphatase			4,75E-02	CASP3,CD44
SMYD3		enzyme			4,75E-02	CEBP,NEURL1
HSPB1	1,504	other			4,75E-02	Cd2,IL1B
UCP2		transporter			4,75E-02	HK2,IL1B
TNFRSF21		transmembrane receptor			4,75E-02	CASP3,CD28
INHBB		growth factor			4,75E-02	Hamp/Hamp2,SERPINE1
PHB2		transcription regulator			4,75E-02	BMP2,IL6ST
IL-17 dimer		complex			4,75E-02	CSF3,IL1B
PHLPH1		enzyme			4,75E-02	CEBP,VMN3
PSMB8		peptidase			4,75E-02	NFKBIA,TNFAIP3
LBP		transporter			4,75E-02	CD14,IL1B
mi-515		microRNA			4,75E-02	CD44,SERPINE1
mi-7		microRNA			4,75E-02	KLF4,SLC2A3
LAMA5		other			4,75E-02	Cd2,CSF3
KLF10		transcription regulator			4,75E-02	GATA3,SERPINE1
DDX17		enzyme			4,75E-02	FOSL1,JUN
Mir200		group			4,75E-02	JUN,LRP1
CCAT2		other			4,75E-02	CASP3,LATS2

GAB1	1.515	other				4.75E-02	CASP3,IL1B
C5		other				4.75E-02	Cd2,IL1B
batimastat		chemical - protease inhibitor				4.75E-02	ANG,SDC4
cefenine		chemical drug				4.75E-02	Cd2,IL1B
pyruvaldehyde		chemical - endogenous mamma				4.75E-02	ICAM1,NQO1
bombesin		chemical - endogenous mamma				4.75E-02	KLK3,ZB1B16
SMAD2		transcription regulator		-0.317	bias	4.77E-02	CRISPLD2,GADD45B,Hamp/Hamp2,RUNX2,SERPINE1
CD3E		transmembrane receptor				4.81E-02	FAS,JUN,LCP2,NFKBIA
SGK1		kinase	Activated	2.000	bias	4.81E-02	CEBPA,SLC2A3,SLC34A2,SMO
sildenafil		chemical drug				4.81E-02	CCNA2,IL1B,NQO1,SERPINE1
INS		other		1.432		4.82E-02	APQA1,Cc2,FADS3,FAS,FOSL1,ICAM1,JUN
cocaine		chemical drug	Activated	2.415	bias	4.85E-02	Cc2,FOSL1,GADD45B,ICAM1,JUN,LAMC2,MEST,Tpm1
PXR ligand-PXR-Retinoic acid-4		complex				4.97E-02	ALAS1,CYP3A7,UGT1A7 (includes others)
FOXO1		transcription regulator				4.97E-02	DML,GAP43,JUN
progesterone		chemical drug				4.97E-02	HK2,ICAM1,NFKBIA
miR-124-3p (and other miRNAs)		mature microRNA	Inhibited	-2.978	bias	5.00E-02	B4GALT1,BTG3,Cc2,CDC47,CEBPA,F11R,JAG1,LITAF,TSC22D4
NR3C2		ligand-dependent nuclear recep		1.954		5.89E-02	BCL2A1,BMP4,Cc2,ICAM1,IL1B,SERPINE1
DNMT3A		enzyme	Inhibited	-2.000		2.09E-01	BLNK,IRF5,PLCB4,SDC4,Tcf7