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Lessons from neonatal β -cell epigenomic for diabetes prevention and treatment

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Abstract

Pancreatic β -cell expansion and functional maturation during the birth-to-weaning period plays an essential role in the adaptation of plasma insulin levels to metabolic needs. These events are driven by epigenetic programs triggered by growth factors, hormones and nutrients. These mechanisms operating in the neonatal period can be at least in part reactivated in adult life to increase the functional β -cell mass and face conditions of increased insulin demand such as obesity or pregnancy. In this review, we will highlight the importance of studying these signalling pathways and epigenetic programs to understand the causes of different forms of diabetes and to permit the design of novel therapeutic strategies to prevent and treat this metabolic disorder affecting hundreds of million people worldwide.

β -cell replication, newborn, epigenetic, weaning, obesity, diabetes

Insulin, secreted by pancreatic β -cells residing within the islet of Langerhans, is the only hypoglycemic hormone promoting glucose utilization and storage in insulin-sensitive tissues. The amount of insulin released is precisely adjusted to meet the organism needs and avoid chronic hyperglycemia or life-threatening hypoglycemic episodes. This is achieved, thanks to a continuous adaptation of the mass and secretory activity of β -cells. This adaptive capacity has inspired academics, clinicians and pharmaceutical companies in search for novel strategies to prevent and treat diabetes mellitus, a chronic metabolic disorder expected to affect more than 600 million people by 2040. In mammals, β -cells continue to expand during the birth-to-weaning period before achieving full secretory competence [1]. These early postnatal events are characterised by strong epigenetic plasticity [2], permitting to couple changes in the nutritional environment to reprogramming of gene expression and of cellular activities. The study of the mechanisms underlying these phenomena, provides a unique opportunity to identify humoral factors and intracellular pathways driving β -cell proliferation and the acquisition of full secretory competence. This review provides an overview of the key signalling pathways connecting changes in nutrients, growth factors and hormones occurring during the suckling and weaning period to epigenetic mechanisms that control β -cell mass expansion and functional maturation. A better understanding of these mechanisms will be instrumental for the generation of fully operational insulin-secreting cells capable of replacing β -cells that are lost in Type 1 diabetes (T1D) patients. These pathways functioning during the neonatal period can be reactivated later in life to compensate for weight gain, pregnancy or a decrease in insulin sensitivity. Thus, a detailed knowledge of the components of these signalling cascades may also pave the way to novel therapeutic strategies to treat Type 2 (T2D) and gestational diabetes.

β -cells during the suckling period: functionally immature but optimised for proliferation

Since the proliferative capacity of β -cells in adults is limited, expansion of insulin-secreting cells during the suckling period is critical to generate enough cells to control blood glucose levels throughout life. In rodents, the expansion of the BCM results from increased β -cell size and replication [3,4], but also from duct cell differentiation that accounts for 30%–50% of the insulin-secreting cells produced during the first postnatal month [5,6]. In human, the BCM is largely established before the age of 20 [7] and the expansion, which mostly relies on β -cell replication [3], occurs mainly during the first 5 years [8,9]. The mechanisms involved in cell cycle regulation include the interconnection of kinase cascades (e.g. Jak2/Stat5, Nfat, mTorc1, Mapk/Jnk3) with transcription factors and non-coding RNAs such as microRNAs and long non-coding RNAs (**Box 1**). During the suckling period, cell cycle entry is triggered by

different cyclins [10,11]. These mechanisms are not specific to β -cells, suggesting that neonate β -cells are equipped with specific receptors and/or transporters that connect signals such as nutrients and/or growth factors (GFs) to classical proliferative pathways. A major source of these humoral factors is the maternal milk. The importance of milk quality for neonatal β -cell growth has been confirmed by exposing postpartum females to under- or overnutrition during the suckling period [13]. Indeed, this alters milk composition and can lead to premature perinatal maturation in the offspring [13]. Likewise, in rodents maternal under- or overnutrition during lactation is accompanied by alteration of neonate β -cell proliferation, resulting in a reduced BCM [14–16]. Maternal milk contains vitamins, immune cells, hormones, prebiotics, microbiota and various GFs [17]. Newborn β -cells express several GF and hormone receptors capable of inducing *Ccnd1/2* expression through activation of signalling pathways (**Box 2**). The presence of these receptors is essential to allow GFs and hormones particularly abundant in the neonate islet microenvironment to modulate β -cell proliferation.

Changes in maternal nutrition during gestation can affect postnatal β -cell functions during the lactation period. In rodents, maternal caloric restriction (CR) or low- protein (LP) diet during gestation leads to reduced birthweight and to a reduction in the offspring's BCM at birth [18], reflecting an imbalance between β -cell replication and apoptosis [19]. Later in life, this can affect the compensatory capacity of β -cells under conditions of increased insulin needs, favouring diabetes development [19]. β -cell proliferation is also compromised in neonatal rats and mice born from dams fed with a high-fat diet during gestation [20,21]. Reduced BCM caused by maternal undernutrition or overnutrition may be linked to changes in the level of GFs in maternal milk [22]. However, the gut and the innate immune system could also be a source of GFs. Indeed, β -cell expansion and maturation coincide with the development of intestinal and innate immunity (II). During suckling, intestinal tract colonization by commensal microbes contributes to microbiota formation and intestinal barrier maturation [23]. Interestingly, in zebrafish, administration of gram-negative *Aeromonas bacterial species* in the intestine of germ-free larvae stimulates β -cell proliferation and BCM expansion [24]. It is not yet known whether intestinal bacteria have analogous effects in mammals. Gut microbiota maturation during suckling is accompanied by increased circulating levels of Glucagon-like peptide 1 (GLP-1) [25], an enteroendocrine hormone produced by intestinal L-cell. GLP-1 stimulates β -cell proliferation and neogenesis in adult rodents [26] and inhibits β -cell apoptosis [27]. Beside GLP-1, GFs released by II cells that are particularly abundant in neonate islets may also promote BCM expansion [28]. At birth, II cells develop to protect neonates against infections originating from the extrauterine environment [29] but regulate also tissue growth during

development and repair [30]. In newborn islets, CCR2⁺ myeloid cells produce several mitogenic factors, including insulin-like growth factor 2, follistatin-like proteins and connective tissue growth factors [28]. The absence of CCR2⁺ cells leads to a reduced BCM [28], suggesting that mitogenic factors secreted by islet-resident II cells play a key role in β -cell proliferation during the suckling period [28,31].

Epigenetic programming of β -cell proliferation and metabolism during the suckling period

Adaptation to maternal milk nutrition requires profound modifications in gene expression. This is achieved through reprogramming of the DNA and RNA methylation profile as well as in changes in histone methylation, acetylation, phosphorylation or ubiquitylation. These epigenetic mechanisms are crucial for activating the expression of genes controlling metabolism and proliferation of immature β -cell during the breastfeeding period [32,33]. In immature β -cells, the expression of genes involved in cell cycle control and in anaerobic glycolysis correlates with changes in histone 3 trimethylation at lysine 27 and 4 (H3K27me3 and H3K4me3, respectively) [34-36]. H3K4 trimethylation at gene promoters and distal regulatory enhancers favours the recruitment of the transcription machinery and of chromatin remodelling complexes [37] and is generally accompanied by H3K27 acetylation and low levels of the repressive H3K27me3 marks. On the contrary, gene repression occurs at sites in which H3K27me3 is abundant while H3K4me3 is rare [38]. In neonatal β -cells, the CDK inhibitor genes *Cdkn1a* and *Cdkn1c* display elevated levels of repressive H3K27me3 marks while the gene coding for c-Myc, which plays a key role in proliferation, shows an enrichment in activating H3K4me3 marks [39]. Likewise, H3K4me3 is abundant in the regulatory regions of the genes coding for hexokinase (Hk) 3 and lactate/proton symporter monocarboxylate transporter-1 (*Mct1*), two enzymes essential for β -cell insulin secretion in response to low glucose and pyruvate, respectively [39,40]. Trimethylation of H3K27 and H3K4 is regulated by histone methyltransferase (HMT) and demethylase (HDM). HMT and HDM activities are controlled by key signalling pathways during the suckling period. The enhancer of zeste homolog 2 (*EZH2*) is a HMT subunit of the polycomb repressive complex 2 (PRC2) that trimethylates H3K27 [41]. mTorc1 signalling positively regulates *EZH2* activity [42,43], resulting in *Cdkn1c* downregulation and β -cell proliferation [42,43]. Other findings support a role for mTorc1 signaling in the epigenetic regulation of immature β -cell functions. Indeed, mTorc1 diminishes the expression of DNA methyl transferase 3a (*Dnmt3a*), a critical *de novo*

DNA epigenetic modifier [44]. This leads to hypomethylation and, thereby, activation of genes coding for Hk1, Hk2 and lactate dehydrogenase (Ldha) [44]. The same mechanism appears to apply to many genes involved in proliferation. Indeed, during the suckling period, 30% of the genes involved in G1/S phase progression and 59% of the genes involved in G2/M are upregulated by mTorc1 signaling [42]. Therefore, mTorc1 is likely to promote proliferation via global hypomethylation of cell cycle-related genes. Several GFs operating during the suckling period are able to trigger mTorc1 signaling, resulting in modifications in DNA and histone methylation [45,46]. Epigenetic regulation of gene expression in immature β -cells triggered by mTorc1 requires inhibition of the Smad pathway. In general, upon activation Smad protein complexes accumulate in the nucleus where they participate to the recruitment of HMT subunits, leading to H3K4 trimethylation, and induction of gene expression [47]. Several genes involved in proliferation, including the cell cycle blocker Cdkn2a, are regulated by Smads possibly through H3K4 trimethylation [48]. During the suckling period, inactivation of the Smad pathway leads to a reduction of H3K4me3 and to Cdkn2a silencing and repression of genes necessary for β -cell maturation [49]. Inappropriate activation of Smads during this critical period, results in the induction of Cdkn2a, which in turn, stops neonatal β -cell proliferation and in premature maturation [48]. Fetuin-A, a glycoprotein released by the liver, inhibits the Smad pathway in neonatal islets [48], supporting the idea that humoral factors in maternal milk and/or released by developing organs orchestrate the epigenetic programming of immature β -cells during the suckling period.

The nutritional switch during the suckling-weaning transition promotes β -cell maturation

Full β -cell maturation is achieved upon weaning [50], when infants switch from maternal breastmilk feeding, rich in fat and poor in carbohydrates, to solid and carbohydrate-enriched food. This is associated with changes in the gastrointestinal tract enabling the digestion and absorption of solid foods. During weaning, β -cells acquire the ability to sense changes in blood glucose levels and metabolize glucose to produce metabolic signals that trigger exocytosis of insulin-containing granules. β -cell terminal differentiation is likely to be achieved in two sequential stages, including the repression of the immature phenotype and the appearance of glucose-responsiveness [44,51]. In this regard, research carried out in the last few years suggests that the nutritional change drives major epigenetic reprogramming in β -cells (**Fig. 1**), permitting to stop proliferation and to reduce anaerobic glycolysis. Fetuin-A concentration declines from birth to weaning [48] while the islet concentration of TGF β , a strong inducer of

Smad pathway, increases [52], allowing H3K4 trimethylation of *Cdkn2a*, *Cdkn1a* and *Cdkn1c*, and causing cell cycle arrest [35,48]. Blockade of proliferation might also result from the decline in the expression of GFs receptors as exemplified by the HGF receptor c-Met. During weaning, the expression of MEG3 increases [41] and this lncRNA forms a complex with EZH2. This leads to a rise in H3K27 trimethylation in the c-Met promoter with a consequent reduction of β -cell proliferation [41]. The expression of PDGFRA is also reduced during weaning, in this case as a consequence of changes in the miRNA profile, in particular a rise of miR-29 [53]. This miRNA can profoundly affect also basal insulin secretion by silencing *Mct-1* and the transcriptional repressor REST [7,55,56]. The genes coding for *Ldha*, *Hk1* and *Hk2*, which are major players in the anaerobic glycolysis of neonatal β -cells, are also silenced during the suckling-weaning transition. During this period, DNA methylation of the genes coding for these enzymes increases due to enhanced Dnmt3a activity [44], which coincides with a switch from mTorc1 to AMPK and mTorc2 signalling [44,54]. Silencing of *Ldha*, *Hk1* and *Hk2* allows β -cells to switch glucose metabolism from anaerobic glycolysis towards oxidative phosphorylation. A drop in FA and a rise in blood glucose levels are probably major drivers of the modification in mTorc signalling. Indeed, silencing of mTorc1 and DNA methylation occur concomitantly when maternal milk is replaced in the diet by carbohydrate consumption [44, 54]. In mice, continuing milk fat consumption from the neonatal period until adulthood maintains mTorc1 signalling and β -cells remain immature [54]. Moreover, glucose promotes important changes in the DNA methylation profile of many genes [55]. In mice, increased expression of genes controlling glucose-induced insulin secretion including *Znt8*, *NeuroD1*, *Glut2*, *Urocortin 3 (Ucn3)* and *Kir6.2* relies on H3K4 trimethylation [36]. Elevated transcription of *Pdx1*, *Abcc8*, *Syt4/7* and *Snap25* has been associated with chromatin opening due to H3K27me3. Gene activation during the second stage of β -cell maturation includes also histone H4 arginine 3 asymmetric dimethylation (H4R3me2a). This epigenetic mark is mediated by protein arginine methyltransferase 1 (*Prmt1*) [56]. In neonatal islets, the genes coding for the transcription factors *Nkx6.1*, *Nkx2.2*, *MafA*, *NeuroD1* and *Pdx1* are enriched with the H4R3me2a. The expression of these genes is further enhanced at weaning by RNA adenosine methylation mediated by methyltransferase-like 3 and 4 [51]. These transcription factors activate thousands of genes involved in glucose oxidative phosphorylation and sensing, and induce the expression of ion channels subunits, mitochondrial shuttles, electron transport chain proteins and of components of the secretory machinery [56-58].

The epigenomic code of neonatal β -cells as a paradigm for adaptative proliferation under conditions of increased insulin demand

After weaning, the BCM remains relatively stable. However, under conditions of increased insulin demand an expansion of the BCM can be observed [59]. Obesity and pregnancy are associated with a diminished sensitivity of insulin target tissues. Thus, expansion of the BCM is pivotal for providing enough insulin and preserving normoglycemia [60,61]. BCM expansion in obesity and pregnancy necessitates a reduction in the expression of CDK inhibitors and a rise in the level of different cyclins, an observation confirmed in the islets from obese non-diabetic donors [62-65]. The re-expression of cell cycle-related genes is associated with DNA hypomethylation and ectopic expression of c-Myc [66]. In addition, the expression of ncRNAs is induced and proliferation pathways (e.g. JNK3, Nfatc2) are activated [65,67,68], suggesting that β -cell adaptation to an increased metabolic demand may rely on a subset of β -cells returning to an immaturity, neonatal-like, status via epigenetic reprogramming [54] (**Fig. 2, Key Figure**). At present, we don't know whether this reprogramming is always associated with a reduction in glucose responsiveness or if part of the cells may proliferate while retaining glucose-dependent insulin secretion.

In obesity and pregnancy, the metabolic demand comes from nutrient overload and systemic insulin resistance [69]. Release of FA from insulin-resistant adipocyte and the postprandial lipid fluctuations, results in an increased plasma FA concentration. This may create a FA-enriched environment within the islets, potentially mimicking the conditions occurring during the suckling period. The fact that FA modify H3K27 trimethylation [70], and induce a global change in DNA methylation in human islets [71] supports the hypothesis of a role of lipids in β -cell adaptation to obesity and pregnancy. In obesity and pregnancy there is also an increase in local and circulating GF, including HGF, IGF-1, PDGF and mitogenic hormones such as prolactin [46,72,73]. This environment may reactivate the epigenetic profile of immature β -cells, causing the cells to resume proliferation. This immature and proliferative state induced by metabolic overload is probably transient and under normal conditions most β -cells undergoing this process will recover full glucose responsiveness. Failure of proliferative β -cells to recover full secretory competence may contribute to the loss of functional BCM in type 2 diabetes (T2D). Islets from patients with T2D have been shown to harbor also some dedifferentiated β -cells displaying progenitor-like characteristics [74]. Unlike immature neonatal β -cells that proliferate during the suckling period, dedifferentiated cells do not produce insulin and express several markers of progenitor cells. If these dedifferentiated cells do or can

proliferate remain an unmet question. Nonetheless, it is possible that these dedifferentiated cells coexist with proliferating immature β -cells. Indeed, neonatal-like β -cells have been identified in islets of T2D patients and in mice model of T2D [54,66]. These cells express insulin but are poorly responsive to glucose. They are characterized by mTorc1 activation, elevation of c-Myc expression and broad hypomethylation of cell cycle genes. Genetic predisposition with persistent metabolic overload could lead to alterations in epigenetic reprogramming either affecting the capacity of β -cells to resume proliferation or causing dedifferentiation to a progenitor-like state. Chronic hyperlipidemia and hyperglycemia induce major changes in DNA methylome and could be the drivers of this epigenomic dysregulation leading to different degrees of β -cells immaturity and loss of functional BCM [55,71].

Translating the knowledge of neonatal β -cell physiology into therapy.

Restoration of a functional BCM sufficient to compensate for insulin resistance is crucial for achieving long-term glycemic control in diabetes (**Box 3**). Thus, targeting the epigenetic mechanisms controlling β -cell replication and maturation is an attractive strategy to prevent and treat T2D. Some current medications that stimulate insulin secretion, including sulfonylurea and GLP-1 receptor agonists (GLP-1RA) promote changes in DNA methylation [75,76]. The modifications of the DNA methylome triggered by GLP-1RA are correlated with NAFTc1 activation, induction of cell cycle regulators and β -cell replication [77,78]. In addition, GLP-1RA stimulates mTorc1 [79] and Jnk activity [65]. Although GLP-1RA improves glycemic control, full normalization of blood glucose levels is not readily observed in patients treated with any of the available GLP-1 mimetics [80]. In addition, like sulfonylurea, these drugs can have adverse secondary effects and are inefficient in preserving long-term glycemic control [80]. Chronic use of these compounds may even lead to deterioration of β -cell function [81]. These concerns prompted the search for alternative drugs with mitogenic properties and less side effects. In this perspective, GF involved in postnatal BCM expansion may be attractive candidates, as exemplified by HGF, which has been reported to induce Ccnd1 and Ccnd2 expression and promote β -cell proliferation under insulin resistance conditions [82]. In addition, HGF improves systemic insulin sensitivity and inflammation and does not lead to cancers in individuals without genetic abnormalities in the c-Met receptor [82]. However, synthetic HGF production costs are prohibitive and the manufactured protein is unstable, preventing its clinical application [83]. Alternative molecules mimicking the effect of HGF are now considered promising candidates for T2D treatment [83].

Beside inspiring the search for new therapeutic compounds, current knowledge of the processes occurring in the postnatal period suggest that preservation of neonate BCM expansion and maturation can prevent diabetes development in adulthood. This hypothesis is supported by two population-based studies showing that children who are never breastfed have a twofold increased risk of T1D when compared with those who were breastfed [84]. Management of breastfeeding duration and of quality of maternal milk, could help maintaining the epigenetic program of neonate β -cells and the level of nutrients and growth factors crucial for stimulating the mitogenic pathways. This is in line with the recommendations of the World Health Organisation which support exclusive breastfeeding for infants for the first six months of life, with nutritionally adequate foods, to continue up to two years of age or beyond [85].

Transplantation of insulin-secreting cells produced from human stem cells constitute an attractive approach for T1D treatment, which results from autoimmune destruction of β -cells. Islets or pancreas transplantation can be an alternative to insulin injections when appropriate glycemic control is not achieved by conventional treatment. However, this practice remains marginal as islets from two or three human donors are required for each recipient. To circumvent this issue, cell transplantation strategies based on alternative and unlimited sources of surrogate β -cells have been envisaged. At present, β -cells generated from stem cells are still not functionally equivalent to fully mature β -cells [86]. It is postulated that the signalling pathways driving cell replication remain active in β -cells derived from stem cells and represent a limiting factor for the differentiation of fully functional insulin-secreting cells [86]. Thus, targeting the epigenetic program that account for β -cell maturation using humoral factors driving this stage during postnatal development of β -cells and/or pharmacological manipulation of epigenetic modifier may potentially improve the generation β -cell surrogates for transplantation purposes.

Concluding Remarks and Future Perspectives

Here, we highlighted the signals and epigenetic pathways governing early postnatal β -cell proliferation and maturation. These pathways can be at least in part reactivated in adulthood to allow the adaptation of β -cells to metabolic conditions of increased insulin demand. Several questions remain (see outstanding questions), including the connection between the mitogenic pathways and epigenetic mechanisms, and the impact of long-term reactivation of these pathways on insulin secretion. We believe that activation of these mechanisms allows β -cell compensation to metabolic cues and thereby, can be a promising strategy for restoring the

functional BCM in diabetes. Finally, we propose that studying the humoral factors involved in postnatal BCM expansion can potentially lead to the identification of next natural-based antidiabetic.

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Conflict of interest statement

The authors declare no competing interests

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FIGURE LEGENDS

Figure I (text box): Molecular signature of immature neonatal β -cell. At birth, as the pancreas continues to develop and expand, β -cells display a significant proliferative capacity. This proliferative capacity results from the synergy of multiple signalling pathway triggered by a variety of humoral factors that converge to activate cell cycle entry and β -cell replication.

Figure 1: Signaling pathways and epigenetic reprogramming involved in the nutritional switch at the suckling-weaning transition.

During the postnatal period, pancreatic β -cells undergo a maturation process leading to an enhanced secretory capacity in response to glucose, which is accompanied by a reduced proliferative rate. This phenotypic and functional transition appears to be driven by hormonal and growth factors present in mother's milk and in the systemic circulation. This transition is also largely influenced by nutrients and mirrors the shift from a fatty acid-rich diet to a predominantly carbohydrate diet occurring at weaning. From a cellular point of view, this results in epigenetic reprogramming and in changes in the expression of multiple genes. The liver, a major organ in glucose homeostasis, participates in the cellular and molecular remodelling of β -cell activities by adapting the production and secretion of Fetuin-A. * Genes whose activation relies on H3K4 trimethylation; † Genes whose activation relies on H3K27me3 trimethylation; Ω Genes whose activation relies on H4R3me2a trimethylation

Figure 2: Epigenetic reprogramming of mature β -cells to expand the functional β -cell mass under insulin resistance conditions

During pregnancy or obesity, compensatory mechanisms are put in place to increase the functional β -cell mass and compensate for the increased insulin needs. Nutrients and humoral factors reactivate the epigenetic program of neonatal immature β -cells to induce cell cycle entry and β -cell expansion, permitting to maintain normoglycemia. The reprogramming of mature β -cells may or may not involve a transient loss of glucose responsiveness in proliferating β -cells. In genetically predisposed individuals, the epigenetic reprogramming fails or causes a loss of β -cell identity and dedifferentiation of insulin-secreting cells to a pancreatic multiprogenitor-like state. In this case, the amount of insulin produced is insufficient to preserve blood glucose homeostasis, resulting in the development of diabetes.

Highlights

Expansion of β -cell mass during suckling period relies on epigenetic program connected to specific signalling pathways of humoral factors

Maternal milk, innate immunity and intestinal microbiota are keys for the control of the epigenetic mechanisms governing cell cycle entry pathways during the lactating period

Nutritional switch during suckling-weaning transition induces a change in the epigenetic pathways leading to the growth arrest and β -cell maturation

Pathways involved in postnatal constitutive and adaptive β -cell replication are reactivated during pregnancy and obesity

In diabetes, activation of epigenetic pathways involved in neonate β -cell proliferation is impaired

Understanding how to manipulate these pathways can be foreseen as a possible therapeutic treatment option to restore the lost BCM in diabetes.

-Outstanding Questions Box.

- Are there differences in the mechanisms inducing β -cell mass expansion under obesity and pregnancy conditions?
- Does proliferation of reprogrammed neonatal-like β -cells always require a transient loss of glucose responsiveness?
- What is the role of intestinal bacteria and innate immune cells in the induction of β -cell epigenetic pathways during early postnatal β -cell proliferation and maturation?
- Do chronic inflammation and changes in microbiota contribute to the alteration of epigenetic pathways in β -cells
- Are defective signalling pathways elicited by nutrients and humoral factors the leading cause of altered epigenetic reprogramming in diabetes?
- Do genetic risk factors interfere with epigenetic reprogramming in diabetes patients?
- Are defective epigenetic pathways affecting neonatal BCM expansion and β -cell function in offspring of parents with T2D?
- Could the epigenetic pathways governing β -cell proliferation be modulated to expand the functional BCM in diabetic patients?

Figure 1

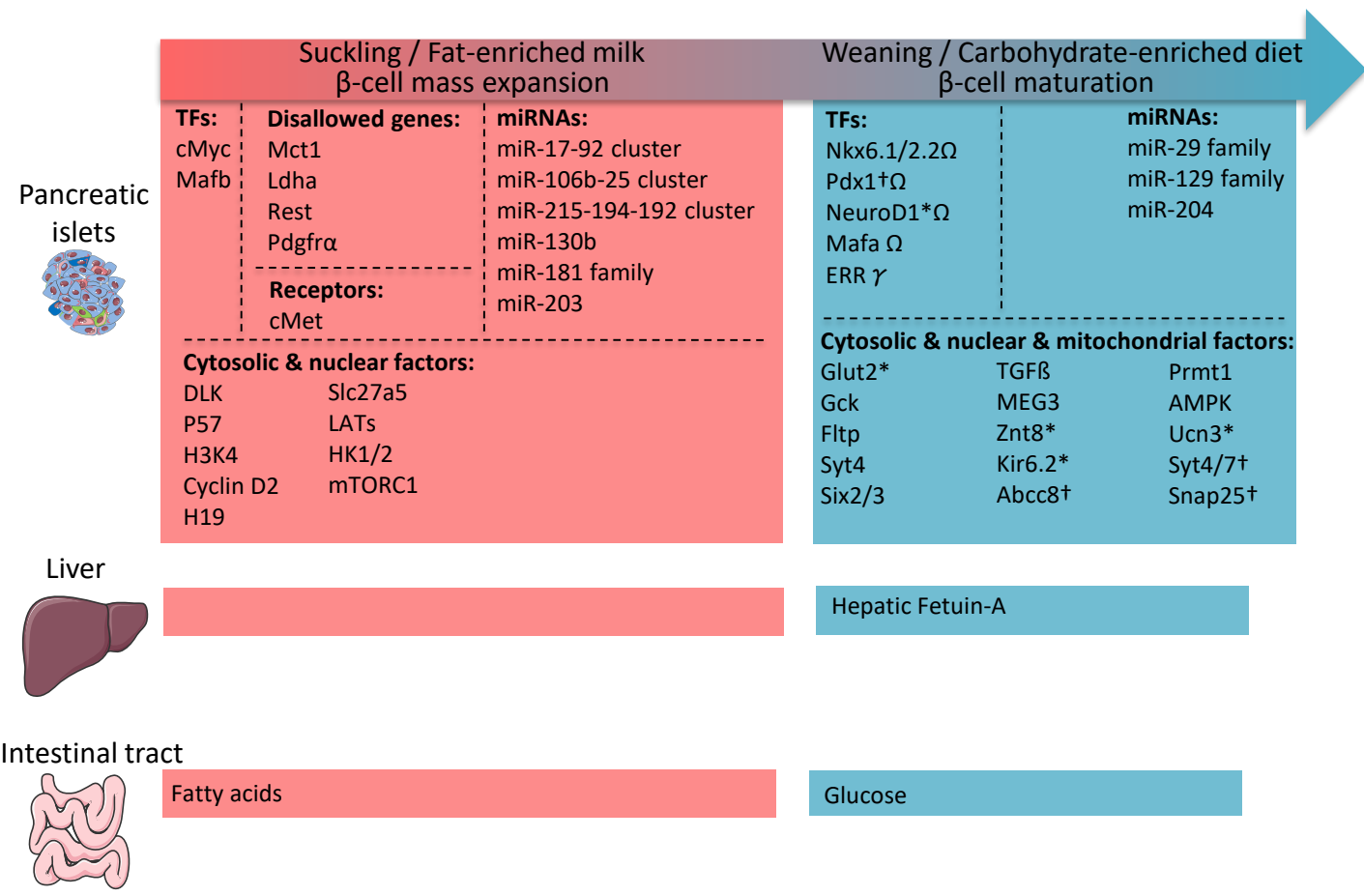


Figure 2

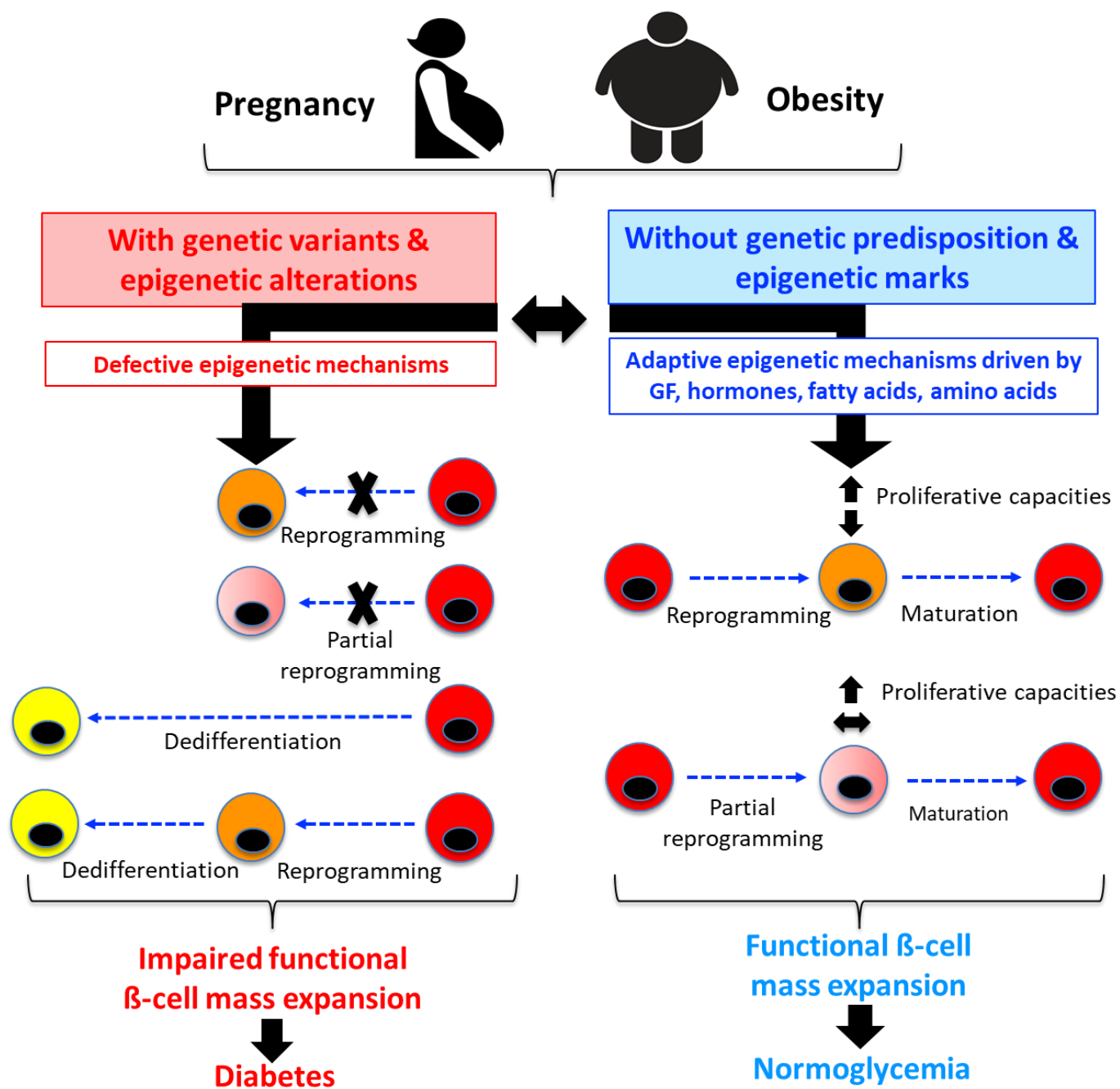
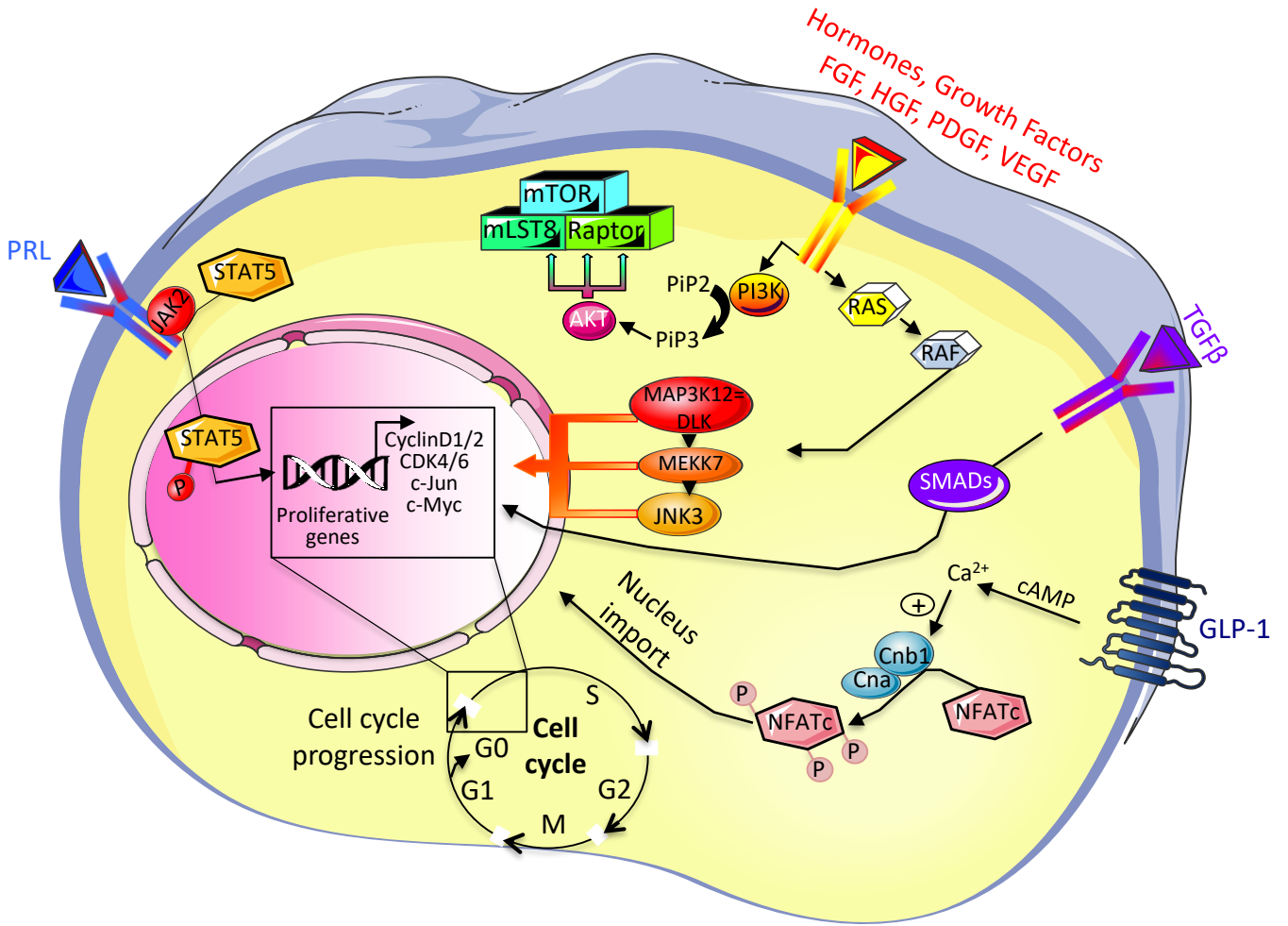


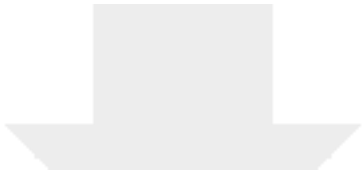
Figure I



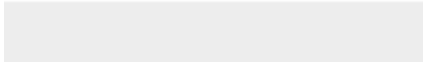



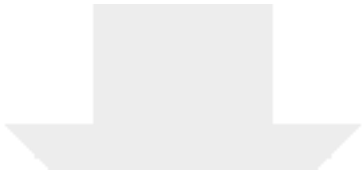
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