



**HAL**  
open science

# **ERR $\alpha$ : unraveling its role as a key player in cell migration**

Jean-Marc Vanacker, Christelle Forcet

► **To cite this version:**

Jean-Marc Vanacker, Christelle Forcet. ERR $\alpha$ : unraveling its role as a key player in cell migration. *Oncogene*, 2024, 43 (6), pp.379 - 387. 10.1038/s41388-023-02899-w . hal-04727434

**HAL Id: hal-04727434**

**<https://hal.science/hal-04727434v1>**

Submitted on 11 Oct 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 ERR $\alpha$ : Unraveling its Role as a Key Player in Cell Migration

2 Jean-Marc Vanacker<sup>1</sup> and Christelle Forcet<sup>2</sup>

3  
4 <sup>1</sup> Present address: Centre de Recherche en Cancérologie de Lyon, CNRS UMR5286, Inserm  
5 U1052, Université de Lyon, France

6 <sup>2</sup> To whom correspondence should be addressed: Christelle Forcet, [christelle.forcet@ens-](mailto:christelle.forcet@ens-lyon.fr)  
7 [lyon.fr](http://lyon.fr), Institut de Génomique Fonctionnelle de Lyon, UMR5242, Ecole Normale Supérieure  
8 de Lyon, Centre National de la Recherche Scientifique, Université Claude Bernard-Lyon 1,  
9 France

10 **Abstract**

11 Cell migration is essential throughout the life of multicellular organisms, and largely depends  
12 on the spatial and temporal regulation of cytoskeletal dynamics, cell adhesion and signal  
13 transduction. Interestingly, Estrogen-related receptor alpha (ERR $\alpha$ ) has been identified as a  
14 major regulator of cell migration in both physiological and pathological conditions. ERR $\alpha$  is an  
15 orphan member of the nuclear hormone receptor superfamily of transcription factors and  
16 displays many biological functions. ERR $\alpha$  is a global regulator of energy metabolism, and it is  
17 also highly involved in bone homeostasis, development, differentiation, immunity and cancer  
18 progression. Importantly, in some instances, the regulation of these biological processes relies  
19 on the ability to orchestrate cell movements. Therefore, this review describes how ERR $\alpha$ -  
20 mediated cell migration contributes not only to tissue homeostasis but also to tumorigenesis  
21 and metastasis, and highlights the molecular and cellular mechanisms by which ERR $\alpha$  finely  
22 controls the cell migratory potential.

23 **Keywords:** ERR $\alpha$ , cell migration, development, homeostasis, cancer

24 **Running title:** ERR $\alpha$ , a key player in cell migration

25

## 26 **Introduction**

27 Cell migration is a crucial process driving morphogenesis throughout embryonic development.  
28 In the adult, cell movements participate in immune surveillance, tissue repair and renewal  
29 among other physiological processes (reviewed in <sup>1</sup>). In addition, abnormal cell migration  
30 contributes to a wide variety of diseases such as chronic inflammatory diseases, mental  
31 retardation and cancer cell dissemination (reviewed in <sup>2</sup>). Depending on the context, cells can  
32 migrate either individually or collectively in response to guidance cues (reviewed in <sup>3,4</sup>). In  
33 most cases, cell movements require a polarized organization, an active remodeling of the actin  
34 and microtubule cytoskeletons, an interaction with the extracellular matrix (ECM) through  
35 integrin-mediated focal adhesions (FA) and the activation of migration-related signaling  
36 pathways (reviewed in <sup>5-7</sup>) (Fig. 1). Although cell migration has been extensively studied, the  
37 complex mechanisms involved in the regulation of these events are still incompletely  
38 understood.

39 Estrogen-related receptor alpha (ERR $\alpha$ , encoded by *ESRRA*) is an orphan nuclear receptor  
40 acting as a transcription factor. It exerts multiple essential biological functions through its  
41 capacity to control specific target gene expression and, particularly, its involvement in cell  
42 metabolism and cancer progression has been widely described (reviewed in <sup>8-10</sup>). Importantly,  
43 ERR $\alpha$  has been shown to play a crucial role in the regulation of cell movements during both  
44 development and adulthood and it also regulates cancer cell migration (Fig. 2). Herein, the  
45 review focuses on the ERR $\alpha$ -dependent mechanisms that contribute to cell migration in these  
46 different contexts.

47

## 48 **Structure and regulation of ERR $\alpha$**

49           ERR $\alpha$  (NR3B1) has been identified in 1988 based on the high sequence similarity within  
50 its DNA binding domain to that of the Estrogen receptor alpha (ER $\alpha$ )<sup>11</sup>. ERR $\alpha$  belongs to a  
51 nuclear receptor subfamily that comprises two other isoforms in mammals encoded by  
52 distinct genes: ERR $\beta$  (NR3B2) and ERR $\gamma$  (NR3B3). However, since no natural ligands have been  
53 identified so far, the ERRs are considered orphan nuclear receptors (reviewed in<sup>12,13</sup>).

54 As other nuclear receptors, ERR $\alpha$  displays a typical conserved structural organization,  
55 comprising a highly variable amino-terminal domain (the A/B domain), a centrally located  
56 DNA-binding domain (DBD) that includes two Zn fingers, a flexible hinge region and a carboxy-  
57 terminal ligand-binding domain (LBD) containing a transcription transactivation region  
58 (reviewed in<sup>14,15</sup>). The ERR $\alpha$ -DBD specifically binds to the consensus DNA sequence  
59 TnAAGGTCA, referred to as estrogen-related response element (ERRE)<sup>16,17</sup>. Strikingly, the  
60 sequence-dependent DNA shape of this binding site contributes to the stabilization of the  
61 ERR $\alpha$  homodimer and facilitates its asymmetric positioning on DNA<sup>18,19</sup>. As shown by  
62 structural analysis, the ERR $\alpha$ -LBD includes a putative small binding ligand pocket (LBP) almost  
63 completely filled with bulky side chains of amino acids that confers an active conformation to  
64 ERR $\alpha$  in a ligand independent-manner<sup>20</sup>. However, the existence of ligands regulating ERR $\alpha$   
65 activity by inducing conformational changes and/or modulating the recruitment of cofactors,  
66 cannot be excluded. In this way, specific ERR $\alpha$  synthetic ligands such as compound A,  
67 compound 29 and XCT790 have been identified. These compounds which have the ability to  
68 enter the ERR $\alpha$ -LBP by significantly changing its conformation and consequently deactivate  
69 the receptor, are called inverse agonists (reviewed in<sup>12,13</sup>). Importantly, ERR $\alpha$  activity mostly  
70 depends on its association with cofactors that are differentially expressed in cells and tissues  
71<sup>21,22</sup>. In addition, post-translational modifications such as phosphorylation, sumoylation or  
72 acetylation of ERR $\alpha$  can modulate its transcriptional activity in a cell type, cofactor and

73 promoter-dependent manner <sup>23-27</sup>. The modulation of ERR $\alpha$  expression is also crucial for the  
74 regulation of its functions (reviewed in <sup>12</sup>).

75

## 76 **The ERR isoforms**

77 As mentioned above, the ERR subfamily consists of three ERR isoforms (ERR $\alpha$ ,  $\beta$  and  $\gamma$ ). All  
78 three isoforms show a high sequence identity in their DBD and their LBD is less conserved. The  
79 ERRs recognize the same specific DNA sequences and thus exhibit some overlapping functions  
80 by regulating similar targets genes in a ligand-independent manner. However, they also  
81 display differential activities which may depend on their tissue specificity or different  
82 expression levels.

83 Similar to ERR $\alpha$ , ERR $\gamma$  is strongly expressed in tissues with high energy demand and plays a  
84 role in the regulation of energy metabolism (reviewed in <sup>15,28</sup>). In addition, analysis of knockout  
85 mice has revealed that both ERR $\alpha$  and ERR $\gamma$  act as major regulators of heart functions <sup>29,30</sup>  
86 (reviewed in <sup>15</sup>). ERR $\gamma$  is also involved in the control of the differentiation of mesenchymal  
87 stem cells and in the maintenance of bone homeostasis (reviewed in <sup>31</sup>). At first glance, ERR $\alpha$   
88 and ERR $\gamma$  appear to play opposite roles in cancer cells, respectively inducing or inhibiting  
89 cancer progression. ERR $\gamma$  is weakly expressed in endometrial, colorectal, prostate and gastric  
90 cancers. By contrast, it is highly expressed in breast and ovarian cancers and this correlates  
91 with a favorable prognosis <sup>32</sup>(reviewed in <sup>21,33</sup>). Specifically, ERR $\gamma$  has been shown to inhibit  
92 breast, gastric and colorectal cancer cell proliferation and tumor growth, in part, by repressing  
93 the Wnt signaling pathway or by inducing oxidative metabolism and mesenchymal-to-  
94 epithelial transition <sup>34,35,32</sup>. However, a pro-tumoral activity of ERR $\gamma$  has also emerged.  
95 Notably, its upregulation promotes cancer cell proliferation and invasion <sup>36-40</sup> (reviewed in <sup>33</sup>).

96 Interestingly, in the same way as  $ERR\alpha$ ,  $ERR\gamma$  can drive cell migration to facilitate cancer  
97 progression <sup>40</sup>.  
98  $ERR\beta$  is mainly expressed in embryonic cells and the  $ERR\beta$  knockout demonstrates a major  
99 role of this receptor in the regulation of placental formation, the maintenance of pluripotency  
100 of embryonic stem cells and the specification of epithelial cells of the inner ear (reviewed in  
101 <sup>15,31</sup>).  $ERR\beta$  is globally poorly or not expressed in adult and cancer tissues (reviewed in <sup>21</sup>).  
102 However,  $ERR\beta$  is significantly expressed in the brain and involved in the regulation of stress  
103 response, food intake, satiety and whole-body energy balance (reviewed in <sup>15</sup>). Interestingly,  
104  $ERR\gamma$  appear to have opposite effects on these processes, suggesting a tight tissue-dependent  
105 regulation of the ERR isoform activity or expression. Splicing  $ERR\beta$  isoforms have been  
106 identified and shown to be expressed in glioblastoma cell lines and tumors <sup>41,42</sup>. In particular,  
107 the long  $ERR\beta2$  isoform plays an antitumor role by inducing apoptotic cell death and  
108 restricting glioblastoma cell growth and migration <sup>42</sup>.  $ERR\beta$  and the  $ERR\beta2$  isoform have also  
109 been shown to inhibit prostate and breast cancer cell proliferation <sup>43</sup> (reviewed in <sup>21</sup>).

110

### 111 **Main biological functions of $ERR\alpha$**

#### 112 *$ERR\alpha$ is a key regulator of cellular metabolism*

113  $ERR\alpha$  is widely expressed in embryos and adult tissues. Of interest,  $ERR\alpha$  has been identified  
114 as a master regulator of cellular energy metabolism, mostly in tissues with high-energy  
115 demand such as the skeletal muscle, kidney, liver, heart and adipose tissue. Importantly,  $ERR\alpha$   
116 binds to the promoter regions of many genes involved in oxidative phosphorylation, ATP  
117 synthesis, fatty acid oxidation, pyruvate metabolism, tricarboxylic acid (TCA) cycle, glycolysis,  
118 mitochondrial biogenesis and mitophagy (reviewed in <sup>9,44</sup>). These metabolic functions of  $ERR\alpha$   
119 mainly involve the peroxisome proliferator-activated receptor  $\gamma$  ( $PPAR\gamma$ )-coactivator 1 $\alpha$  (PGC-

120 1 $\alpha$ ) and PGC-1 $\beta$  coactivators (<sup>45,46</sup> and reviewed in <sup>47</sup>). However, in some cases, the cofactors  
121 RIP140 and NCOR1 can also be involved (reviewed in <sup>15</sup>). In addition, a crosstalk between ERR $\alpha$   
122 and the thyroid hormone receptors (THR) has been shown <sup>48,49</sup>. Notably, TH induces  
123 mitochondrial metabolic pathways such as oxidative phosphorylation, fatty acid oxidation and  
124 TCA cycle through ERR $\alpha$  in a THRB1 and PGC-1 $\alpha$ -dependent manner. ERR $\alpha$  also contributes to  
125 the TH-mediated regulation of mitochondrial fission, biogenesis and mitophagy <sup>49</sup>.  
126 Interestingly, TH has been shown to modulate breast cancer cell migration <sup>50,51</sup>. A coordinated  
127 ERR $\alpha$ -THR effect may thus be possible, although not demonstrated, in this regulation.  
128 Unsurprisingly, the alteration of the metabolic pathways regulated by ERR $\alpha$  is associated with  
129 human metabolic diseases such as heart failure, diabetes and obesity (reviewed in <sup>15</sup>). ERR $\alpha$   
130 also contributes to the specific metabolic adaptations of cancer cells (reviewed in <sup>9,44</sup>).

131

### 132 *ERR $\alpha$ modulates the differentiation of multiple mesenchymal lineages*

133 ERR $\alpha$  has been shown to control the differentiation of mesenchymal stem cells towards  
134 specific cell fates. For instance, the expression of ERR $\alpha$  increases early during myogenesis in  
135 parallel with that of the PGC-1 $\alpha$  coactivator, and both factors contribute to the myogenic  
136 program *in vitro* and *ex vivo* (<sup>52-56</sup> and reviewed in <sup>15</sup>). Particularly, ERR $\alpha$  promotes myocyte  
137 differentiation through the modulation of mitochondrial metabolism and MAPK signaling (<sup>30,54</sup>  
138 and reviewed in <sup>15,57</sup>). Similarly, ERR $\alpha$  may contribute to muscle regeneration in mice by  
139 regulating the expression of metabolic genes <sup>58</sup>. Furthermore, ERR $\alpha$  plays a major role in bone  
140 homeostasis by repressing osteoblast differentiation both *in vitro* and *in vivo* ( and reviewed  
141 in <sup>15,57</sup>). Additionally, a role of ERR $\alpha$  in the differentiation of adipocytes and chondrocytes in  
142 culture is supported by several studies (<sup>59,62,63</sup> and reviewed in <sup>57</sup>).

143

144 *ERR $\alpha$  is involved in cancer progression and invasion*

145 Importantly, ERR $\alpha$  is strongly expressed in various types of cancers, and its elevated  
146 expression is associated with metastasis and poor prognosis<sup>64-74</sup>.

147 Many studies have demonstrated that ERR $\alpha$  plays a role in tumor growth and progression.

148 Notably, ERR $\alpha$  promotes proliferation of colon, pancreatic, lung and breast cancer lines either  
149 by acting downstream of the HER2/IGF-1 pathways or by modulating the expression of the  
150 p21 cell cycle inhibitor, members of the cyclin family or other cell cycle regulators (<sup>74-77</sup> and

151 reviewed in <sup>21,78</sup>). In addition, ERR $\alpha$  stimulates angiogenesis by directly inducing the  
152 expression of the vascular endothelial growth factor (VEGF) in several cancer cell lines<sup>79-81</sup>.

153 Furthermore, ERR $\alpha$  enhances Hypoxia-Inducible Factor 1 $\alpha$  (HIF-1 $\alpha$ )-mediated transcription  
154 and consequently facilitates tumor and blood vessel growth in mice under hypoxic conditions

155 <sup>81,82</sup>. ERR $\alpha$  also contributes to the metabolic switch of cancer cells, also termed the Warburg  
156 effect, by stimulating aerobic glycolysis<sup>83,84</sup>. Moreover, ERR $\alpha$  contributes to Epithelial-

157 Mesenchymal Transition (EMT), and promotes cell migration and extracellular matrix (ECM)  
158 invasion (<sup>85-87</sup> and reviewed in <sup>9</sup>, also see below).

159

160 **ERR $\alpha$ -mediated regulation of cell migration**

161 *ERR $\alpha$  promotes the migration of cells during development and adult tissue homeostasis*  
162 *without interfering with their differentiation*

163 Gastrulation is an early developmental process during which cell migration leads to massive  
164 reorganization of the embryo, allowing the establishment of the three embryonic tissue layers.

165 Later, cells migrate within layers and differentiate to form tissues and organs (reviewed in <sup>88</sup>).

166 Interestingly, ERR $\alpha$  function is not required for cell fate determination in zebrafish embryos,  
167 but it plays a major role in controlling different morphogenetic movements during zebrafish



168 gastrulation<sup>89</sup>. However, the molecular mechanisms by which ERR $\alpha$  regulates these cellular  
169 movements have not yet been characterized. *WNT11* regulates hypoblast cell movements  
170 during zebrafish gastrulation and it also has been identified as a transcriptional target of ERR $\alpha$   
171 that promotes cancer cell migration<sup>(90,91)</sup>, also see below). Altogether, this suggests that the  
172 *wnt11*-dependent signaling pathway could be involved downstream of ERR $\alpha$  to control  
173 orientated cell movements at the onset of gastrulation (Fig. 3).

174 Furthermore, ERR $\alpha$  has been shown to modulate osteoblast differentiation and bone  
175 formation (see above). It also regulates the migration of osteoclasts. Indeed, loss of ERR $\alpha$   
176 activity leads to actin filament disorganization, reduced adhesion and inhibition of  
177 transmigration of mature osteoclasts *in vitro*. It also results in a decreased expression of  
178 osteopontin, integrin  $\beta$ 3 and altered localization of c-src that may contribute to the adhesion  
179 and migration defects observed<sup>92</sup> (Fig. 3). Thus, ERR $\alpha$  may participate in the regulation of  
180 bone homeostasis and remodeling by acting on the osteoblast lineage but also by controlling  
181 osteoclast migration. In addition, ERR $\alpha$  regulates the migration of macrophages *ex vivo* and *in*  
182 *vivo*; this probably depends on its capacity to modulate the expression of *TNFAIP1* and the  
183 stability of the RhoA GTPase in these cells<sup>85</sup> (Fig. 3). Of interest, inhibition of cell migration  
184 resulting from the loss of function of ERR $\alpha$  does not result from an impaired differentiation of  
185 the osteoclast precursors and macrophages in these conditions<sup>85,92</sup>.

186

187 *ERR $\alpha$  can behave as a negative or positive modulator of vascular cell migration and*  
188 *angiogenesis*

189         Angiogenesis is a process by which new vessels form; this involves the proliferation,  
190 migration and differentiation of endothelial cells (EC). ERR $\alpha$  is a major regulator of  
191 angiogenesis under both physiological and pathological conditions (reviewed in<sup>9</sup>, see also

192 below). Interestingly, this function of ERR $\alpha$  relies in part on its ability to regulate EC migration.  
193 ERR $\alpha$  has been shown to be expressed in EC from different tissues and it can either repress or  
194 enhance EC migration and angiogenesis, depending on the cellular context and the availability  
195 of cofactors. Gene expression analysis of ERR $\alpha$ -deficient EC indicates that the receptor mainly  
196 acts as a transcriptional repressor of target genes associated with angiogenesis, cell adhesion  
197 and cell migration<sup>93</sup>. In particular, ERR $\alpha$  modulates the expression of the vascular endothelial  
198 growth factor (VEGF) and also inhibits the expression of several migratory and cell-adhesion  
199 genes such as *Pecam*, *Mmp3*, *Cdh3* and *Esam1* which are all involved in angiogenic regulation  
200 (Fig. 3). As a consequence, ERR $\alpha$  plays a role in limiting angiogenesis by negatively controlling  
201 EC migration, tube formation and sprouting in response to growth factors *in vitro* and *in vivo*  
202<sup>93</sup>.

203 In contrast, ERR $\alpha$  facilitates angiogenesis through the induction of VEGF expression and  
204 secretion from several cell types<sup>79–82,94–96</sup>. In response to a deprivation in nutrients and  
205 oxygen, the cofactor PGC-1 $\alpha$  coactivates ERR $\alpha$  to induce the expression of VEGF, and this may  
206 contribute to the physiological response to ischemia<sup>94</sup> (Fig. 3). Similarly, flavonoids of  
207 *Scutellaria baicalensis* root such as Baicalin stimulate the expression of VEGF through the  
208 ERR $\alpha$ -PGC-1 $\alpha$  pathway, and consequently induce EC migration and sprout formation<sup>80</sup>. In  
209 addition, ERR $\alpha$  regulates the neovascularisation process through VEGF to facilitate tumoral  
210 growth and progression in mice. ERR $\alpha$  also enhances the expression of osteoprotegerin that  
211 can contribute to the angiogenic process<sup>95,97</sup>. Furthermore, ERR $\alpha$  interacts with and stabilizes  
212 HIF-1 $\alpha$ , and stimulates the expression of its target genes including VEGF (Fig. 3). The functional  
213 interaction between ERR $\alpha$  and HIF-1 $\alpha$  plays thus an important role in adapting cancer cells to  
214 *in vitro* and *in vivo* hypoxic conditions, and promotes angiogenesis, tumoral growth and  
215 invasion<sup>81,82</sup>. In addition, ERR $\alpha$  induces the expression of eNOS in EC, an enzyme that

216 generates nitric oxide (NO). As a consequence, ERR $\alpha$  may promote tumor progression through  
217 the NO-mediated regulation of EC migration, vascular permeability, blood vessel remodeling  
218 and angiogenesis<sup>98,99</sup> (Fig. 3).

219 ERR $\alpha$  also positively controls the migration of vascular smooth muscle cells (VSMCs). VSMCs  
220 are important components of blood vessel walls that maintain structural integrity and drive  
221 the contraction of the vascular wall. The platelet-derived growth factor (PDGF), mainly  
222 produced by VSMCs, vascular endothelial cells, platelets or macrophages in the injured  
223 vascular walls is involved in vascular remodeling (reviewed in<sup>100</sup>). Interestingly, ERR $\alpha$  is  
224 required both *in vitro* and *in vivo* for platelet-derived growth factor (PDGF)-induced  
225 proliferation and migration of VSMC through the regulation of RhoA/p27/Cdks and Wnt4/ $\beta$ -  
226 catenin pathways<sup>101</sup> (Fig. 3). In this way, ERR $\alpha$  acts as an effector of PDGF in controlling  
227 vascular remodeling, and thus may contribute to the development of cardiovascular diseases  
228 such as atherosclerosis and restenosis<sup>100,101</sup>.

229

### 230 *ERR $\alpha$ plays a role in the induction of Epithelial-Mesenchymal Transition*

231 EMT is a cellular process that leads to the conversion of epithelial cells into  
232 mesenchymal cells. EMT occurs during embryonic development and becomes reactivated in  
233 pathological contexts such as inflammation and cancer progression. During EMT, epithelial  
234 cells lose their polarity and cell-cell junctions, and gain migratory and invasive properties  
235 (reviewed in<sup>102</sup>).

236 ERR $\alpha$  has been shown to induce EMT in cancer cells and consecutively to promote their  
237 migration. Interestingly, multiple mechanisms are involved in ERR $\alpha$ -induced EMT (Fig. 3).

238 Depletion of ERR $\alpha$  in a range of cancer cell lines has been shown to increase the expression of  
239 E-cadherin, a marker of epithelial cells, and to decrease the expression of vimentin, fibronectin

240 and N-cadherin which mark a mesenchymal phenotype <sup>74,103–109</sup>. Interestingly, in most of these  
241 cancer cells, ERR $\alpha$  drives EMT and maintains the mesenchymal phenotype by regulating the  
242 expression of the transcription factors SNAIL, SLUG and/or Zinc-finger E-box-binding 1 (ZEB1)  
243 <sup>74,103,106,107,110,111</sup>. In gallbladder cancer cells, ERR $\alpha$  promotes EMT and cell migration through  
244 the regulation of the expression of Nectin cell adhesion molecule 4 (Nectin-4) and the  
245 activation of PI3K/AKT pathway <sup>107</sup>. In addition, ERR $\alpha$  regulates cell migration *in vitro*, tumor  
246 growth and invasion *in vivo* via the activation of the fibronectin and STAT3 pathways that  
247 promote EMT <sup>104–106</sup>. In turn, the JAK2/STAT3 pathway positively regulates the expression of  
248 ERR $\alpha$  to induce EMT <sup>111</sup>. ERR $\alpha$  also regulates the expression and the secretion of TGF- $\beta$  by  
249 osteosarcoma and endometrial cancer cell lines, which can activate ERR $\alpha$  expression via a  
250 positive feedback mechanism. As a consequence, ERR $\alpha$  mediates TGF- $\beta$ -induced SNAIL  
251 activation, EMT and cell migration <sup>106,112,113</sup>.

252 Surprisingly, the ERR $\alpha$ -knockout mice exhibit no evident developmental abnormalities which  
253 is unexpected given the key role of ERR $\alpha$  in the regulation of EMT (see above). They were  
254 initially found to display reduced adiposity, peripheral fat deposits and resistance to high-fat  
255 diet-induced obesity <sup>114</sup>. In addition, they show a decrease capacity in mitochondrial  
256 biogenesis and oxidative metabolism in the brown adipose tissue and they are consequently  
257 defective in adaptive thermogenesis <sup>115</sup>. ERR $\alpha$  deficiency also produces behavioral  
258 disturbances associated with synaptic dysfunction <sup>116,117</sup>. To some extent, ERR $\alpha$  and ERR $\gamma$  have  
259 overlapping functions, suggesting that the absence of a phenotype associated with a defective  
260 EMT might be attributed to functional redundancy between ERR isoforms during  
261 development.

262

263 *A crosstalk between ER $\alpha$ , ERBB2 and ERR $\alpha$  in breast cancers*

264 Based on the structural homology shared by ERR $\alpha$  and ER $\alpha$ , a potential functional  
265 relationship between these receptors has been suggested for years in breast cancers.  
266 However, a genome-wide analysis indicated that most of the ERR $\alpha$  target genes are distinct  
267 from those regulated by ER $\alpha$  in breast cancer cell lines and tumors samples, demonstrating  
268 that ERR $\alpha$  plays a role in breast cancers that is mainly independent of ER $\alpha$  <sup>118,119</sup>. Nonetheless,  
269 ERR $\alpha$  and ER $\alpha$  regulate a small fraction of common target genes either through binding to  
270 distinct but closely located estrogen-response elements (EREs) and ERREs or through  
271 competitive binding to overlapping ERE / ERRE motifs. Interestingly, several of these common  
272 target genes are linked to the ErbB2 signaling <sup>119</sup>. Specifically, ERR $\alpha$  and its cofactor PGC-1 $\beta$   
273 are involved in the transcriptional regulation of *ErbB2* and several co-amplified genes located  
274 within the *ErbB2* amplicon that play a role in survival and cell migration *in vitro*, and tumor  
275 growth *in vivo* <sup>120</sup>. In turn, the transcriptional ERR $\alpha$  activity is regulated by the EGF/ErbB2  
276 signaling pathway in breast cancer cell lines <sup>24,64</sup> (Fig. 3). Therefore, reciprocal regulation of  
277 ERR $\alpha$  and ErbB2 contributes to breast tumor development, progression and tamoxifen  
278 resistance <sup>120</sup>.

279

### 280 *ERR $\alpha$ is a crucial factor regulating cancer cell migration*

281 ERR $\alpha$  has been identified as a major regulator of cancer cell migration and invasion (<sup>73,85–</sup>  
282 <sup>87,91,118,121,122</sup>) (Fig. 3). Given the importance of altered metabolism in cancers as well as the  
283 fact that ERR $\alpha$  modulates different aspects of energy storage and consumption, it could be  
284 argued that all cancers phenotypes in which the receptor is involved are a consequence of its  
285 metabolic effects. However, ERR $\alpha$  regulates cancer cell migration in cells that do not express  
286 PGC-1 $\alpha$  or  $-\beta$  <sup>86</sup>. Furthermore, RNA-Seq approaches have shown that ERR $\alpha$  does not modulate  
287 the expression of metabolic targets in these cells although CHIP-Seq experiments indicate that

288 ERR $\alpha$  is bound to the regulatory regions of these genes <sup>123</sup>. Altogether, this points to a critical  
289 effect of the coregulators bound by ERR $\alpha$ , that control different transcriptional targets and  
290 thus phenotypic outcome <sup>124</sup>.

291 Several studies demonstrated an interplay between ERR $\alpha$  and the Wnt/ $\beta$ -catenin signaling  
292 <sup>91,101,125</sup>. In cancer cells, ERR $\alpha$  and  $\beta$ -catenin interact, and depend on each other to regulate  
293 the expression of genes known to be involved in cell migration such as *WNT11*, *MSX1* and *N-*  
294 *cadherin*. Specifically, the ERR $\alpha$ / $\beta$ -catenin/WNT11 axis plays a role in promoting prostate and  
295 breast cancer cell migration *in vitro* <sup>91</sup>. Moreover, ERR $\alpha$  interacts with LSD1 and induces its  
296 demethylase activity on the lysine 9 of histone 3 at the promoter of common target genes,  
297 resulting in their transcriptional activation. In this way, ERR $\alpha$  and LSD1 promote breast cancer  
298 cell invasion *in vitro* through the stimulation of the Matrix Metalloproteinase 1 (MMP1)  
299 expression <sup>86</sup>. Noteworthy, the nuclear respiratory factor 1 (NRF1) is required for the  
300 recruitment of LSD1 at the transcriptional start site of the ERR $\alpha$ -LSD1-positively regulated  
301 target genes and participates in the regulation of MMP1 expression and breast cancer cell  
302 invasion <sup>87</sup>. Other matrix metalloproteinases, such as MMP13, also regulated by ERR $\alpha$ , could  
303 be involved in the degradation of the basement membrane, facilitating cell invasion <sup>95</sup>. In  
304 addition, ERR $\alpha$  promotes the proliferation, migration and invasion of pancreatic cancer cell  
305 lines by enhancing the expression of the plasminogen activator inhibitor 1 (PAI1) and  
306 consequently activating the mitogen-activated protein kinase/extracellular signal-regulated  
307 kinase (MEK/ERK) pathway <sup>74</sup>.

308 Surprisingly, ERR $\alpha$  can also have a negative impact on breast cancer cell proliferation and  
309 migration *in vitro* and can decrease lung colonization *in vivo* by down-regulating the  
310 expression of the 40S ribosomal S6 kinase 1 (S6K1), a downstream effector of the mTOR  
311 pathway. As a consequence, ERR $\alpha$  knockdown leads to an upregulation of these cellular

312 processes and sensitizes the cells to mTOR inhibitors under reduced serum or glucose  
313 conditions <sup>126</sup>. Interestingly, a connection between ERR $\alpha$  and mTOR signaling has been found  
314 previously, and in particular, ERR $\alpha$  has been implicated in the mTOR-mediated control of  
315 energy metabolism in the mouse liver <sup>127</sup>. Therefore, it is possible that, when ERR $\alpha$  contributes  
316 to the metabolic adaptation of the cells, it can repress or activate cell proliferation and  
317 migration depending on the cellular context. In line with this hypothesis, other studies  
318 indicated that the cofactor PGC-1 $\alpha$  requires ERR $\alpha$  to suppress prostate cancer metastasis; this  
319 relies on their capacity to modulate metabolic programs and to decrease the expression of  
320 specific genes, such as MYC, involved in cytoskeletal remodeling and prostate cancer cell  
321 invasion <sup>128,129</sup>. On the other hand, ERR $\alpha$  has been shown to promote breast cancer metastasis  
322 to the bone, and the receptor activator of nuclear factor  $\kappa$  B (RANK) identified as an ERR $\alpha$   
323 target gene may contribute to this process. In this context, ERR $\alpha$  stimulates mTOR/S6K  
324 signaling and breast cancer cell migration *in vitro* in a RANK-dependent manner <sup>130</sup>.

325 Upregulated expression of the long non-coding RNA (lncRNA) SPRY4 intronic transcript 1  
326 (SPRY4-T1) has been found to be associated with a poor prognosis in hepatocellular carcinoma  
327 (HCC). *In vitro*, the knock-down of SPRY4-T1 leads to the downregulation of the ERR $\alpha$   
328 expression at the mRNA level and the effects of SPRY4-T1 on HCC cell proliferation, colony  
329 formation, cell migration and invasion involve ERR $\alpha$ , suggesting a functional interaction  
330 between SPRY4-T1 and ERR $\alpha$  <sup>121</sup>. Furthermore, ectopic expression of the microRNA 137 (miR-  
331 137) has been shown to reduce the expression of ERR $\alpha$  by directly targeting the 3'UTR region  
332 of its mRNA in breast cancer cell lines. As a consequence, miR-137 decreases the proliferative  
333 and invasive capacities of the cells, at least in part, through the negative regulation of the  
334 ERR $\alpha$  target genes *CCNE1* and *WNT11* <sup>77</sup>. Similarly, miR-135a and miR-497 down-regulate the  
335 expression of ERR $\alpha$  and decrease cancer cell migration and invasion *in vitro* <sup>131,132</sup>. Notably,

336 miR-497 can control cell behavior by reducing the expression of the macrophage migration  
337 inhibitory factor (MIF) and the activation of MMP9, two factors also regulated by ERR $\alpha$  <sup>132</sup>.  
338 Importantly, deregulated expression of these miRNA has been reported in various types of  
339 cancers (<sup>77,131,132</sup>). This may thus contribute to the aberrant expression of ERR $\alpha$  in cancers,  
340 thereby facilitating cell proliferation, migration and invasion.

341

#### 342 *ERR $\alpha$ coordinates the basic processes of cell migration*

343 Cell migration mainly depends on the dynamic organization of the actin and microtubule  
344 cytoskeletons, and requires adhesion to the ECM (reviewed in <sup>5,7</sup>) (Fig. 1). Although numerous  
345 studies have reported a role of ERR $\alpha$  in cell migration, its involvement in cell adhesion has  
346 only been recently suggested. Zou and colleagues previously noticed that ERR $\alpha$  facilitates the  
347 attachment of prostate cancer cells to fibronectin, an ECM protein, but they did not explore  
348 the underlying mechanisms <sup>81</sup>. As mentioned above, another report showed that ERR $\alpha$   
349 depletion in ECs leads to the upregulation of genes linked to cell adhesion and cell migration  
350 <sup>93</sup>. Furthermore, bioinformatics analyses revealed that the RANK-ERR $\alpha$  regulatory interactome  
351 contains proteins associated with ECM regulation, cell adhesion and cell migration, some of  
352 which being encoded by putative ERR $\alpha$  target genes <sup>130</sup>. Altogether, these studies have  
353 proposed new potential effectors of ERR $\alpha$  involved in cell adhesion and migration that need  
354 further investigation.

355 Recent evidences indicated that ERR $\alpha$  plays an important role in regulating both the actin  
356 cytoskeleton and cell adhesion (Fig. 3). In that way, ERR $\alpha$  has been shown to regulate the actin  
357 cytoskeletal organization, the adhesion and migratory capacities of osteoclasts *in vitro* <sup>92</sup>. In  
358 addition, ERR $\alpha$  promotes orientated migration of breast cancer cells by modulating the  
359 stability of the RhoA GTPase *in vitro*. Interestingly, increased RhoA activity resulting from ERR $\alpha$



360 depletion induce cell disorientation that may result from impaired actin cytoskeletal  
361 organization and defective lamellipodium formation<sup>85</sup>. Thereafter, it has been demonstrated  
362 that ERR $\alpha$  controls actin polymerisation in these cells through the modulation of the RhoA-  
363 ROCK-LIMK-cofilin pathway. In addition, ERR $\alpha$  tightly regulates the expression of mitogen-  
364 activated protein kinase kinase kinase kinase (MAP4K4), and consequently facilitates the  
365 turnover of focal adhesions, the main adhesive structures of the cells<sup>133</sup>. Thus, these data  
366 establish a role for ERR $\alpha$  in coordinating focal adhesions and actin dynamics, that may  
367 contribute to cell migration in both physiological and pathological conditions.

368

### 369 **Concluding remarks**

370 ERR $\alpha$  has been shown to play a role in various biological processes that contribute to  
371 embryonic development, physiology and pathologies. Interestingly, as summarized here,  
372 ERR $\alpha$  is a key regulator of cell migration in all of these contexts (Fig. 2). ERR $\alpha$  controls the  
373 morphogenetic movement of cells during gastrulation in the embryo and also tightly modulate  
374 the migration of different cell types in the adult organism, thereby ensuring tissue  
375 homeostasis. In addition, ERR $\alpha$  has been widely implicated in cancer cell migration and  
376 invasion. Consequently, ERR $\alpha$  has often been proposed as a therapeutic target to inhibit  
377 cancer cell dissemination. However, global pharmacological modulation of ERR $\alpha$  activity or  
378 expression could cause undesired side-effects as they would impact on the physiological  
379 effects of the receptor. This strategy may thus be reconsidered. Recently, new cofactors of  
380 ERR $\alpha$  have been shown to be involved in the modulation of distinct sets of ERR $\alpha$ -target genes  
381<sup>123</sup>, suggesting that the capacity of ERR $\alpha$  to regulate a given cellular process depends on its  
382 association with specific cofactors in a context-dependent manner. In that way, cofactors such  
383 as LSD1 or SET7 regulate a precise subset of ERR $\alpha$ -target genes involved in cancer cell

384 migration<sup>86,123</sup>. Targeting the complex comprising ERR $\alpha$  and one of these cofactors may thus  
385 constitute a promising alternative approach to limit cancer spread. However, further  
386 investigations are required to achieve a better understanding of the cofactor-dependent  
387 mode of action of ERR $\alpha$  in tumors and other pathological contexts. Besides, it appears also  
388 important to dig more deeply into the factors and the mechanisms involved in the ERR $\alpha$ -  
389 mediated cell movements in physiological environments.

390

### 391 **Acknowledgements**

392 Work in our laboratory is funded by Ligue contre le Cancer (comité Rhône), ANSES (Agence  
393 nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, grant  
394 EST15-076), JoRiss/ENS research program and Région Auvergne-Rhône-Alpes (grant SCUSI  
395 OPE2017\_004). The authors thanks Violaine Tribollet for helpful discussions.

396

### 397 **Author contributions**

398 CF drafted the manuscript and prepare the figures. JMV provide critical feedbacks and  
399 contributed to the revisions of the manuscript. JM and CF approved the final version of the  
400 manuscript.

401

### 402 **Conflict of Interest**

403 The authors declare that the research was conducted in the absence of any commercial or  
404 financial relationships that could be construed as a potential conflict of interest.

405

406

407 .

- 409 1 Mayor R, Etienne-Manneville, S. The front and rear of collective cell migration. *Nat*  
410 *Rev Mol Cell Biol* 2016; **17**: 97–109.
- 411 2 Bravo-Cordero JJ, Hodgson L, Condeelis J. Directed cell invasion and migration  
412 during metastasis. *Current Opinion in Cell Biology* 2012; **24**: 277–283.
- 413 3 De Pascalis C, Etienne-Manneville S. Single and collective cell migration: the  
414 mechanics of adhesions. *Mol Biol Cell* 2017; **28**: 1833–1846.
- 415 4 SenGupta S, Parent CA, Bear JE. The principles of directed cell migration. *Nat Rev*  
416 *Mol Cell Biol* 2021; **22**: 529–547.
- 417 5 Gardel ML, Schneider IC, Aratyn-Schaus Y, Waterman CM. Mechanical Integration  
418 of Actin and Adhesion Dynamics in Cell Migration. *Annu Rev Cell Dev Biol* 2010; **26**: 315–  
419 333.
- 420 6 Lawson CD, Ridley AJ. Rho GTPase signaling complexes in cell migration and  
421 invasion. *J Cell Biol* 2018; **217**: 447–457.
- 422 7 Seetharaman S, Etienne-Manneville S. Cytoskeletal Crosstalk in Cell Migration.  
423 *Trends in Cell Biology* 2020; **30**: 720–735.
- 424 8 Villena JA, Kralli A. ERR $\alpha$ : a metabolic function for the oldest orphan. *Trends*  
425 *Endocrinol Metab* 2008; **19**: 269–276.
- 426 9 Tam IS, Giguère V. There and back again: The journey of the estrogen-related  
427 receptors in the cancer realm. *The Journal of Steroid Biochemistry and Molecular Biology*  
428 2016; **157**: 13–19.
- 429 10 Ranhotra HS. The estrogen-related receptors in metabolism and cancer: newer  
430 insights. *Journal of Receptors and Signal Transduction* 2018; **38**: 95–100.
- 431 11 Giguère V, Yang N, Segui P, Evans RM. Identification of a new class of steroid  
432 hormone receptors. *Nature* 1988; **331**: 91–94.
- 433 12 Crevet L, Vanacker J-M. Regulation of the expression of the estrogen related receptors  
434 (ERRs). *Cell Mol Life Sci* 2020; **77**: 4573–4579.
- 435 13 Tripathi M, Yen PM, Singh BK. Estrogen-Related Receptor Alpha: An Under-  
436 Appreciated Potential Target for the Treatment of Metabolic Diseases. *IJMS* 2020; **21**: 1645.
- 437 14 Sever R, Glass CK. Signaling by Nuclear Receptors. *Cold Spring Harbor Perspectives*  
438 *in Biology* 2013; **5**: a016709–a016709.
- 439 15 Huss JM, Garbacz WG, Xie W. Constitutive activities of estrogen-related receptors:  
440 Transcriptional regulation of metabolism by the ERR pathways in health and disease.  
441 *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 2015; **1852**: 1912–1927.
- 442 16 Sladek R, Bader JA, Giguère V. The orphan nuclear receptor estrogen-related receptor  
443 alpha is a transcriptional regulator of the human medium-chain acyl coenzyme A  
444 dehydrogenase gene. *Mol Cell Biol* 1997; **17**: 5400–5409.
- 445 17 Vanacker J-M. Transcriptional Activities of the Orphan Nuclear Receptor ERR  
446 (Estrogen Receptor-Related Receptor- ). *Molecular Endocrinology* 1999; **13**: 764–773.
- 447 18 Mohideen-Abdul K, Tazibt K, Bourguet M, Hazemann I, Lebars I, Takacs M *et al.*  
448 Importance of the Sequence-Directed DNA Shape for Specific Binding Site Recognition by  
449 the Estrogen-Related Receptor. *Front Endocrinol* 2017; **8**: 140.
- 450 19 Patel AKM, Vilela P, Shaik TB, McEwen AG, Hazemann I, Brilllet K *et al.*  
451 Asymmetric dimerization in a transcription factor superfamily is promoted by allosteric  
452 interactions with DNA. *Nucleic Acids Research* 2023; **51**: 8864–8879.
- 453 20 Kallen J, Schlaeppli J-M, Bitsch F, Filipuzzi I, Schilb A, Riou V *et al.* Evidence for  
454 Ligand-independent Transcriptional Activation of the Human Estrogen-related Receptor  $\alpha$   
455 (ERR $\alpha$ ). *J Biol Chem* 2004; **279**: 49330–49337.
- 456 21 Bianco S, Sailland J, Vanacker J-M. ERRs and cancers: Effects on metabolism and on

457 proliferation and migration capacities. *The Journal of Steroid Biochemistry and Molecular*  
458 *Biology* 2012; **130**: 180–185.

459 22 Deblois G, Giguère V. Functional and physiological genomics of estrogen-related  
460 receptors (ERRs) in health and disease. *Biochimica et Biophysica Acta (BBA) - Molecular*  
461 *Basis of Disease* 2011; **1812**: 1032–1040.

462 23 Ariazi EA, Kraus RJ, Farrell ML, Jordan VC, Mertz JE. Estrogen-Related Receptor 1  
463 Transcriptional Activities Are Regulated in Part via the ErbB2/HER2 Signaling Pathway.  
464 *Molecular Cancer Research* 2007; **5**: 71–85.

465 24 Barry JB, Giguere V. Epidermal Growth Factor–Induced Signaling in Breast Cancer  
466 Cells Results in Selective Target Gene Activation by Orphan Nuclear Receptor Estrogen-  
467 Related Receptor A. *Cancer Res* 2005; **65**: 6120–6129.

468 25 Tremblay AM, Wilson BJ, Yang X-J, Giguère V. Phosphorylation-Dependent  
469 Sumoylation Regulates Estrogen-Related Receptor- $\alpha$  and - $\gamma$  Transcriptional Activity through  
470 a Synergy Control Motif. *Molecular Endocrinology* 2008; **22**: 570–584.

471 26 Vu EH, Kraus RJ, Mertz JE. Phosphorylation-Dependent Sumoylation of Estrogen-  
472 Related Receptor  $\alpha$ 1. *Biochemistry* 2007; **46**: 9795–9804.

473 27 Wilson BJ, Tremblay AM, Deblois G, Sylvain-Drolet G, Giguère V. An Acetylation  
474 Switch Modulates the Transcriptional Activity of Estrogen-Related Receptor  $\alpha$ . *Mol*  
475 *Endocrinol* 2010; **24**: 1349–1358.

476 28 Audet-walsh É, Giguère V. The multiple universes of estrogen-related receptor  $\alpha$  and  $\gamma$   
477 in metabolic control and related diseases. *Acta Pharmacol Sin* 2015; **36**: 51–61.

478 29 Alaynick WA, Kondo RP, Xie W, He W, Dufour CR, Downes M *et al*. ERR $\gamma$  Directs  
479 and Maintains the Transition to Oxidative Metabolism in the Postnatal Heart. *Cell*  
480 *Metabolism* 2007; **6**: 13–24.

481 30 Dufour CR, Wilson BJ, Huss JM, Kelly DP, Alaynick WA, Downes M *et al*. Genome-  
482 wide Orchestration of Cardiac Functions by the Orphan Nuclear Receptors ERR $\alpha$  and  $\gamma$ . *Cell*  
483 *Metabolism* 2007; **5**: 345–356.

484 31 Carnesecchi J, Vanacker J-M. Estrogen-Related Receptors and the control of bone cell  
485 fate. *Molecular and Cellular Endocrinology* 2016; **432**: 37–43.

486 32 Guo X, Yue L, Li M, Dai A, Sun J, Fang L *et al*. Nuclear receptor estrogen-related  
487 receptor gamma suppresses colorectal cancer aggressiveness by regulating Wnt/ $\beta$ -catenin  
488 signaling. *Carcinogenesis* 2022; **43**: 865–873.

489 33 Gulwani D, Upadhyay P, Goel R, Sarangthem V, Debraj Singh T. Unfolding of  
490 Imminent Bio-Signatures in the Prognosis of Thyroid Cancer; The Emergence of Estrogen  
491 Related Receptor Gamma (ERR $\gamma$ ) as a Hurricane. *Asian Pac J Cancer Prev* 2023; **24**: 375–  
492 387.

493 34 Tiraby C, Hazen BC, Gantner ML, Kralli A. Estrogen-Related Receptor gamma  
494 promotes mesenchymal-to-epithelial transition and suppresses breast tumor growth. *Cancer*  
495 *Res* 2011; **71**: 2518–2528.

496 35 Kang M-H, Choi H, Oshima M, Cheong J-H, Kim S, Lee JH *et al*. Estrogen-related  
497 receptor gamma functions as a tumor suppressor in gastric cancer. *Nat Commun* 2018; **9**:  
498 1920.

499 36 Riggins RB, Lan JP-J, Zhu Y, Klimach U, Zwart A, Cavalli LR *et al*. ERR $\gamma$  mediates  
500 Tamoxifen resistance in novel models of invasive lobular breast cancer. *Cancer Res* 2008; **68**:  
501 8908–8917.

502 37 Ijichi N, Shigekawa T, Ikeda K, Horie-Inoue K, Fujimura T, Tsuda H *et al*. Estrogen-  
503 related receptor  $\gamma$  modulates cell proliferation and estrogen signaling in breast cancer. *The*  
504 *Journal of Steroid Biochemistry and Molecular Biology* 2011; **123**: 1–7.

505 38 Heckler MM, Thakor H, Schafer CC, Riggins RB. ERK/MAPK regulates ERR $\gamma$   
506 expression, transcriptional activity, and receptor-mediated Tamoxifen resistance in ER+

507 breast cancer. *FEBS J* 2014; **281**: 2431–2442.

508 39 Kim J-H, Choi Y-K, Byun J-K, Kim M-K, Kang YN, Kim SH *et al.* Estrogen-related  
509 receptor  $\gamma$  is upregulated in liver cancer and its inhibition suppresses liver cancer cell  
510 proliferation via induction of p21 and p27. *Exp Mol Med* 2016; **48**: e213–e213.

511 40 Hua T, Wang X, Chi S, Liu Y, Feng D, Zhao Y *et al.* Estrogen-related receptor  $\gamma$   
512 promotes the migration and metastasis of endometrial cancer cells by targeting S100A4.  
513 *Oncol Rep* 2018; **40**: 823–832.

514 41 Zhou W, Liu Z, Wu J, Liu J, Hyder SM, Antoniou E *et al.* Identification and  
515 Characterization of Two Novel Splicing Isoforms of Human Estrogen-Related Receptor  $\beta$ .  
516 *The Journal of Clinical Endocrinology & Metabolism* 2006; **91**: 569–579.

517 42 Tiek DM, Khatib SA, Trepicchio CJ, Heckler MM, Divekar SD, Sarkaria JN *et al.*  
518 Estrogen-related receptor  $\beta$  activation and isoform shifting by cdc2-like kinase inhibition  
519 restricts migration and intracranial tumor growth in glioblastoma. *FASEB J* 2019; **33**: 13476–  
520 13491.

521 43 Heckler MM, Zeleke TZ, Divekar SD, Fernandez AI, Tiek DM, Woodrick J *et al.*  
522 Antimitotic activity of DY131 and the estrogen-related receptor beta 2 (ERR $\beta$ 2) splice variant  
523 in breast cancer. *Oncotarget* 2016; **7**: 47201–47220.

524 44 Ranhotra HS. Estrogen-related receptor alpha in select host functions and cancer: new  
525 frontiers. *Mol Cell Biochem* 2022; **477**: 1349–1359.

526 45 Huss JM, Kopp RP, Kelly DP. Peroxisome Proliferator-activated Receptor  
527 Coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) Coactivates the Cardiac-enriched Nuclear Receptors Estrogen-  
528 related Receptor- $\alpha$  and - $\gamma$ . *J Biol Chem* 2002; **277**: 40265–40274.

529 46 Schreiber SN, Knutti D, Brogli K, Uhlmann T, Kralli A. The Transcriptional  
530 Coactivator PGC-1 Regulates the Expression and Activity of the Orphan Nuclear Receptor  
531 Estrogen-Related Receptor  $\alpha$  (ERR $\alpha$ ). *J Biol Chem* 2003; **278**: 9013–9018.

532 47 Deblois G, Giguère V. Oestrogen-related receptors in breast cancer: control of cellular  
533 metabolism and beyond. *Nature Reviews Cancer* 2013; **13**: 27–36.

534 48 Vanacker J-M, Bonnelye E, Delmarre C, Laudet V. Activation of the thyroid hormone  
535 receptor  $\alpha$  gene promoter by the orphan nuclear receptor ERR $\alpha$ . *Oncogene* 1998; **17**: 2429–  
536 2435.

537 49 Singh BK, Sinha RA, Tripathi M, Mendoza A, Ohba K, Sy JAC *et al.* Thyroid  
538 hormone receptor and ERR $\alpha$  coordinately regulate mitochondrial fission, mitophagy,  
539 biogenesis, and function. *Sci Signal* 2018; **11**: eaam5855.

540 50 Flamini MI, Uzair ID, Pennacchio GE, Neira FJ, Mondaca JM, Cuello-Carrión FD *et al.*  
541 Thyroid Hormone Controls Breast Cancer Cell Movement via Integrin  
542  $\alpha$ V/ $\beta$ 3/SRC/FAK/PI3-Kinases. *Horm Cancer* 2017; **8**: 16–27.

543 51 Uzair ID, Conte Grand J, Flamini MI, Sanchez AM. Molecular Actions of Thyroid  
544 Hormone on Breast Cancer Cell Migration and Invasion via Cortactin/N-WASP. *Front*  
545 *Endocrinol (Lausanne)* 2019; **10**: 139.

546 52 Bonnelye E, Vanacker JM, Spruyt N, Alric S, Fournier B, Desbiens X *et al.*  
547 Expression of the estrogen-related receptor 1 (ERR-1) orphan receptor during mouse  
548 development. *Mechanisms of Development* 1997; **65**: 71–85.

549 53 Huss JM, Torra IP, Staels B, Giguère V, Kelly DP. Estrogen-Related Receptor  $\alpha$   
550 Directs Peroxisome Proliferator-Activated Receptor  $\alpha$  Signaling in the Transcriptional  
551 Control of Energy Metabolism in Cardiac and Skeletal Muscle. *Mol Cell Biol* 2004; **24**:  
552 9079–9091.

553 54 Murray J, Huss JM. Estrogen-related receptor  $\alpha$  regulates skeletal myocyte  
554 differentiation via modulation of the ERK MAP kinase pathway. *American Journal of*  
555 *Physiology-Cell Physiology* 2011; **301**: C630–C645.

556 55 Shao D, Liu Y, Liu X, Zhu L, Cui Y, Cui A *et al.* PGC-1 $\beta$ -Regulated mitochondrial

557 biogenesis and function in myotubes is mediated by NRF-1 and ERR $\alpha$ . *Mitochondrion* 2010;  
558 **10**: 516–527.

559 56 Wei W, Schwaid AG, Wang X, Wang X, Chen S, Chu Q *et al.* Ligand Activation of  
560 ERR $\alpha$  by Cholesterol Mediates Statin and Bisphosphonate Effects. *Cell Metabolism* 2016; **23**:  
561 479–491.

562 57 Carnesecchi J, Vanacker J-M. Estrogen-Related Receptors and the control of bone cell  
563 fate. *Molecular and Cellular Endocrinology* 2016; **432**: 37–43.

564 58 LaBarge S, McDonald M, Smith-Powell L, Auwerx J, Huss JM. Estrogen-related  
565 receptor- $\alpha$  (ERR $\alpha$ ) deficiency in skeletal muscle impairs regeneration in response to injury.  
566 *The FASEB Journal* 2014; **28**: 1082–1097.

567 59 Delhon I, Gutzwiller S, Morvan F, Rangwala S, Wyder L, Evans G *et al.* Absence of  
568 Estrogen Receptor-Related- $\alpha$  Increases Osteoblastic Differentiation and Cancellous Bone  
569 Mineral Density. *Endocrinology* 2009; **150**: 4463–4472.

570 60 Teyssier C, Gallet M, Rabier B, Monfoulet L, Dine J, Macari C *et al.* Absence of  
571 ERR $\alpha$  in Female Mice Confers Resistance to Bone Loss Induced by Age or Estrogen-  
572 Deficiency. *PLoS ONE* 2009; **4**: e7942.

573 61 Gallet M, Saïdi S, Haÿ E, Photsavang J, Marty C, Sailland J *et al.* Repression of  
574 osteoblast maturation by ERR $\alpha$  accounts for bone loss induced by estrogen deficiency. *PLoS*  
575 *ONE* 2013; **8**: e54837.

576 62 Bonnelye E, Zirngibl RA, Jurdic P, Aubin JE. The Orphan Nuclear Estrogen  
577 Receptor-Related Receptor- $\alpha$  Regulates Cartilage Formation *in Vitro* : Implication of Sox9.  
578 *Endocrinology* 2007; **148**: 1195–1205.

579 63 Rajalin A-M, Pollock H, Aarnisalo P. ERR $\alpha$  regulates osteoblastic and adipogenic  
580 differentiation of mouse bone marrow mesenchymal stem cells. *Biochemical and Biophysical*  
581 *Research Communications* 2010; **396**: 477–482.

582 64 Ariazi EA, Clark GM, Mertz JE. Estrogen-related Receptor alpha and Estrogen-related  
583 Receptor gamma Associate with Unfavorable and Favorable Biomarkers, Respectively, in  
584 Human Breast Cancer. 2002; **62**: 6510–6518.

585 65 Suzuki T, Miki Y, Moriya T, Shimada N, Ishida T, Hirakawa H *et al.* Estrogen-  
586 Related Receptor Alpha in Human Breast Carcinoma as a Potent Prognostic Factor. 2004; **64**:  
587 4670–4676.

588 66 Cavallini A, Notarnicola M, Giannini R, Montemurro S, Lorusso D, Visconti A *et al.*  
589 Oestrogen receptor-related receptor alpha (ERR $\alpha$ ) and oestrogen receptors (ER $\alpha$  and ER $\beta$ )  
590 exhibit different gene expression in human colorectal tumour progression. *European Journal*  
591 *of Cancer* 2005; **41**: 1487–1494.

592 67 Sun P, Sehoul J, Denkert C, Mustea A, Könsgen D, Koch I *et al.* Expression of  
593 estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor  
594 biomarkers in ovarian cancer cells. *J Mol Med* 2005; **83**: 457–467.

595 68 Cheung CP, Yu S, Wong KB, Chan LW, Lai FMM, Wang X *et al.* Expression and  
596 Functional Study of Estrogen Receptor-Related Receptors in Human Prostatic Cells and  
597 Tissues. *The Journal of Clinical Endocrinology & Metabolism* 2005; **90**: 1830–1844.

598 69 Fujimura T, Takahashi S, Urano T, Kumagai J, Ogushi T, Horie-Inoue K *et al.*  
599 Increased expression of estrogen-related receptor  $\alpha$  (ERR $\alpha$ ) is a negative prognostic predictor  
600 in human prostate cancer. *International Journal of Cancer* 2007; **120**: 2325–2330.

601 70 Fujimoto J, Alam SM, Jahan I, Sato E, Sakaguchi H, Tamaya T. Clinical implication  
602 of estrogen-related receptor (ERR) expression in ovarian cancers. *The Journal of Steroid*  
603 *Biochemistry and Molecular Biology* 2007; **104**: 301–304.

604 71 Fujimoto J, Sato E. Clinical implication of estrogen-related receptor (ERR) expression  
605 in uterine endometrial cancers. *The Journal of Steroid Biochemistry and Molecular Biology*  
606 2009; **116**: 71–75.

607 72 Tiwari A, Swamy S, Gopinath KS, Kumar A. Genomic amplification upregulates  
608 estrogen-related receptor alpha and its depletion inhibits oral squamous cell carcinoma tumors  
609 in vivo. *Sci Rep* 2015; **5**: 17621.

610 73 Li P, Wang J, Wu D, Ren X, Wu W, Zuo R *et al.* ERR $\alpha$  is an aggressive factor in lung  
611 adenocarcinoma indicating poor prognostic outcomes. *Cancer Manag Res* 2019; **11**: 8111–  
612 8123.

613 74 Liu S-L, Wu X-S, Li F-N, Yao W-Y, Wu Z-Y, Dong P *et al.* ERR $\alpha$  promotes  
614 pancreatic cancer progression by enhancing the transcription of PAI1 and activating the  
615 MEK/ERK pathway. *Am J Cancer Res* 2020; **10**: 3622–3643.

616 75 Bernatchez G, Giroux V, Lassalle T, Carpentier AC, Rivard N, Carrier JC. ERR $\alpha$   
617 metabolic nuclear receptor controls growth of colon cancer cells. *Carcinogenesis* 2013; **34**:  
618 2253–2261.

619 76 Bianco S, Lanvin O, Tribollet V, Macari C, North S, Vanacker J-M. Modulating  
620 estrogen receptor-related receptor-alpha activity inhibits cell proliferation. *J Biol Chem* 2009;  
621 **284**: 23286–23292.

622 77 Zhao Y, Li Y, Lou G, Zhao L, Xu Z, Zhang Y *et al.* MiR-137 Targets Estrogen-  
623 Related Receptor Alpha and Impairs the Proliferative and Migratory Capacity of Breast  
624 Cancer Cells. *PLoS One* 2012; **7**: e39102.

625 78 Mukherjee T, Malik P, Hoidal J. The emerging role of estrogen related receptor $\alpha$  in  
626 complications of non-small cell lung cancers (Review). *Oncol Lett* 2021; **21**: 258.

627 79 Stein RA, Gaillard S, McDonnell DP. Estrogen-related receptor alpha induces the  
628 expression of vascular endothelial growth factor in breast cancer cells. *J Steroid Biochem Mol*  
629 *Biol* 2009; **114**: 106–112.

630 80 Zhang K, Lu J, Mori T, Smith-Powell L, Synold TW, Chen S *et al.* Baicalin increases  
631 VEGF expression and angiogenesis by activating the ERR{alpha}/PGC-1 {alpha} pathway.  
632 *Cardiovasc Res* 2011; **89**: 426–435.

633 81 Zou C, Yu S, Xu Z, Wu D, Ng C-F, Yao X *et al.* ERR $\alpha$  augments HIF-1 signalling by  
634 directly interacting with HIF-1 $\alpha$  in normoxic and hypoxic prostate cancer cells. *The Journal*  
635 *of Pathology* 2014; **233**: 61–73.

636 82 Ao A, Wang H, Kamarajugadda S, Lu J. Involvement of estrogen-related receptors in  
637 transcriptional response to hypoxia and growth of solid tumors. *Proc Natl Acad Sci USA*  
638 2008; **105**: 7821–7826.

639 83 Tennessen JM, Baker KD, Lam G, Evans J, Thummel CS. The Drosophila estrogen-  
640 related receptor directs a metabolic switch that supports developmental growth. *Cell Metab*  
641 2011; **13**: 139–148.

642 84 Cai Q, Lin T, Kamarajugadda S, Lu J. Regulation of glycolysis and the Warburg effect  
643 by estrogen-related receptors. *Oncogene* 2013; **32**: 2079–2086.

644 85 Sailland J, Tribollet V, Forcet C, Billon C, Barenton B, Carnesecchi J *et al.* Estrogen-  
645 related receptor  $\alpha$  decreases RHOA stability to induce orientated cell migration. *Proc Natl*  
646 *Acad Sci USA* 2014; **111**: 15108–15113.

647 86 Carnesecchi J, Forcet C, Zhang L, Tribollet V, Barenton B, Boudra R *et al.* ERR $\alpha$   
648 induces H3K9 demethylation by LSD1 to promote cell invasion. *Proc Natl Acad Sci USA*  
649 2017; **114**: 3909–3914.

650 87 Zhang L, Carnesecchi J, Cerutti C, Tribollet V, Périan S, Forcet C *et al.* LSD1-ERR $\alpha$   
651 complex requires NRF1 to positively regulate transcription and cell invasion. *Sci Rep* 2018; **8**:  
652 10041.

653 88 Weng S, Wallingford JB. May the force be with you. *eLife* 2018; **7**: e36662.

654 89 Bardet P-L, Horard B, Laudet V, Vanacker J-M. The ERR $\alpha$  orphan nuclear receptor  
655 controls morphogenetic movements during zebrafish gastrulation. *Developmental Biology*  
656 2005; **281**: 102–111.

657 90 Ulrich F, Concha ML, Heid PJ, Voss E, Witzel S, Roehl H *et al.* Slb/Wnt11 controls  
658 hypoblast cell migration and morphogenesis at the onset of zebrafish gastrulation.  
659 *Development* 2003; **130**: 5375–5384.

660 91 Dwyer MA, Joseph J, Wade HE, Eaton ML, Kunder RS, Kazmin D *et al.* WNT11  
661 expression is induced by ERR $\alpha$  and  $\beta$ -catenin and acts in an autocrine manner to increase  
662 cancer cell migration. *Cancer Res* 2010; **70**: 9298–9308.

663 92 Bonnelye E, Saltel F, Chabadel A, Zirngibl RA, Aubin JE, Jurdic P. Involvement of  
664 the orphan nuclear estrogen receptor-related receptor  $\alpha$  in osteoclast adhesion and  
665 transmigration. *J Mol Endocrinol* 2010; **45**: 365–377.

666 93 Likhite N, Yadav V, Milliman EJ, Sopariwala DH, Lorca S, Narayana NP *et al.* Loss  
667 of Estrogen-Related Receptor Alpha Facilitates Angiogenesis in Endothelial Cells. *Mol Cell*  
668 *Biol* 2019; **39**: e00411-18.

669 94 Arany Z, Foo S-Y, Ma Y, Ruas JL, Bommi-Reddy A, Girnun G *et al.* HIF-  
670 independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1 $\alpha$ .  
671 *Nature* 2008; **451**: 1008–1012.

672 95 Fradet A, Sorel H, Bouazza L, Goehrig D, Depalle B, Bellahcene A *et al.* Dual  
673 Function of ERR in Breast Cancer and Bone Metastasis Formation: Implication of VEGF and  
674 Osteoprotegerin. *Cancer Research* 2011; **71**: 5728–5738.

675 96 Zhang L-D, Chen L, Zhang M, Qi H-J, Chen L, Chen H-F *et al.* Downregulation of  
676 ERR $\alpha$  inhibits angiogenesis in human umbilical vein endothelial cells through regulating  
677 VEGF production and PI3K/Akt/STAT3 signaling pathway. *European Journal of*  
678 *Pharmacology* 2015; **769**: 167–176.

679 97 Benslimane-Ahmim Z, Pereira J, Lokajczyk A, Dizier B, Galy-Fauroux I, Fischer A-  
680 M *et al.* Osteoprotegerin regulates cancer cell migration through SDF-1/CXCR4 axis and  
681 promotes tumour development by increasing neovascularization. *Cancer Letters* 2017; **395**:  
682 11–19.

683 98 Sumi D, Ignarro LJ. Estrogen-related receptor 1 up-regulates endothelial nitric oxide  
684 synthase expression. *Proceedings of the National Academy of Sciences* 2003; **100**: 14451–  
685 14456.

686 99 Xia W, Yin J, Zhang S, Guo C, Li Y, Zhang Y *et al.* Parkin Modulates ERR $\alpha$ /eNOS  
687 Signaling Pathway in Endothelial Cells. *Cell Physiol Biochem* 2018; **49**: 2022–2034.

688 100 Hu W, Huang Y. Targeting the platelet-derived growth factor signalling in  
689 cardiovascular disease. *Clin Exp Pharmacol Physiol* 2015; **42**: 1221–1224.

690 101 Li Q, Zhu L, Zhang L, Chen H, Zhu Y, Du Y *et al.* Inhibition of estrogen related  
691 receptor  $\alpha$  attenuates vascular smooth muscle cell proliferation and migration by regulating  
692 RhoA/p27 Kip1 and  $\beta$ -Catenin/Wnt4 signaling pathway. *European Journal of Pharmacology*  
693 2017; **799**: 188–195.

694 102 Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial–mesenchymal  
695 transition. *Nat Rev Mol Cell Biol* 2014; **15**: 178–196.

696 103 Huang J, Guan B, Yin L, Liu F, Hu B, Zheng Q *et al.* Effects of estrogen-related  
697 receptor alpha (ERR $\alpha$ ) on proliferation and metastasis of human lung cancer A549 cells. *J*  
698 *Huazhong Univ Sci Technol [Med Sci]* 2014; **34**: 875–881.

699 104 Wu Y-M, Chen Z-J, Liu H, Wei W-D, Lu L-L, Yang X-L *et al.* Inhibition of ERR $\alpha$   
700 suppresses epithelial mesenchymal transition of triple negative breast cancer cells by directly  
701 targeting fibronectin. *Oncotarget* 2015; **6**: 25588–25601.

702 105 Chen H, Pan J, Zhang L, Chen L, Qi H, Zhong M *et al.* Downregulation of estrogen-  
703 related receptor alpha inhibits human cutaneous squamous cell carcinoma cell proliferation  
704 and migration by regulating EMT via fibronectin and STAT3 signaling pathways. *European*  
705 *Journal of Pharmacology* 2018; **825**: 133–142.

706 106 Yoriki K, Mori T, Kokabu T, Matsushima H, Umemura S, Tarumi Y *et al.* Estrogen-



707 related receptor alpha induces epithelial-mesenchymal transition through cancer-stromal  
708 interactions in endometrial cancer. *Sci Rep* 2019; **9**: 6697.

709 107 Wang L, Yang M, Guo X, Yang Z, Liu S, Ji Y *et al*. Estrogen-related receptor- $\alpha$   
710 promotes gallbladder cancer development by enhancing the transcription of Nectin-4. *Cancer*  
711 *Sci* 2020; **111**: 1514–1527.

712 108 Mao X, Lei H, Yi T, Su P, Tang S, Tong Y *et al*. Lipid reprogramming induced by the  
713 TFEB-ERR $\alpha$  axis enhanced membrane fluidity to promote EC progression. *J Exp Clin Cancer*  
714 *Res* 2022; **41**: 28.

715 109 Li F-N, Zhang Q-Y, Li O, Liu S-L, Yang Z-Y, Pan L-J *et al*. ESRR $\alpha$  promotes gastric  
716 cancer development by regulating the CDC25C/CDK1/CyclinB1 pathway via DSN1. *Int J*  
717 *Biol Sci* 2021; **17**: 1909–1924.

718 110 Lam SS, Mak AS, Yam JW, Cheung AN, Ngan HY, Wong AS. Targeting Estrogen-  
719 Related Receptor Alpha Inhibits Epithelial-to-Mesenchymal Transition and Stem Cell  
720 Properties of Ovarian Cancer Cells. *Mol Ther* 2014; **22**: 743–751.

721 111 Ma J-H, Qi J, Lin S-Q, Zhang C-Y, Liu F, Xie W-D *et al*. STAT3 Targets ERR- $\alpha$  to  
722 Promote Epithelial–Mesenchymal Transition, Migration, and Invasion in Triple-Negative  
723 Breast Cancer Cells. *Mol Cancer Res* 2019; **17**: 2184–2195.

724 112 Chen Y, Zhang K, Li Y, He Q. Estrogen-related receptor  $\alpha$  participates transforming  
725 growth factor- $\beta$  (TGF- $\beta$ ) induced epithelial-mesenchymal transition of osteosarcoma cells.  
726 *Cell Adh Migr* 2016; **11**: 338–346.

727 113 Huang X, Wang X, Shang J, Zhaang Z, Cui B, Lin Y *et al*. Estrogen related receptor  
728 alpha triggers the migration and invasion of endometrial cancer cells via up regulation of  
729 TGFB1. *Cell Adh Migr* 2018; **12**: 538–547.

730 114 Luo J, Sladek R, Carrier J, Bader J-A, Richard D, Giguere V. Reduced Fat Mass in  
731 Mice Lacking Orphan Nuclear Receptor Estrogen-Related Receptor Alpha. *Mol Cell Biol*  
732 2003; **23**: 7947–7956.

733 115 Villena JA, Hock MB, Chang WY, Barcas JE, Giguère V, Kralli A. Orphan nuclear  
734 receptor estrogen-related receptor  $\alpha$  is essential for adaptive thermogenesis. *Proc Natl Acad*  
735 *Sci USA* 2007; **104**: 1418–1423.

736 116 Cui H, Lu Y, Khan MZ, Anderson RM, McDaniel L, Wilson HE *et al*. Behavioral  
737 Disturbances in Estrogen-Related Receptor alpha-Null Mice. *Cell Reports* 2015; **11**: 344–350.

738 117 De Jesús-Cortés H, Lu Y, Anderson RM, Khan MZ, Nath V, McDaniel L *et al*. Loss  
739 of estrogen-related receptor alpha disrupts ventral-striatal synaptic function in female mice.  
740 *Neuroscience* 2016; **329**: 66–73.

741 118 Stein RA, Chang C, Kazmin DA, Way J, Schroeder T, Wergin M *et al*. Estrogen-  
742 Related Receptor  $\alpha$  Is Critical for the Growth of Estrogen Receptor–Negative Breast Cancer.  
743 *Cancer Res* 2008; **68**: 8805–8812.

744 119 Deblois G, Hall JA, Perry M-C, Laganier J, Ghahremani M, Park M *et al*. Genome-  
745 Wide Identification of Direct Target Genes Implicates Estrogen-Related Receptor as a  
746 Determinant of Breast Cancer Heterogeneity. *Cancer Research* 2009; **69**: 6149–6157.

747 120 Deblois G, Chahrour G, Perry M-C, Sylvain-Drolet G, Muller WJ, Giguère V.  
748 Transcriptional Control of the ERBB2 Amplicon by ERR $\alpha$  and PGC-1 $\beta$  Promotes Mammary  
749 Gland Tumorigenesis. *Cancer Res* 2010; **70**: 10277–10287.

750 121 Yu G, Lin J, Liu C, Hou K, Liang M, Shi B. Long non-coding RNA SPRY4-IT1  
751 promotes development of hepatic cellular carcinoma by interacting with ERR $\alpha$  and predicts  
752 poor prognosis. *Sci Rep* 2017; **7**. doi:10.1038/s41598-017-16781-9.

753 122 Avena P, De Luca A, Chimento A, Nocito MC, Sculco S, La Padula D *et al*. Estrogen  
754 Related Receptor Alpha (ERR $\alpha$ ) a Bridge between Metabolism and Adrenocortical Cancer  
755 Progression. *Cancers (Basel)* 2022; **14**: 3885.

756 123 Cerutti C, Zhang L, Tribollet V, Shi J-R, Brillet R, Gillet B *et al*. Computational

757 identification of new potential transcriptional partners of ERR $\alpha$  in breast cancer cells: specific  
758 partners for specific targets. *Sci Rep* 2022; **12**: 3826.

759 124 Cerutti C, Shi J-R, Vanacker J-M. Multifaceted Transcriptional Network of Estrogen-  
760 Related Receptor Alpha in Health and Disease. *Int J Mol Sci* 2023; **24**: 4265.

761 125 Auld KL, Berasi SP, Liu Y, Cain M, Zhang Y, Huard C *et al.* Estrogen-related  
762 receptor  $\alpha$  regulates osteoblast differentiation via Wnt/ $\beta$ -catenin signaling. *Journal of*  
763 *Molecular Endocrinology* 2012; **48**: 177–191.

764 126 Berman AY, Manna S, Schwartz NS, Katz YE, Sun Y, Behrmann CA *et al.* ERR $\alpha$   
765 regulates the growth of triple-negative breast cancer cells via S6K1-dependent mechanism.  
766 *Sig Transduct Target Ther* 2017; **2**: 17035.

767 127 Chaveroux C, Eichner LJ, Dufour CR, Shatnawi A, Khoutorsky A, Bourque G *et al.*  
768 Molecular and Genetic Crosstalks between mTOR and ERR $\alpha$  Are Key Determinants of  
769 Rapamycin-Induced Nonalcoholic Fatty Liver. *Cell Metabolism* 2013; **17**: 586–598.

770 128 Torrano V, Valcarcel-Jimenez L, Cortazar AR, Liu X, Urosevic J, Castillo-Martin M  
771 *et al.* The metabolic co-regulator PGC1 $\alpha$  suppresses prostate cancer metastasis. *Nat Cell Biol*  
772 2016; **18**: 645–656.

773 129 Valcarcel-Jimenez L, Macchia A, Crosas-Molist E, Schaub-Clerigué A, Camacho L,  
774 Martín-Martín N *et al.* PGC1 $\alpha$  Suppresses Prostate Cancer Cell Invasion through ERR $\alpha$   
775 Transcriptional Control. *Cancer Res* 2019; **79**: 6153–6165.

776 130 Vargas G, Bouchet M, Bouazza L, Reboul P, Boyault C, Gervais M *et al.* ERR $\alpha$   
777 promotes breast cancer cell dissemination to bone by increasing RANK expression in primary  
778 breast tumors. *Oncogene* 2019; **38**: 950–964.

779 131 Tribollet V, Barenton B, Kroiss A, Vincent S, Zhang L, Forcet C *et al.* miR-135a  
780 Inhibits the Invasion of Cancer Cells via Suppression of ERR $\alpha$ . *PLoS ONE* 2016; **11**:  
781 e0156445.

782 132 Han L, Liu B, Jiang L, Liu J, Han S. MicroRNA-497 downregulation contributes to  
783 cell proliferation, migration, and invasion of estrogen receptor alpha negative breast cancer by  
784 targeting estrogen-related receptor alpha. *Tumor Biol* 2016; **37**: 13205–13214.

785 133 Tribollet V, Cerutti C, Gélœn A, Berger E, De Mets R, Balland M *et al.* ERR $\alpha$   
786 coordinates actin and focal adhesion dynamics. *Cancer Gene Ther* 2022; **29**: 1429–1438.  
787

788 **Figure legends**

789

790 **Figure 1: Core mechanisms of cell migration**

791 Cell migration, whether during embryonic development or in adulthood, plays a crucial role in  
792 various biological processes. At the onset of movement, cells undergo polarization and extend  
793 protrusions in the direction of migration. These protrusions are predominantly driven by the  
794 actin cytoskeleton and are stabilized by adhering to the extracellular matrix. Subsequently,  
795 these adhesions generate traction stresses, which enable the cells to propel forward, and  
796 disassembly of adhesion at the rear facilitates cell detachment. In addition, the microtubule  
797 cytoskeleton, which governs intracellular trafficking and signaling also participates in  
798 regulating the different steps of cell migration.

799

800 **Figure 2: ERR $\alpha$  regulates cell migration in both physiological and pathological conditions**

801 ERR $\alpha$  is involved in regulating morphogenetic movements during gastrulation and it also  
802 influences the movements of various cell types that participate to tissue remodelling and  
803 homeostasis. Furthermore, ERR $\alpha$ -mediated cell migration contributes to cardiovascular  
804 diseases and cancer progression.

805

806 **Figure 3: Molecular mechanisms through which ERR $\alpha$  finely controls migration potential**

807 ERR $\alpha$  orchestrates cell movements through diverse mechanisms. ERR $\alpha$  engages in specific  
808 cofactor interactions, regulates gene expression and signaling pathways. As a result, these  
809 actions culminate in the modulation of cell migration and determine cellular responses based  
810 on the context. Figure adapted from images created with [BioRender.com](https://www.biorender.com).

811