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► **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

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

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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 THR $\beta$ 1 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.

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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