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► To cite this version:

Jean-Marc Vanacker, Christelle Forcet. ERR α : 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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ERR α : Unraveling its Role as a Key Player in Cell Migration

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Abstract

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

Keywords: ERR α , cell migration, development, homeostasis, cancer

Running title: ERR α , a key player in cell migration

Introduction

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

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

Structure and regulation of ERR α

ERR α (NR3B1) has been identified in 1988 based on the high sequence similarity within its DNA binding domain to that of the Estrogen receptor alpha (ER α)¹¹. ERR α belongs to a nuclear receptor subfamily that comprises two other isoforms in mammals encoded by distinct genes: ERR β (NR3B2) and ERR γ (NR3B3). However, since no natural ligands have been identified so far, the ERRs are considered orphan nuclear receptors (reviewed in^{12,13}).

As other nuclear receptors, ERR α displays a typical conserved structural organization, comprising a highly variable amino-terminal domain (the A/B domain), a centrally located DNA-binding domain (DBD) that includes two Zn fingers, a flexible hinge region and a carboxy-terminal ligand-binding domain (LBD) containing a transcription transactivation region (reviewed in^{14,15}). The ERR α -DBD specifically binds to the consensus DNA sequence TnAAGGTCA, referred to as estrogen-related response element (ERRE)^{16,17}. Strikingly, the sequence-dependent DNA shape of this binding site contributes to the stabilization of the ERR α homodimer and facilitates its asymmetric positioning on DNA^{18,19}. As shown by structural analysis, the ERR α -LBD includes a putative small binding ligand pocket (LBP) almost completely filled with bulky side chains of amino acids that confers an active conformation to ERR α in a ligand independent-manner²⁰. However, the existence of ligands regulating ERR α activity by inducing conformational changes and/or modulating the recruitment of cofactors, cannot be excluded. In this way, specific ERR α synthetic ligands such as compound A, compound 29 and XCT790 have been identified. These compounds which have the ability to enter the ERR α -LBP by significantly changing its conformation and consequently deactivate the receptor, are called inverse agonists (reviewed in^{12,13}). Importantly, ERR α activity mostly depends on its association with cofactors that are differentially expressed in cells and tissues^{21,22}. In addition, post-translational modifications such as phosphorylation, sumoylation or acetylation of ERR α can modulate its transcriptional activity in a cell type, cofactor and

promoter-dependent manner ^{23–27}. The modulation of ERR α expression is also crucial for the regulation of its functions (reviewed in ¹²).

The ERR isoforms

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

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

Interestingly, in the same way as $ERR\alpha$, $ERR\gamma$ can drive cell migration to facilitate cancer progression⁴⁰.

$ERR\beta$ is mainly expressed in embryonic cells and the $ERR\beta$ knockout demonstrates a major role of this receptor in the regulation of placental formation, the maintenance of pluripotency of embryonic stem cells and the specification of epithelial cells of the inner ear (reviewed in^{15,31}). $ERR\beta$ is globally poorly or not expressed in adult and cancer tissues (reviewed in²¹). However, $ERR\beta$ is significantly expressed in the brain and involved in the regulation of stress response, food intake, satiety and whole-body energy balance (reviewed in¹⁵). Interestingly, $ERR\gamma$ appear to have opposite effects on these processes, suggesting a tight tissue-dependent regulation of the ERR isoform activity or expression. Splicing $ERR\beta$ isoforms have been identified and shown to be expressed in glioblastoma cell lines and tumors^{41,42}. In particular, the long $ERR\beta2$ isoform plays an antitumor role by inducing apoptotic cell death and restricting glioblastoma cell growth and migration⁴². $ERR\beta$ and the $ERR\beta2$ isoform have also been shown to inhibit prostate and breast cancer cell proliferation⁴³ (reviewed in²¹).

Main biological functions of $ERR\alpha$

$ERR\alpha$ is a key regulator of cellular metabolism

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

1α) and PGC-1β coactivators (^{45,46} and reviewed in ⁴⁷). However, in some cases, the cofactors RIP140 and NCOR1 can also be involved (reviewed in ¹⁵). In addition, a crosstalk between ERRα and the thyroid hormone receptors (THR) has been shown ^{48,49}. Notably, TH induces mitochondrial metabolic pathways such as oxidative phosphorylation, fatty acid oxidation and TCA cycle through ERRα in a THRβ1 and PGC-1α-dependent manner. ERRα also contributes to the TH-mediated regulation of mitochondrial fission, biogenesis and mitophagy ⁴⁹. Interestingly, TH has been shown to modulate breast cancer cell migration^{50,51}. A coordinated ERRα-THR effect may thus be possible, although not demonstrated, in this regulation. Unsurprisingly, the alteration of the metabolic pathways regulated by ERRα is associated with human metabolic diseases such as heart failure, diabetes and obesity (reviewed in ¹⁵). ERRα also contributes to the specific metabolic adaptations of cancer cells (reviewed in ^{9,44}).

ERRα modulates the differentiation of multiple mesenchymal lineages

ERRα has been shown to control the differentiation of mesenchymal stem cells towards specific cell fates. For instance, the expression of ERRα increases early during myogenesis in parallel with that of the PGC-1α coactivator, and both factors contribute to the myogenic program *in vitro* and *ex vivo* (^{52–56} and reviewed in ¹⁵). Particularly, ERRα promotes myocyte differentiation through the modulation of mitochondrial metabolism and MAPK signaling (^{30,54} and reviewed in ^{15,57}). Similarly, ERRα may contribute to muscle regeneration in mice by regulating the expression of metabolic genes⁵⁸. Furthermore, ERRα plays a major role in bone homeostasis by repressing osteoblast differentiation both *in vitro* and *in vivo* (and reviewed in ^{15,57}). Additionally, a role of ERRα in the differentiation of adipocytes and chondrocytes in culture is supported by several studies (^{59,62,63} and reviewed in ⁵⁷).

ERR α is involved in cancer progression and invasion

Importantly, ERR α is strongly expressed in various types of cancers, and its elevated expression is associated with metastasis and poor prognosis^{64–74}.

Many studies have demonstrated that ERR α plays a role in tumor growth and progression. Notably, ERR α promotes proliferation of colon, pancreatic, lung and breast cancer lines either by acting downstream of the HER2/IGF-1 pathways or by modulating the expression of the p21 cell cycle inhibitor, members of the cyclin family or other cell cycle regulators (^{74–77} and reviewed in ^{21,78}). In addition, ERR α stimulates angiogenesis by directly inducing the expression of the vascular endothelial growth factor (VEGF) in several cancer cell lines^{79–81}. Furthermore, ERR α enhances Hypoxia-Inducible Factor 1 α (HIF-1 α)-mediated transcription and consequently facilitates tumor and blood vessel growth in mice under hypoxic conditions^{81,82}. ERR α also contributes to the metabolic switch of cancer cells, also termed the Warburg effect, by stimulating aerobic glycolysis^{83,84}. Moreover, ERR α contributes to Epithelial-Mesenchymal Transition (EMT), and promotes cell migration and extracellular matrix (ECM) invasion (^{85–87} and reviewed in ⁹, also see below).

ERR α -mediated regulation of cell migration

ERR α promotes the migration of cells during development and adult tissue homeostasis without interfering with their differentiation

Gastrulation is an early developmental process during which cell migration leads to massive reorganization of the embryo, allowing the establishment of the three embryonic tissue layers. Later, cells migrate within layers and differentiate to form tissues and organs (reviewed in ⁸⁸). Interestingly, ERR α function is not required for cell fate determination in zebrafish embryos, but it plays a major role in controlling different morphogenetic movements during zebrafish

gastrulation⁸⁹. However, the molecular mechanisms by which $ERR\alpha$ regulates these cellular movements have not yet been characterized. *WNT11* regulates hypoblast cell movements during zebrafish gastrulation and it also has been identified as a transcriptional target of $ERR\alpha$ that promotes cancer cell migration^(90,91), also see below). Altogether, this suggests that the *wnt11*-dependent signaling pathway could be involved downstream of $ERR\alpha$ to control orientated cell movements at the onset of gastrulation (Fig. 3).

Furthermore, $ERR\alpha$ has been shown to modulate osteoblast differentiation and bone formation (see above). It also regulates the migration of osteoclasts. Indeed, loss of $ERR\alpha$ activity leads to actin filament disorganization, reduced adhesion and inhibition of transmigration of mature osteoclasts *in vitro*. It also results in a decreased expression of osteopontin, integrin $\beta 3$ and altered localization of c-src that may contribute to the adhesion and migration defects observed⁹² (Fig. 3). Thus, $ERR\alpha$ may participate in the regulation of bone homeostasis and remodeling by acting on the osteoblast lineage but also by controlling osteoclast migration. In addition, $ERR\alpha$ regulates the migration of macrophages *ex vivo* and *in vivo*; this probably depends on its capacity to modulate the expression of *TNFAIP1* and the stability of the RhoA GTPase in these cells⁸⁵ (Fig. 3). Of interest, inhibition of cell migration resulting from the loss of function of $ERR\alpha$ does not result from an impaired differentiation of the osteoclast precursors and macrophages in these conditions^{85,92}.

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

Angiogenesis is a process by which new vessels form; this involves the proliferation, migration and differentiation of endothelial cells (EC). $ERR\alpha$ is a major regulator of angiogenesis under both physiological and pathological conditions (reviewed in⁹, see also

below). Interestingly, this function of ERR α relies in part on its ability to regulate EC migration. ERR α has been shown to be expressed in EC from different tissues and it can either repress or enhance EC migration and angiogenesis, depending on the cellular context and the availability of cofactors. Gene expression analysis of ERR α -deficient EC indicates that the receptor mainly acts as a transcriptional repressor of target genes associated with angiogenesis, cell adhesion and cell migration⁹³. In particular, ERR α modulates the expression of the vascular endothelial growth factor (VEGF) and also inhibits the expression of several migratory and cell-adhesion genes such as *Pecam*, *Mmp3*, *Cdh3* and *Esam1* which are all involved in angiogenic regulation (Fig. 3). As a consequence, ERR α plays a role in limiting angiogenesis by negatively controlling EC migration, tube formation and sprouting in response to growth factors *in vitro* and *in vivo*⁹³.

In contrast, ERR α facilitates angiogenesis through the induction of VEGF expression and secretion from several cell types^{79–82,94–96}. In response to a deprivation in nutrients and oxygen, the cofactor PGC-1 α coactivates ERR α to induce the expression of VEGF, and this may contribute to the physiological response to ischemia⁹⁴ (Fig. 3). Similarly, flavonoids of *Scutellaria baicalensis* root such as Baicalin stimulate the expression of VEGF through the ERR α -PGC-1 α pathway, and consequently induce EC migration and sprout formation⁸⁰. In addition, ERR α regulates the neovascularisation process through VEGF to facilitate tumoral growth and progression in mice. ERR α also enhances the expression of osteoprotegerin that can contribute to the angiogenic process^{95,97}. Furthermore, ERR α interacts with and stabilizes HIF-1 α , and stimulates the expression of its target genes including VEGF (Fig. 3). The functional interaction between ERR α and HIF-1 α plays thus an important role in adapting cancer cells to *in vitro* and *in vivo* hypoxic conditions, and promotes angiogenesis, tumoral growth and invasion^{81,82}. In addition, ERR α induces the expression of eNOS in EC, an enzyme that

generates nitric oxide (NO). As a consequence, ERR α may promote tumor progression through the NO-mediated regulation of EC migration, vascular permeability, blood vessel remodeling and angiogenesis^{98,99} (Fig. 3).

ERR α also positively controls the migration of vascular smooth muscle cells (VSMCs). VSMCs are important components of blood vessel walls that maintain structural integrity and drive the contraction of the vascular wall. The platelet-derived growth factor (PDGF), mainly produced by VSMCs, vascular endothelial cells, platelets or macrophages in the injured vascular walls is involved in vascular remodeling (reviewed in¹⁰⁰). Interestingly, ERR α is required both *in vitro* and *in vivo* for platelet-derived growth factor (PDGF)-induced proliferation and migration of VSMC through the regulation of RhoA/p27/Cdks and Wnt4/ β -catenin pathways¹⁰¹ (Fig. 3). In this way, ERR α acts as an effector of PDGF in controlling vascular remodeling, and thus may contribute to the development of cardiovascular diseases such as atherosclerosis and restenosis^{100,101}.

ERR α plays a role in the induction of Epithelial-Mesenchymal Transition

EMT is a cellular process that leads to the conversion of epithelial cells into mesenchymal cells. EMT occurs during embryonic development and becomes reactivated in pathological contexts such as inflammation and cancer progression. During EMT, epithelial cells lose their polarity and cell-cell junctions, and gain migratory and invasive properties (reviewed in¹⁰²).

ERR α has been shown to induce EMT in cancer cells and consecutively to promote their migration. Interestingly, multiple mechanisms are involved in ERR α -induced EMT (Fig. 3). Depletion of ERR α in a range of cancer cell lines has been shown to increase the expression of E-cadherin, a marker of epithelial cells, and to decrease the expression of vimentin, fibronectin

and N-cadherin which mark a mesenchymal phenotype^{74,103–109}. Interestingly, in most of these cancer cells, ERR α drives EMT and maintains the mesenchymal phenotype by regulating the expression of the transcription factors SNAIL, SLUG and/or Zinc-finger E-box-binding 1 (ZEB1)^{74,103,106,107,110,111}. In gallbladder cancer cells, ERR α promotes EMT and cell migration through the regulation of the expression of Nectin cell adhesion molecule 4 (Nectin-4) and the activation of PI3K/AKT pathway¹⁰⁷. In addition, ERR α regulates cell migration *in vitro*, tumor growth and invasion *in vivo* via the activation of the fibronectin and STAT3 pathways that promote EMT^{104–106}. In turn, the JAK2/STAT3 pathway positively regulates the expression of ERR α to induce EMT¹¹¹. ERR α also regulates the expression and the secretion of TGF- β by osteosarcoma and endometrial cancer cell lines, which can activate ERR α expression via a positive feedback mechanism. As a consequence, ERR α mediates TGF- β -induced SNAIL activation, EMT and cell migration^{106,112,113}.

Surprisingly, the ERR α -knockout mice exhibit no evident developmental abnormalities which is unexpected given the key role of ERR α in the regulation of EMT (see above). They were initially found to display reduced adiposity, peripheral fat deposits and resistance to high-fat diet-induced obesity¹¹⁴. In addition, they show a decrease capacity in mitochondrial biogenesis and oxidative metabolism in the brown adipose tissue and they are consequently defective in adaptive thermogenesis¹¹⁵. ERR α deficiency also produces behavioral disturbances associated with synaptic dysfunction^{116,117}. To some extent, ERR α and ERR γ have overlapping functions, suggesting that the absence of a phenotype associated with a defective EMT might be attributed to functional redundancy between ERR isoforms during development.

A crosstalk between ER α , ERBB2 and ERR α in breast cancers

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

ERR α is a crucial factor regulating cancer cell migration

ERR α has been identified as a major regulator of cancer cell migration and invasion (^{73,85–87,91,118,121,122}) (Fig. 3). Given the importance of altered metabolism in cancers as well as the fact that ERR α modulates different aspects of energy storage and consumption, it could be argued that all cancers phenotypes in which the receptor is involved are a consequence of its metabolic effects. However, ERR α regulates cancer cell migration in cells that do not express PGC-1 α or β ⁸⁶. Furthermore, RNA-Seq approaches have shown that ERR α does not modulate the expression of metabolic targets in these cells although ChIP-Seq experiments indicate that

ERR α is bound to the regulatory regions of these genes¹²³. Altogether, this points to a critical effect of the coregulators bound by ERR α , that control different transcriptional targets and thus phenotypic outcome¹²⁴.

Several studies demonstrated an interplay between ERR α and the Wnt/ β -catenin signaling^{91,101,125}. In cancer cells, ERR α and β -catenin interact, and depend on each other to regulate the expression of genes known to be involved in cell migration such as *WNT11*, *MSX1* and *N-cadherin*. Specifically, the ERR α / β -catenin/WNT11 axis plays a role in promoting prostate and breast cancer cell migration *in vitro*⁹¹. Moreover, ERR α interacts with LSD1 and induces its demethylase activity on the lysine 9 of histone 3 at the promoter of common target genes, resulting in their transcriptional activation. In this way, ERR α and LSD1 promote breast cancer cell invasion *in vitro* through the stimulation of the Matrix Metalloproteinase 1 (MMP1) expression⁸⁶. Noteworthy, the nuclear respiratory factor 1 (NRF1) is required for the recruitment of LSD1 at the transcriptional start site of the ERR α -LSD1-positively regulated target genes and participates in the regulation of MMP1 expression and breast cancer cell invasion⁸⁷. Other matrix metalloproteinases, such as MMP13, also regulated by ERR α , could be involved in the degradation of the basement membrane, facilitating cell invasion⁹⁵. In addition, ERR α promotes the proliferation, migration and invasion of pancreatic cancer cell lines by enhancing the expression of the plasminogen activator inhibitor 1 (PAI1) and consequently activating the mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) pathway⁷⁴.

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

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

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

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

$ERR\alpha$ coordinates the basic processes of cell migration

Cell migration mainly depends on the dynamic organization of the actin and microtubule cytoskeletons, and requires adhesion to the ECM (reviewed in^{5,7}) (Fig. 1). Although numerous studies have reported a role of $ERR\alpha$ in cell migration, its involvement in cell adhesion has only been recently suggested. Zou and colleagues previously noticed that $ERR\alpha$ facilitates the attachment of prostate cancer cells to fibronectin, an ECM protein, but they did not explore the underlying mechanisms⁸¹. As mentioned above, another report showed that $ERR\alpha$ depletion in ECs leads to the upregulation of genes linked to cell adhesion and cell migration⁹³. Furthermore, bioinformatics analyses revealed that the RANK- $ERR\alpha$ regulatory interactome contains proteins associated with ECM regulation, cell adhesion and cell migration, some of which being encoded by putative $ERR\alpha$ target genes¹³⁰. Altogether, these studies have proposed new potential effectors of $ERR\alpha$ involved in cell adhesion and migration that need further investigation.

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

depletion induce cell disorientation that may result from impaired actin cytoskeletal organization and defective lamellipodium formation⁸⁵. Thereafter, it has been demonstrated that ERR α controls actin polymerisation in these cells through the modulation of the RhoA-ROCK-LIMK-cofilin pathway. In addition, ERR α tightly regulates the expression of mitogen-activated protein kinase kinase kinase kinase (MAP4K4), and consequently facilitates the turnover of focal adhesions, the main adhesive structures of the cells¹³³. Thus, these data establish a role for ERR α in coordinating focal adhesions and actin dynamics, that may contribute to cell migration in both physiological and pathological conditions.

Concluding remarks

ERR α has been shown to play a role in various biological processes that contribute to embryonic development, physiology and pathologies. Interestingly, as summarized here, ERR α is a key regulator of cell migration in all of these contexts (Fig. 2). ERR α controls the morphogenetic movement of cells during gastrulation in the embryo and also tightly modulate the migration of different cell types in the adult organism, thereby ensuring tissue homeostasis. In addition, ERR α has been widely implicated in cancer cell migration and invasion. Consequently, ERR α has often been proposed as a therapeutic target to inhibit cancer cell dissemination. However, global pharmacological modulation of ERR α activity or expression could cause undesired side-effects as they would impact on the physiological effects of the receptor. This strategy may thus be reconsidered. Recently, new cofactors of ERR α have been shown to be involved in the modulation of distinct sets of ERR α -target genes¹²³, suggesting that the capacity of ERR α to regulate a given cellular process depends on its association with specific cofactors in a context-dependent manner. In that way, cofactors such as LSD1 or SET7 regulate a precise subset of ERR α -target genes involved in cancer cell

migration^{86,123}. Targeting the complex comprising ERR α and one of these cofactors may thus constitute a promising alternative approach to limit cancer spread. However, further investigations are required to achieve a better understanding of the cofactor-dependent mode of action of ERR α in tumors and other pathological contexts. Besides, it appears also important to dig more deeply into the factors and the mechanisms involved in the ERR α -mediated cell movements in physiological environments.

Acknowledgements

Work in our laboratory is funded by Ligue contre le Cancer (comité Rhône), ANSES (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, grant EST15-076), JoRiss/ENS research program and Région Auvergne-Rhône-Alpes (grant SCUSI OPE2017_004). The authors thanks Violaine Tribollet for helpful discussions.

Author contributions

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

Conflict of Interest

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

- 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 α : 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, Brillet 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 α
455 (ERR α). *J Biol Chem* 2004; **279**: 49330–49337.
- 456 21 Bianco S, Sailland J, Vanacker J-M. ERRs and cancers: Effects on metabolism and on

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

biogenesis and function in myotubes is mediated by NRF-1 and ERR α . *Mitochondrion* 2010; **10**: 516–527.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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

74 Liu S-L, Wu X-S, Li F-N, Yao W-Y, Wu Z-Y, Dong P *et al*. ERR α 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.

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

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.

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.

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

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.

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.

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

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.

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.

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.

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

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

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

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

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

- 90 Ulrich F, Concha ML, Heid PJ, Voss E, Witzel S, Roehl H *et al.* Slb/Wnt11 controls hypoblast cell migration and morphogenesis at the onset of zebrafish gastrulation. *Development* 2003; **130**: 5375–5384.
- 91 Dwyer MA, Joseph J, Wade HE, Eaton ML, Kunder RS, Kazmin D *et al.* WNT11 expression is induced by ERR α and β -catenin and acts in an autocrine manner to increase cancer cell migration. *Cancer Res* 2010; **70**: 9298–9308.
- 92 Bonnelye E, Saltel F, Chabadel A, Zirngibl RA, Aubin JE, Jurdic P. Involvement of the orphan nuclear estrogen receptor-related receptor α in osteoclast adhesion and transmigration. *J Mol Endocrinol* 2010; **45**: 365–377.
- 93 Likhite N, Yadav V, Milliman EJ, Sopariwala DH, Lorca S, Narayana NP *et al.* Loss of Estrogen-Related Receptor Alpha Facilitates Angiogenesis in Endothelial Cells. *Mol Cell Biol* 2019; **39**: e00411-18.
- 94 Arany Z, Foo S-Y, Ma Y, Ruas JL, Bommi-Reddy A, Girnun G *et al.* HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1 α . *Nature* 2008; **451**: 1008–1012.
- 95 Fradet A, Sorel H, Bouazza L, Goehrig D, Depalle B, Bellahcene A *et al.* Dual Function of ERR in Breast Cancer and Bone Metastasis Formation: Implication of VEGF and Osteoprotegerin. *Cancer Research* 2011; **71**: 5728–5738.
- 96 Zhang L-D, Chen L, Zhang M, Qi H-J, Chen L, Chen H-F *et al.* Downregulation of ERR α inhibits angiogenesis in human umbilical vein endothelial cells through regulating VEGF production and PI3K/Akt/STAT3 signaling pathway. *European Journal of Pharmacology* 2015; **769**: 167–176.
- 97 Benslimane-Ahmim Z, Pereira J, Lokajczyk A, Dizier B, Galy-Fauroux I, Fischer A-M *et al.* Osteoprotegerin regulates cancer cell migration through SDF-1/CXCR4 axis and promotes tumour development by increasing neovascularization. *Cancer Letters* 2017; **395**: 11–19.
- 98 Sumi D, Ignarro LJ. Estrogen-related receptor 1 up-regulates endothelial nitric oxide synthase expression. *Proceedings of the National Academy of Sciences* 2003; **100**: 14451–14456.
- 99 Xia W, Yin J, Zhang S, Guo C, Li Y, Zhang Y *et al.* Parkin Modulates ERR α /eNOS Signaling Pathway in Endothelial Cells. *Cell Physiol Biochem* 2018; **49**: 2022–2034.
- 100 Hu W, Huang Y. Targeting the platelet-derived growth factor signalling in cardiovascular disease. *Clin Exp Pharmacol Physiol* 2015; **42**: 1221–1224.
- 101 Li Q, Zhu L, Zhang L, Chen H, Zhu Y, Du Y *et al.* Inhibition of estrogen related receptor α attenuates vascular smooth muscle cell proliferation and migration by regulating RhoA/p27 Kip1 and β -Catenin/Wnt4 signaling pathway. *European Journal of Pharmacology* 2017; **799**: 188–195.
- 102 Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial–mesenchymal transition. *Nat Rev Mol Cell Biol* 2014; **15**: 178–196.
- 103 Huang J, Guan B, Yin L, Liu F, Hu B, Zheng Q *et al.* Effects of estrogen-related receptor alpha (ERR α) on proliferation and metastasis of human lung cancer A549 cells. *J Huazhong Univ Sci Technol [Med Sci]* 2014; **34**: 875–881.
- 104 Wu Y-M, Chen Z-J, Liu H, Wei W-D, Lu L-L, Yang X-L *et al.* Inhibition of ERR α suppresses epithelial mesenchymal transition of triple negative breast cancer cells by directly targeting fibronectin. *Oncotarget* 2015; **6**: 25588–25601.
- 105 Chen H, Pan J, Zhang L, Chen L, Qi H, Zhong M *et al.* Downregulation of estrogen-related receptor alpha inhibits human cutaneous squamous cell carcinoma cell proliferation and migration by regulating EMT via fibronectin and STAT3 signaling pathways. *European Journal of Pharmacology* 2018; **825**: 133–142.
- 106 Yoriki K, Mori T, Kokabu T, Matsushima H, Umemura S, Tarumi Y *et al.* Estrogen-

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

identification of new potential transcriptional partners of ERR α in breast cancer cells: specific partners for specific targets. *Sci Rep* 2022; **12**: 3826.

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

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

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

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

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

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

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

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

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

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

Figure legends

Figure 1: Core mechanisms of cell migration

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

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

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

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

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