

The emerging role of estrogen related receptor α in complications of non-small cell lung cancers (Review)

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Abstract. Approximately 85% of lung cancer cases are recognized as non-small cell lung cancer (NSCLC) with a perilous (13-17%) 5-year survival in Europe and the USA. Although tobacco smoking has consistently emerged as the leading

cause of NSCLC complications, its consequences are distinctly manifest with respect to sex bias, due to differential gene and sex hormone expression. Estrogen related receptor α (ERR α), a member of the nuclear orphan receptor superfamily is normally expressed in the lungs, and activates various nuclear genes without binding to the ligands, such as estrogens. In NSCLC ERR α expression is significantly higher compared with healthy individuals. It is well established ER α and ER β , have 93% and 60% identity in the DNA and ligand binding domains, respectively. ER α and ERR α have 69% (70% with ERR α -1) and 34% (35% with ERR α -1) identity, respectively; ERR α and ERR β , have 92 and 61% identity, respectively. However, whether there is distinctive ERR α interaction with mammalian estrogens or concurrent involvement in non-ER signalling pathway activation is not known. Relevant to NSCLC, ERR α promotes proliferation, invasion and migration by silencing the tumor suppressor proteins p53 and pRB, and accelerates G₂-M transition during cell division. Epithelial to mesenchymal transition (EMT) and activation of Slug (an EMT associated transcription factor) are the prominent mechanisms by which ERR α activates NSCLC metastasis. Based on these observations, the present article focuses on the feasibility of antiERR α therapy alone and in combination with antiER as a therapeutic strategy for NSCLC complications.

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Abbreviations: ERR, estrogen related receptor; ERs, estrogen receptors; NSCLC, non-small cell lung cancer; EMT, epithelial to mesenchymal transition; CD, cluster of differentiation; MMP, matrix metalloproteinase; PAI, plasminogen activator inhibitor; PTHrP, parathyroid hormone-related protein; EGFR, epidermal growth factor receptor; ELK, Ets like transcription factor-1; KRAS, Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase; CYP, cytochrome P450; PDI, programmed cell death protein 1; GSTM1, glutathione S-transferase Mu 1; cDNA, complementary DNA; GRIP1, glutamate receptor-interacting protein 1; PR, progesterone; HER, human epidermal growth factor receptor-2; NR3B, nuclear receptor 3B; ESRRA, estrogen related receptor α ; ESRRB, estrogen related receptor β ; ESRRG, estrogen related receptor γ ; NTD, N-terminal domain; DBD, DNA binding domain; LBD, ligand binding domain; NR, nuclear receptors; ERRE, ERR response element; HDAC8, histone deacetylase; SIRT1, sirtin 1; PCAF, P300/CBP associated factor; ERE, estrogen response element; SP-1, specificity protein-1; AP-1, activator protein-1; AF, activation function; PPAR γ , peroxisome proliferator-activated receptor γ ; PGC-1, proliferator activated receptor γ co-activator-1; KO, knockout; LUAD, lung adenocarcinoma; ROS, reactive oxygen species; LSCC, lung squamous cell carcinoma; PTEN, phosphate and tensin homolog; MAPK, mitogen activated protein kinase; PI3K, phosphoinositide 3-Kinase; ZEB1, zinc finger E-box-binding homeobox 1; IL-10, interleukin-10; TGF- β , tumor growth factor- β ; CTLA4, cytotoxic T-lymphocyte associated protein 4; TIM-3, T-Cell immunoglobulin and mucin domain-3; DES, diethylstilbestrol; SERM, selective estrogen receptor modulators; SERDs, selective estrogen receptor downregulators

Key words: estrogens, non-small cell lung cancer, estrogen receptors, estrogen related receptor alpha, cell cycle, epithelial mesenchymal transition

Contents

1. Introduction
2. ERRs and their physiological functions
3. ERRs in NSCLCs
4. Role of ERR- α in cell cycle regulation and NSCLC proliferation
5. Role of ERR- α in the invasion and migration of NSCLC cells
6. Conclusions and future perspective

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the most prevalent malignant tumors and accounts for ~85% of the lung cancer related deaths globally (1). As reported in 2017, lung cancer related deaths in Europe were the leading cause of

cancer deaths in both sexes, accounting for 24% male deaths and 15% female deaths (2,3). Data from 2017 predicted a 10.7% fall in 5 years for males (corresponding to 33.3 deaths per one lakh residents), individuals for females a 5.1% increment (accounting for 14.6 deaths per one lakh individuals) (1-3). Unfortunately, current therapies against NSCLCs are ineffective due to the advanced stage tumor progression at diagnosis and post therapy relapses (4,5). Within the USA and Europe, the 5-year overall survival rate of patients with NSCLC is only 13-17% (6).

Numerous studies have indicated that sex disparities exist in the development and complications of lung cancer (7-16). For instance, Jemal *et al* (7) reported higher lung cancer susceptibility in young females compared with males in the USA. Possible reasons for this disparity include sex distinctions in genetics and epigenetics (8,9), sex hormone levels (10,11), sex hormone receptors levels (12), post-menopausal hormone replacement therapy (13,14) and smoking history (15,16). Racial and ethnic differences also contribute to the development and complications of lung cancer (17,18).

Izbicka *et al* (19) used multiplex immunoassays and mass spectrometry to determine the differences in diagnostic biomarkers for sexes in asthma and NSCLC. The results indicated that soluble FAS, matrix metalloproteinase-9 and plasminogen activator inhibitor-1 are strong predictive biomarkers in males, whereas soluble cluster of differentiation 40 was prognostic for cancer in females (19). In another study, Hastings *et al* (20) found that parathyroid hormone-related protein (PTHrP) is commonly expressed in NSCLC. In female NSCLC subjects, a median survival of 55 and 22 months was observed in those expressing vs. not expressing PTHrP (20). In contrast, an overall 38 months survival in male subjects with NSCLC was observed independent of PTHrP status. These results suggest that PTHrP is a predictor of survival in women, but not men after adjusting for stage and histology of the tumor and age (20).

In non-smokers with NSCLC, biomarkers including epidermal growth factor receptor (EGFR), ELK (Ets like transcription factor-1; highly expressed in NSCLC, irrespective of patient's age, sex, smoking status and histology) and KRAS mutations are more frequently observed in women compared with men (21,22). These mutations mostly occur in adenocarcinoma (23). Notably, women exhibit greater benefit compared with men when treated with EGFR inhibitors (24). In contrast, women have less benefit from anti programmed death 1 inhibitors compared with men (25). There is no sex distinction in response to ALK (anaplastic lymphoma kinase) inhibitors (26). Of note, ALK inhibitors are anticancer drugs which act on tumours with ALK varied expressions (27). ALK inhibitors are tyrosine kinase inhibitors and act by inhibiting the proteins responsible for abnormal tumour cell growth (28). The higher response rate to anti-EGFR in women may be due to a greater intrinsic EGFR expression (9,29). Notably, female smokers exhibit a higher likelihood of developing lung cancer compared with males (15). The higher female susceptibility to tobacco carcinogens could be due to an enhanced expression of the cytochrome P450 (CYP) enzyme CYP1A, which is responsible for polycyclic aromatic hydrocarbon activation in human lungs (16). Also, female smokers have a higher frequency of *TP53* gene mutations compared to non-smoking

females or males (30-32). p53, the protein product of *TP53*, is a potent tumor suppressor (33). Women are also more likely to have mutations in the *GSTM1* (Glutathione *S*-transferase Mu 1) gene, which normally inactivates toxic metabolites and has been linked to lung cancer development in smokers (34). Additional studies are needed in both smokers and non-smokers to fully understand the genetic and epigenetic factors contributing to increased lung cancer incidence in women compared with men.

Physiologically, mammalian lungs are continuously exposed to estrogens by the blood circulation (10). Females produce higher levels of estrogens compared with males, owing to higher aromatase (the enzyme involved in conversion of androgen/testosterone to estrogens) synthesis in gonadal tissues (35-37). Besides major synthesis in the gonads such as ovary, aromatases are locally expressed in non-gonadal tissues including the lungs, brain, liver, bone, intestines, skin, blood vessels and spleen (38,39). Hence, estrogens are synthesized within the lungs normally (40) as well as during various pathologic states including NSCLC (41). Estrogen receptors (ERs: ER α and ER β) are also detected in lung tissues in the normal physiological state as well as in lung cancers (42,43). While estrogens are normally involved in lung development (44,45), pathophysiologically these hormones serve an important role in lung carcinogenesis and its complications (46-48). At present, a number of clinical trials are ongoing to assess the efficacy of antiestrogen/antiER therapies against NSCLC development and complications (49,50). This approach has been summarized in multiple comprehensive reviews and is therefore not discussed in the present review.

The estrogen related receptors (ERRs) were initially identified from a cDNA library screen by Giguere *et al* (51). Using rat and human tissue samples, the investigators identified unique clones in kidney and heart cDNA libraries that encoded previously unknown proteins with conserved features of nuclear steroid hormone receptors, particularly ERs (51). The clones were designated as estrogen-related receptor α (ERR α) and estrogen-related receptor β (ERR β) (51). A third isoform of ERR, ERR- γ (ERR γ) was subsequently identified by Eudy *et al* (52) through its linkage to the Usher's Syndrome locus. Hong *et al* (53) using yeast two-hybrid screening and the nuclear receptor co-activator glutamate receptor-interacting protein 1 as bait also identified ERR γ .

ERRs do not bind endogenous estrogens or their derivatives and are therefore recognized as orphan nuclear receptors, exhibiting considerable structural and functional homology with ERs (Fig. 1) (51). The ERRs involvement in ER-dependent signaling is associated with breast cancer cell proliferation (54). ERRs pathological significance is additionally noted by resistance to tamoxifen, a competitive ER inhibitor used for breast cancer treatment (55) and activity in highly metastatic triple negative (ER-, PR-, HER-) (estrogen, progesterone and human Epidermal growth factor receptor 2 negative) (56). Hence, ERRs appear to serve important pathological roles in both explicitly ER positive and negative breast cancers.

Numerous studies have indicated that ERRs serve pathological roles in other estrogen dependent and independent cancers, including ovarian (57), endometrial (58), prostate (59) colon/colorectal (60) and lung (61). Compounds that modulate ERR α activity may serve critical roles in disease progression

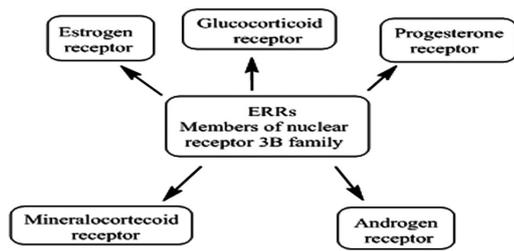


Figure 1. Compositional description of ERRs including estrogen receptors, progesterone receptors, androgen receptors, mineralocorticoid and glucocorticoid receptors. The multiple activities of physiological sustenance infer the significance of ERRs in maintaining homeostasis and regulating the normal functioning. ERRs, estrogen related receptors.

as well as homeostasis (62). No endogenous ligand for $ERR\alpha$ has been identified, although several synthetic antagonists have been reported (63-65). Recently, dietary products, such as genistein, apigenin, resveratrol, rutacarpine, piceatanol, daidzein, flavone and cholesterol have been reported as potential $ERR\alpha$ agonists (66-68). The primary aim of the present review is to highlight the emerging role of ERRs in NSCLCs.

2. ERRs and their physiological functions

Giguere *et al* (51) cloned the first orphan receptors, $ERR\alpha$ and $ERR\beta$, using the $ER\alpha$ DNA-binding domain (DBD) as a probe to screen recombinant DNA libraries. A decade later, Eudy *et al* (52) identified a third isoform of this family, $ERR\gamma$. Based on repetitive genetic analysis, ERRs were grouped into the nuclear receptor 3B family (NR3B) comprising ERs, PRs, androgens, mineralocorticoids and glucocorticoids (69) (Fig. 1). Genes were identified as responsible for the synthesis of $ESRRA$ ($NR3B1$, $ERR\alpha$), $ESRRB$ ($NR3B2$, $ERR\beta$) and G ($NR3B3$, $ERR\gamma$) (70). Several $ERR\beta$ and $ERR\gamma$ splice variants have been identified that display distinct developmental and tissue specific patterns of expression (70,71). Protein sequence analysis by Laudet *et al* (72) revealed an ~68% sequence homology within the DBD of ERRs and classical ERs, while there is considerably less homology (~33%) within the ligand binding domain (LBD) (Fig. 2A). Hence, the DBD is more conserved among ERRs and ERs compared with the LBD, suggesting important structural and functional similarities of $ERR\alpha$ and $ER\alpha$ (72).

ERRs exhibit structural attributes akin to other nuclear receptors (NRs) (73). Typical functional sites of the overall structure include two activation function domains (AF-1 and AF-2), a DBD and a LBD (73). The N-terminus contains the AF-1 domain, which imparts weak ligand independent transcriptional activation in most NRs (73). Diverging from $ERR\alpha$, the β and γ isoforms share an overall structural relatedness particularly in the N-terminal region (Fig. 2B). This feature is relatively uncommon because of generally poor conservation of the N-terminal region even among receptors of the same subfamily (73). Another significant aspect is the presence of conserved motifs in the N-terminal domain of the 3 ERR isoforms, conditional to the post-translational phosphorylation and sumoylation regulated transcriptional events (74,75). The DBDs of ERR comprise 2 strictly conserved zinc finger motifs targeting the receptor to a specific DNA sequence

(TCAAGGTCA), which is designated as the ERR response element (ERRE) (73). All 3 members of ERR subfamily have significant similarity in the ERRE domain, suggesting that a number of genes could be targeted by more than one of the ERR isoforms (73). Several reports have demonstrated ERRs binding to ERRE as monomers, homodimers or heterodimers of 2 distinct ERR isoforms (76,77). The extent of ERREs within the ERR complexes of target genes is not known, but it is known to vary significantly based on the cell type, cellular proliferation state and differentiation and in response to organ specific stimuli (73), such as $PPAR\alpha$ /sirtuin 1 (Sirt1) complex mediated ERR target suppression in the heart (78), and squamous metaplasia in the prostate gland (79) arising due to altered estrogen synthesis. The affinity of $ERR\alpha$ binding with ERREs is modulated by the extent of acetylation of four lysine residues in the Zn^{+2} finger and C-terminal extension of DBD, which is regulated by acetyltransferase P300/CBP-associated factor (PCAF) and deacetylases, histone deacetylase (HDAC8) and SIRT1 (79-81). This deacetylation mechanism is used by HDAC8 and SIRT1 cofactors to link the metabolic status with controlling $ERR\alpha$ target gene selection (80).

The C-terminal LBDs of ERRs have a conserved AF-2 helix motif essential for cofactor interactions (73). A distinctive aspect of ERRs unlike other conventional NRs is their ability to activate transcription without need for exogenous ligands, because the LBD conformation in the absence of ligand supports the involvement of NR co-activators, which are necessary for ERR regulated transcriptional activation (82,83). Inspection of the $ERR\alpha$ and $ERR\gamma$ LBD conformations reveals the importance of amino acids that have bulky side chains occupying the ligand binding pocket, hence mimicking a ligand bound conformation that facilitates cofactor binding (73). As one example, the $ERR\alpha$ LBD crystal structure revealed a significant Phe328 hold of the ligand binding pocket that confers an agonist conformation to the LBD, which further binds the $PPAR\gamma$ co-activator-1 α peptide (84). Of note, $PPAR\gamma$ is a type II proton regulating protein encoded by $PPARG$ gene in humans, substantially prevalent in adipose tissue, colon and macrophages (64). While transcriptional activity of ERRs is mostly independent of agonists, structural studies have revealed an open ligand binding pocket of ~220 cubic Å in $ERR\gamma$ and of ~100 cubic Å in $ERR\alpha$, allowing transcriptional intervention by synthetic molecules (85-89).

ERs ($ER\alpha$ and $ER\beta$) are members of the steroid/nuclear receptor superfamily and are activated via ligand binding (90). Mammalian ERs function both as signal transducers and transcription factors to modulate target gene expression (91). In response to ligand binding, ERs undergo conformational changes and 'activation', accompanied by heat shock protein hsp90, hsp70 or other proteins dissociations (92), forming a ligand-occupied ER dimer (93). Stimulation of target gene expression in response to 17 β -estradiol (E2), or other agonists, is thought to be mediated either via 'direct binding' to DNA specific genes, such as vitellogenin A2 and oxytocin or through 'indirect binding' by transcription factors, such as NF- κ B, specificity protein-1 (SP-1) and activator protein-1 (AP-1) (94). In the former, E2-liganded ER dimer (E2-ER-ER) binds directly to a specific estrogen responsive gene sequence, called an estrogen response element (ERE) before interacting with co-activator proteins and RNA polymerase II transcription initiation complex components

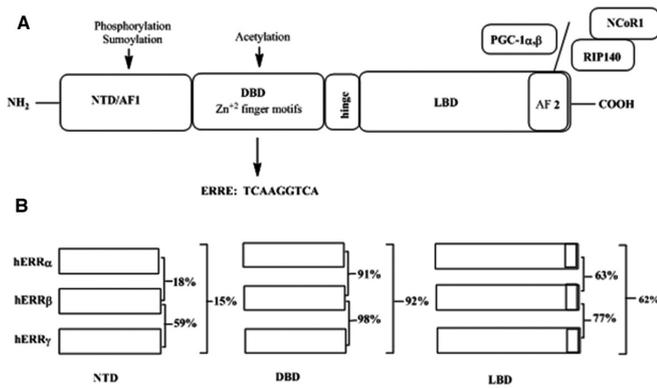


Figure 2. Structural and compositional profile of ERRs. (A) Constitutional binding domains of ERRs. It is notable to observe that DBD and LBD are intervened by a distinctive hinge region, unlike NTD and DBD which interact with each other to a greater extent. Sumoylation refers to post-translational protein modifications effected *via* ~10 kDa polypeptides. The changes involve formation of isopeptide bonds with ϵ -amino groups of acceptor Lys residues. The dynamic process (owing to small ubiquitin related modifier (SUMO) specific isopeptidases) is a series of enzyme catalyzed events, involving an activating enzyme (E1), a conjugating enzyme (E2) and in majority of cases, a SUMO ligase (E3). Acetylation is another post-translational modification, wherein a $\text{CH}_3\text{-COO}$ functional group is introduced to a chemical compound. The characteristic post-translational modifications in NTD (sumoylation) and DBD (acetylation) infer their implicit significance for functional ERR expression. (B) Quantification of constitutional human ERR isoforms, where $\text{ERR}\beta$ and $\text{ERR}\gamma$ share greater sequence conservation compared with $\text{ERR}\alpha$ and $\text{ERR}\beta$, corresponding to each domain. PGC-1, proliferator activated receptor- γ co-activator-1; NCoR1, nuclear receptor corepressor 1 (protein encoded by *NCOR1* gene in humans); RIP140: Receptor interacting protein 140 (a repressor of androgen receptor); ERRE, ERR response element; AF1/2, activation function 1/2 (a ligand-independent transcriptional regulator associated with manifold post-translational modifications); NTD, N-terminal domain; DBD, DNA binding domain; LBD, ligand binding domain; Zn, zinc; ERRs, estrogen related receptors.

resulting in enhanced transcription (95). The EREs are permutations of the 5'-GGTCAnnnTGACC-3' DNA palindrome, wherein 'n' denotes a nonspecific 3 nucleotide spacer located at varying distances from the transcription start site and/or within a gene locus (96). The regulation of gene expression by the E2-ER-ER binding to EREs is referred to as the ER-dependent signaling pathway (97,98). A second mechanism of regulation is the transcriptional modulation of target genes through E2-ER-ER and transcription factors interactions, referred to as 'tethering' (99). The prominent transcription factors involved in this interaction include SP1 (100,101), AP1 (102-104), and a number of other proteins (105). In a comprehensive review, Klinge (106) described the molecular mechanism by which ligand bound ER dimers modulate ERE dependent and independent transcription, i.e. transcription factor dependent transcription of various estrogen regulated genes, such as cytochrome c, insulin like growth factor binding protein 4, early estrogen-induced gene 1 and 4, heat shock 70 kDa protein 8, keratin 8 and nuclease sensitive element binding protein 1.

Like $\text{ER}\alpha$, $\text{ERR}\alpha$ binds to the classical ERE of estrogen responsive genes, characterized by 5'-AGGTCANNNTGACCT-3' sequence (N denoting a typical nucleotide) (106). $\text{ERR}\alpha$ also has binding sites for an extended half of palindromic ERE as ERR response elements (ERRE), having 5'-TNAAGGTCA-3' sequence (91,107,108). Hence, $\text{ERR}\alpha$ can affect $\text{ER}\alpha$ transcriptional activity. Although ERR dimers

can bind to the ERE, $\text{ER}\alpha$ dimers (not those of $\text{ER}\beta$) also can recognize a functional ERRE, hence demonstrating a nearly identical binding specificity (109).

Basic physiological functions of ERRs include a central role in regulating cellular metabolism by modulating genes involved in glycolysis, the TCA cycle and mitochondrial oxidative phosphorylation (Fig. 3) (110). Normally, an association of proliferator activated receptor γ co-activator 1 (PGC-1) with the ERR transcriptional axis controls mitochondrial biogenesis (111). Besides a role in normal physiology, roles of other PGC-1/ERR pathways are observed in cancers, which depend on tissue specific and environmental stimuli (112-116). For instance, the PGC-1/ERR axis has been identified as necessary for tumor cell motility and metastasis driven malignant transformation in breast and melanoma cancer progression, whereas in prostate cancer the same pathway suppresses tumor progression and metastasis (Table I) (111,112,117-122).

$\text{ERR}\alpha$ is present in tissues actively engaged in high glucose and lipid metabolism including heart, kidney, intestinal tract, skeletal muscles and brown adipose tissues (Fig. 3A) (111,120,122-125). Compared to $\text{ERR}\alpha$, $\text{ERR}\beta$ and $\text{ERR}\gamma$ expression is much more restricted, with heart and kidney being the major sites (125,126). Expression of both $\text{ERR}\alpha$ and $\text{ERR}\gamma$ are increased in preadipocytes and pluripotent mesenchymal cells under adipogenic conditions indicating regulation by lipid accumulation (127,128). In the central nervous system and spinal cord, $\text{ERR}\beta$ and $\text{ERR}\gamma$ are expressed during early embryonic development (129-131).

Specific roles for each ERR were demonstrated using ERR specific knockout (KO) mice (132-134). $\text{ERR}\alpha$ KO mice are viable, but exhibit a phenotype characterized by reduced body weight, peripheral fat deposition and resistance to high-fat diet-induced obesity (132). $\text{ERR}\alpha$ KO mice also exhibit cardiac defects in bioenergetics and functional adaptation to pressure overload, but their development and function under normal, unstressed conditions is unaffected (133). $\text{ERR}\alpha$ KO mice also exhibit a loss of normal mitochondrial biogenesis (134). In contrast, $\text{ERR}\beta$ KO mice are lethal due to impaired placenta formation (130). $\text{ERR}\gamma$ KO mice exhibit impaired oxidative phosphorylation of perinatal heart mitochondria resulting in 100% mortality within 48 h of birth (135). In summary, ERRs are essential for maintaining normal physiological functions. While $\text{ERR}\alpha$ is detected in the lung, the exact physiologic role of $\text{ERR}\alpha$ in the lung is not known. $\text{ERR}\beta$ and $\text{ERR}\gamma$, have not yet been detected in lung tissues (136).

3. ERRs in NSCLCs

In recent years, several studies have reported a close association between $\text{ERR}\alpha$ expression and progression of estrogen-dependent tumors including breast, ovarian, endometrial, prostate and lung cancers as well as non-estrogen-dependent tumors such as gastric, colon and colorectal cancers (47,49-51). This suggests the involvement of $\text{ERR}\alpha$ both in estrogen dependent and independent processes for a wide range of tumors (111,137).

Initial studies of various rat and human tissues indicated that high level $\text{ERR}\alpha$ expression was a hallmark of metabolically active organs, such as the heart, liver and brain (128,132,134). Low $\text{ERR}\alpha$ expression was detected in several other organs including lung (51). Subsequently, using embryonic and adult

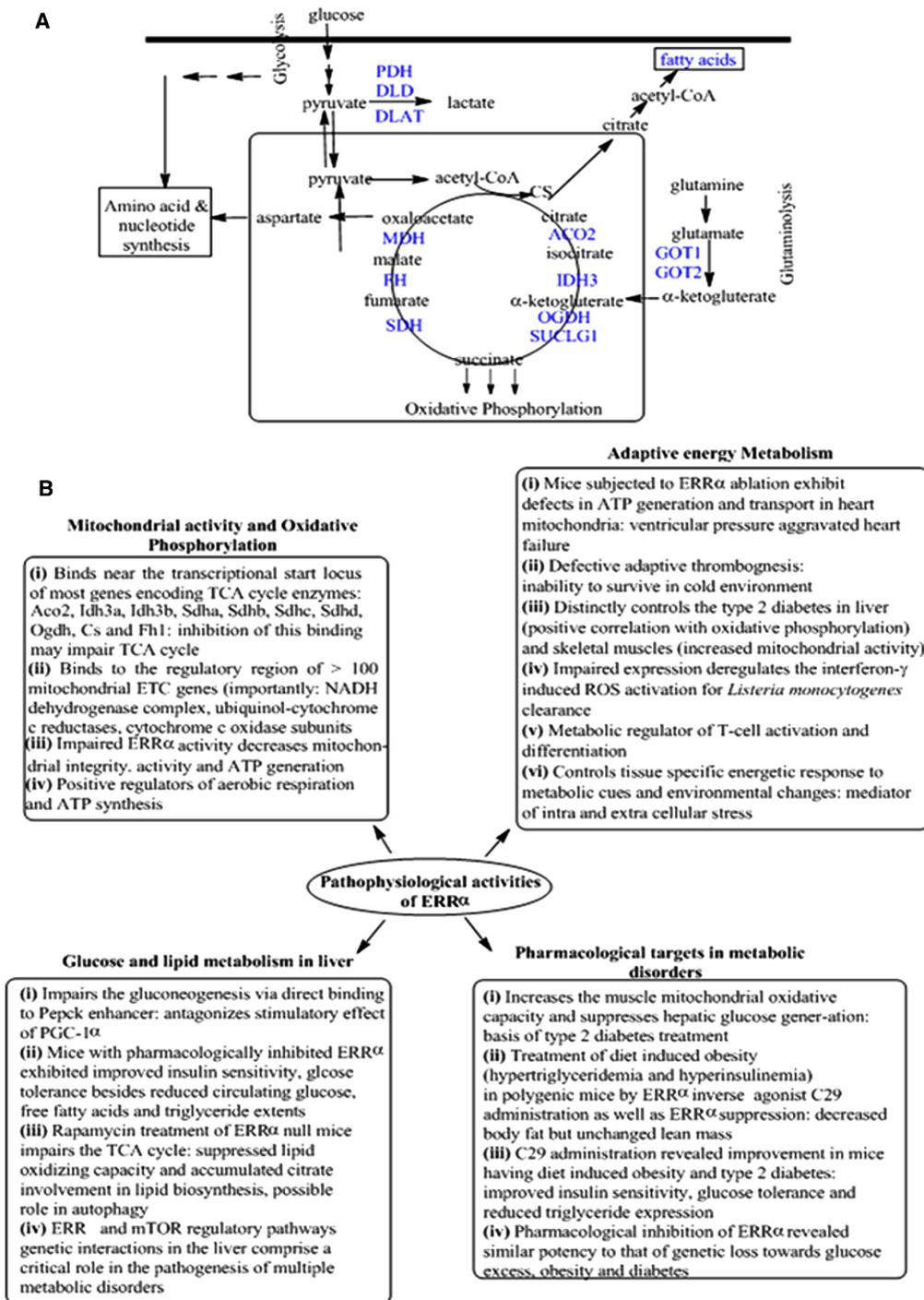


Figure 3. Pathological and physiological significance of ERRα. (A) Regulation of mitochondrial energy production and oxidative phosphorylation, hepatic metabolism of glucose and lipids, distinctive control of type 2 diabetes in liver and skeletal muscles and implication as potential therapeutic target in the treatment of glucose excess, obesity and diabetes. (B) Significance of ERRs mediated signaling control in Krebs (TCA) cycle and oxidative phosphorylation, in which ERRα and ERRγ isoforms serve as central regulatory pillars of metabolic genes and cellular energy metabolism. ERRβ, has been reported to be vital for maintenance of embryonic stem cell pluripotency (110). MDH, malate dehydrogenase; FH, fumarate hydratase; SDH, succinate dehydrogenase; ACO2, aconitase hydratase; IDH3, isocitrate dehydrogenase; DLD, dehydrogenase complex; PDH, pyruvate dehydrogenase; SUCLG1, succinyl-Coenzyme A ligase; GOT1, aspartate aminotransferase, cytoplasmic; GOT2, aspartate aminotransferase, mitochondrial; CS, citrate synthase; ERR, estrogen related receptor; NSCLC, non-small cell lung cancer; ATP, adenosine triphosphate dihydrolipoamide dehydrogenase; DLAT, dihydrolipoyl transacetylase; OGDH, oxoglutarate.

mouse tissues, low ERRα levels were demonstrated in bone and skin (138). ERRα has been detected in human NSCLC samples (59). In rats, ERRβ is detected at low levels in kidney, heart, testis, brain and prostate (49), whereas in mouse, it is weakly expressed in adult kidney and heart (139). ERRγ is detected in embryonic lung tissues including humans, but is

not detected in adult lungs (71). To the best of our knowledge no study to date, has demonstrated ERRβ and ERRγ expression in adult human lungs.

Regarding the role of ERRα in NSCLC, a number of studies demonstrated elevated ERRα expression in NSCLC cells, xenograft NSCLC mouse models and clinical NSCLC

Table I. Summary of published studies demonstrating the characteristic effects of ERR in breast, ovarian, prostate, hepatocellular and colorectal cancers.

A, Breast cancer	ERR α	ERR β	ERR γ	(Refs.)
Deblouis and Giguere, 2013; Gravel, 2018	<ul style="list-style-type: none"> • Significantly expressed in all sub-types • One of the coveted hallmarks and therapeutic target • Strongly active in ERα negative, HER2 positive and triple negative tumors • Enhanced ERRα/PGC-1 axis expression is an unfavourable clinical outcome • Promotes aromatase and c-myc gene expression: Increasing local estrogen production and subsequent malignant transformation of breast epithelium • Serves as transcriptional activator in ER negative tumor cells (competes with estrogen receptors in regulating estrogen responsive genes) • Stimulates bone metastasis of advanced tumors, aggravates estrogen production via sulfotransferase activation: A role linked with conferring resistance to SERM therapy 	<ul style="list-style-type: none"> • Inversely correlated expression with S-phase fraction: Inhibits cellular proliferation • A separate study found it as a proliferative gene • Thereby, no clarity exists about a possible role in tumor manifestation 	<ul style="list-style-type: none"> • Affects the tumor growth <i>via</i> modulating ER expression • Stimulates E-cadherin activity in ER and PR co-expressing tumors • Promotes mesenchymal to epithelial transition • AAAG tetranucleotide polymorphism in the untranslated region associated with breast cancer predisposition • Aggravates tamoxifen resistance in invasive lobular tumors • Exogenous transfection aggravated tumor proliferation 	(111,112)
B, Prostate cancer	ERR α	ERR β	ERR γ	(Refs.)
Audet-Walsh <i>et al</i> , 2015	<ul style="list-style-type: none"> • Enhanced expression promotes the tumor development: Serves as a vital prognostic factor 	<ul style="list-style-type: none"> • Lowly expressed in developing tumors • Overexpression suppresses the proliferation of androgen sensitive and insensitive tumor cells • Transactivates a cyclin dependent kinase inhibitor upstream promoter, p21 gene: Inhibited cell cycle progression 	<ul style="list-style-type: none"> • Lowly expressed in developing tumors • Cancerous lesions and benign foci from radial prostatectomy (after staining and comparing immunoreactive scores) revealed poor expression in tumor tissues • Useful prognostic indicator, though • Several common attributes with ERRβ 	(117)

Table I. Continued.

First author, year	ERR α	ERR β	ERR γ	(Refs.)
C, Ovarian cancer				
Sun <i>et al</i> , 2005	<ul style="list-style-type: none"> ERRα was noticed in all cell lines, with human ERRα (full length cDNA, 2421 bp) and human ERRα-1 (full length cDNA, 2,221 bp) as major isoforms Human ERRα-1 was screened as independent prognostic factor for poor survival with a 95% relative risk 	<ul style="list-style-type: none"> Human ERRβ-1 (in Mdah-2774 and SKOV-3 cell lines) and human ERR β-2 (in SKOV-3 cell line) were the noted isoforms 	<ul style="list-style-type: none"> Positive group exhibited a longer progression free survival than ERRγ negative counterparts Noticed in Mdah-2774, OVCAR-3 and SKOV-3 cell lines 	(118)
D, Gastric cancer				
First author, year	ERR α	ERR β	ERR γ	(Refs.)
Kang <i>et al</i> , 2018	<ul style="list-style-type: none"> No significant observation reported to date 	<ul style="list-style-type: none"> No significant observation reported to date 	<ul style="list-style-type: none"> Recently reported as tumor suppressor using Genomic Analysis approach Both ERRγ and its specific agonist, DY131 inhibited the tumor growth Patients harbouring ERRγ gene signatures revealed improved prognosis Suppresses the transcription of Ant targeting genes (DVL3, LEF1, LGR5, TCF7L2, AXIN2 and CTNNB1) in AGS and MKN28 cells Indirectly influences the β-catenin phosphorylation due to its cytoplasmic location 	(119)
E, Hepatocellular carcinoma				
First author, year	ERR α	ERR β	ERR γ	(Refs.)
Kim <i>et al</i> , 2016; Pons <i>et al</i> , 2005	<ul style="list-style-type: none"> No significant correlation with tumor growth was noticed 	<ul style="list-style-type: none"> No significant correlation with tumor growth was noticed 	<ul style="list-style-type: none"> Aggravating factor for advanced tumor node metastasis and Barcelona Clinic Liver Cancer Stages 	(120,121)

Table I. Continued.

E, Hepatocellular carcinoma	ERR α	ERR β	ERR γ	(Refs.)
First author, year			<ul style="list-style-type: none"> • Treatment with siRNA or inverse agonist (GSK5182) inhibited the cell cycle proliferation <i>via</i> G₁ arrest, increased p21 and p27 expressions and decreased phosphorylated retinoblastoma protein expressions • ERRγ inhibitors could serve as potential therapeutic agents 	
F, Colorectal cancer				
First author, year	ERR α	ERR β	ERR γ	(Refs.)
Zhou <i>et al</i> , 2019	<ul style="list-style-type: none"> • Interaction with ovarian tumor domain comprising OTUB1 promoter • Promotes metastasis <i>via</i> inducing vimentin expression • OTUB1 could therefore be used as a novel ERRα target 	<ul style="list-style-type: none"> • No significant involvement was noticed 	<ul style="list-style-type: none"> • No significant involvement was noticed 	(122)

ERR, estrogen related receptor; SERM, selective estrogen receptor modulators; HER-2, human epidermal growth factor receptor 2; OTUB1, ubiquitin aldehyde binding protein 1; ER, estrogen; PGC, peroxisome proliferator-activated receptor- γ ; CK1, cyclin-dependent kinase inhibitor.

samples, indicating possible diagnostic or post-therapeutic prognostic roles of ERR α in NSCLC (91,138-140). One study elucidated a cell-specific ERR α transactivator functioning through SFRE sequence, wherein ERR α contributed in transcriptional activation in rat osteosarcoma cell line (ROS 17.2/8) and HeLa, NB-E and FREJ4 cells, but not in COS1 and HepG2 cells (138). The investigators reasoned such distinctions in ERR α functioning were due to the osteopontin gene promoter as a transcription regulating target for ERR α (138). Pettersson *et al* (139) observed the expression of nuclear receptors in embryonal carcinoma stem cells. This study found that adequate homodimerization and DNA binding of mERR β was exclusively dependent on interaction with heat shock protein 90, a molecular chaperone known to interact exclusively with steroid hormone receptor subgroup of nuclear receptors (140). In summary, the mouse orphan receptor mERR β exhibited the potential to control the coinciding gene networks with the estrogen receptor, simultaneously participating in signal transduction pathways during a limited time span analogous to chorion formation (138). Wang *et al* (140) demonstrated the tumorigenic potential of ERR α via studying the effect of administered XCT-790, an ERR α specific inverse agonist in A549 NSCLC cells. The findings of the aforementioned study revealed reduced mitochondrial mass and enhanced ROS generation through interception of TCA cycle. These changes manifested in elevated mitochondrial membrane potential and suppressed superoxide dismutase expression (140). It was also noticed that XCT-790 modulated the p53 and pRB signaling pathways (via ROS involvement) and consequently suppressed cell replication (140). These observations led to the generalization that disrupting ERR α regulated cell cycle mechanisms could modulate tumour suppressor activities and arrest the cell cycle (140). The specific role of ERR α in NSCLCs has not been determined, but studies have demonstrated its involvement in regulating the cell cycle and cell-extracellular matrix interactions. These observations infer likely ERR α involvement in regulating cell proliferation as well as subsequent invasion/migration (metastasis). The mechanism by which ERR α regulates NSCLC cell division and migration is discussed in the following sections.

4. Role of ERR α in cell cycle regulation and NSCLC proliferation

Continuous cell cycling without a G₀ phase is a characteristic of most cancer cells (141). The basis for continuous cell cycling is the uninterrupted positive stimulatory signals from mitogens, such as growth factors, amino acids (cysteine, histidine and glycine), hormones (estrogens, thyroid hormones and human growth hormone), and cytokines (TNF- α and IL-2) (142,143). These signals are accompanied by suppressed inhibitory signals mediated by tumor suppressor proteins including p21, p27, p53, pRB and PTEN.

NSCLC cell culture-based investigations demonstrated ERR α specific inverse agonists/small interfering (si) RNA/shRNA effect cell cycle regulation (144). In one such investigation using NSCLC A549 cells, Wang *et al* (140) noticed significant alterations in mitochondrial mass, mitochondrial membrane potential and mitochondrial reactive oxygen species (ROS) generation following the administration

of the ERR α inverse agonist XCT-790. The ROS produced by XCT-790 activated the tumor suppressor proteins p53 and pRB, which arrested the cell cycle in NSCLC cells (140). These *in vitro* cell culture-based observations suggest that in A549 NSCLC cells, ERR α decreases the tumor suppressor proteins p53 and pRB expression by effecting mitochondrial physiology and quenching ROS generation resulting in unopposed cell-cycle progression (Figs. 3A and 4A). Modulation of multiple signaling pathways by ERR α presents implicit cell-division acceleration strategies, which collectively result in tumor progression (Fig. 4B).

In a recent study, Li *et al* (61) used lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LSCC) cells to study the effects of ERR α knock down. Following ERR α knock down, cell cycle phase (G₁-S-G₂-M) specific distribution of LUAD and LSCC cells were monitored using fluorescence-activated cell sorting (61). The results demonstrated that ERR α knockdown in LUAD leads to cell synchronization at the G₂-M phase transition, but the LSCC cells continued with cell cycle progression (61). These observations infer that ERR α is essential for LUAD cells G₂-M transition and subsequent cell division, but not for LSCC cells, indicating a cell line specific activity (Figs. 3A and 4A) (61).

5. Role of ERR α in NSCLC invasion and migration

Capacity for invasion and migration remains a hallmark of cancer cell metastasis to distant organs (145). Epithelial to mesenchymal transition (EMT) is an important early step in invasion and metastasis (141,145). In course of acquiring mesenchymal phenotypes, tumor cells progressively develop enhanced motility and the ability to invade through the tumor vasculature (Fig. 5). Acquiring mesenchymal status is an important feature of tumor progression, drug resistance and metastasis (146,147). Several transcription factors are involved in EMT including Snail, Slug, Twist and Zeb (146,148). Notable markers of EMT initiation and progression involve activation of multiple cellular signalling pathways including MAPK, PI3K and pro-inflammatory transcription factors, such as NF- κ B (146,149).

In lung cancers, circulating tumour cells expressing epithelial cell adhesion molecules have much lower expression compared with other solid tumours, indicating a loss of epithelial markers (150). The EMT phenotype in NSCLC is associated with EGFR mutations, drug resistance (151-153) and formation of cancer stem cells (154). A number of studies have indicated that EMT related to NSCLC requires immune evasion (155,156). In lung adenocarcinoma, intratumoral CD8⁺ Tc (T cytotoxic) cell suppression is mediated through ZEB1, which activates EMT and represses micro RNA-200, an EMT and programmed death ligand-1 suppressor (157).

In an important study, Chae *et al* (158) analyzed the immune landscape in NSCLCs (adenocarcinoma and squamous cell carcinoma) through EMT scores retrieved from a 16 gene signature of canonical EMT markers (158). Inspection revealed a progressively impaired immune response in cancer, whereby suppressed CD4 T-cells and CD4/CD8-T-cells infiltrations were observed in lung adenocarcinoma and squamous cell carcinoma, respectively (158). The response was characterized by a considerably decreased

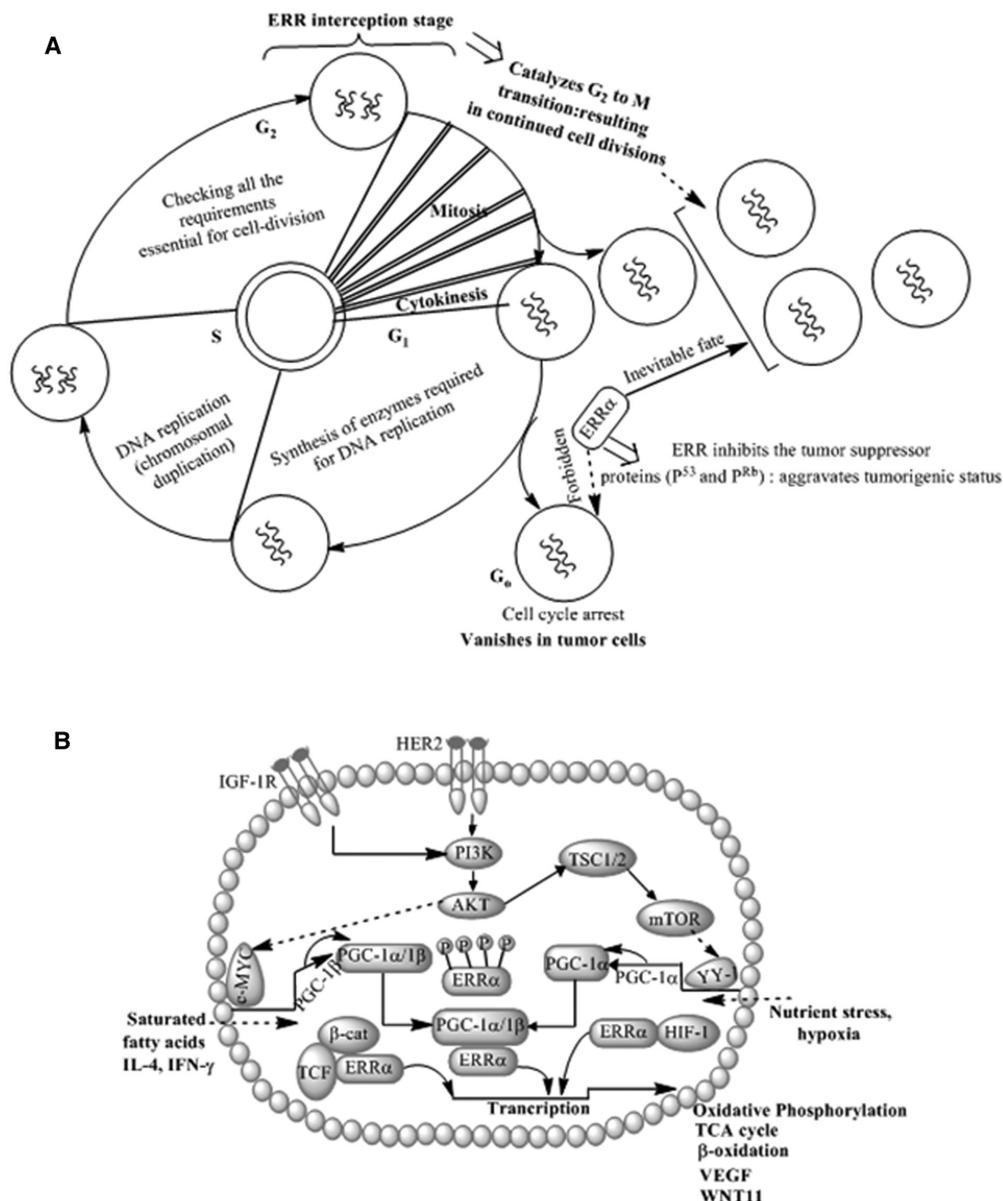


Figure 4. ERR interception of the cell cycle and ERR α /PGC-1 influence on cancer signaling pathways. (A) Prominent ERR effects on cell cycle involve accelerated G₂ to M (mitosis) progression. ERRs dislodge the resting stage (G₀) by stimulating the action of positive factors, culminating in continued cell-divisions. (B) The ERR α /PGC-1 axis (complex) is a prominent suppressor of multiple tumor signaling pathways. PGC-1 α and β are the vital ERR α co-activators and simultaneously function as converging centres for multiple signaling pathways relevant to cancer pathogenesis. Topical research attempts have inferred enhanced PGC-1 β expression via cMYC induction, simultaneously triggered via HER2 activation and insulin like growth factor receptor signaling pathways. Likewise, the switching on of the mTOR/YY-1 pathway secondary to phosphoinositide 3-kinase functional state induces the PGC-1 α expression. Other than cMYC induction and mTOR/YY-1 pathway activation, hypoxia and nutritive stress also function as potential sources of PGC-1 α , while saturated fatty acids and cytokines promote PGC-1 β expression under physiological conditions. The resultant ERR α /PGC-1 α /1 β complex, thereafter, activates the expression of genes corresponding to the TCA cycle, oxidative phosphorylation and numerous other metabolic processes. ERR α has also been revealed to be implicated in interacting with β -cat/TCF complex and HIF-1, exerting a reciprocal modulation on mutual transcriptional activities. Such signaling responses concurrently affect metastasis and angiogenesis. ERR α activity is also affected by the suppressed phosphorylation in the HER2 signaling pathway. ERR, estrogen related receptor; IGF-1, insulin growth factor 1; IGF-1R, insulin growth factor-1 receptor; IL, interleukin; VEGF, vascular endothelial growth factor; HIF-1, hypoxia inducible factor-1; p, phosphorylated; PGC-1, peroxisome proliferator-activated receptor- γ co-activator-1; TSC 1/2, tuberous sclerosis 1/2; HER-2, human epidermal growth factor receptor 2; YY1, Ying Yang 1.

CD4⁺Th cell infiltration in lung adenocarcinoma and of CD4⁺/CD8⁺ Th/Tc cells in squamous cell carcinoma. Additionally, EMT was also found to be associated with enhanced activities of various immunosuppressive cytokines including IL-10 and TGF- β (159,160). The overexpression of targetable immune checkpoint molecules such as CTLA-4 and TIM-3 were noted as being EMT contributory in both NSCLCs. Based on these observations the investigators

conclude that immune exclusion and EMT association drive NSCLC characterization (159,160). The EMT phenotype in NSCLC has been demonstrated as critical not only for tumor progression, but also for poor prognosis (161,162). In a recent study, Thompson *et al* (163) demonstrated the usefulness of an EMT/inflammation signature score in directing checkpoint inhibitor therapy in NSCLC. The results inferred a scenario wherein EMT reversal maybe instrumental in augmenting

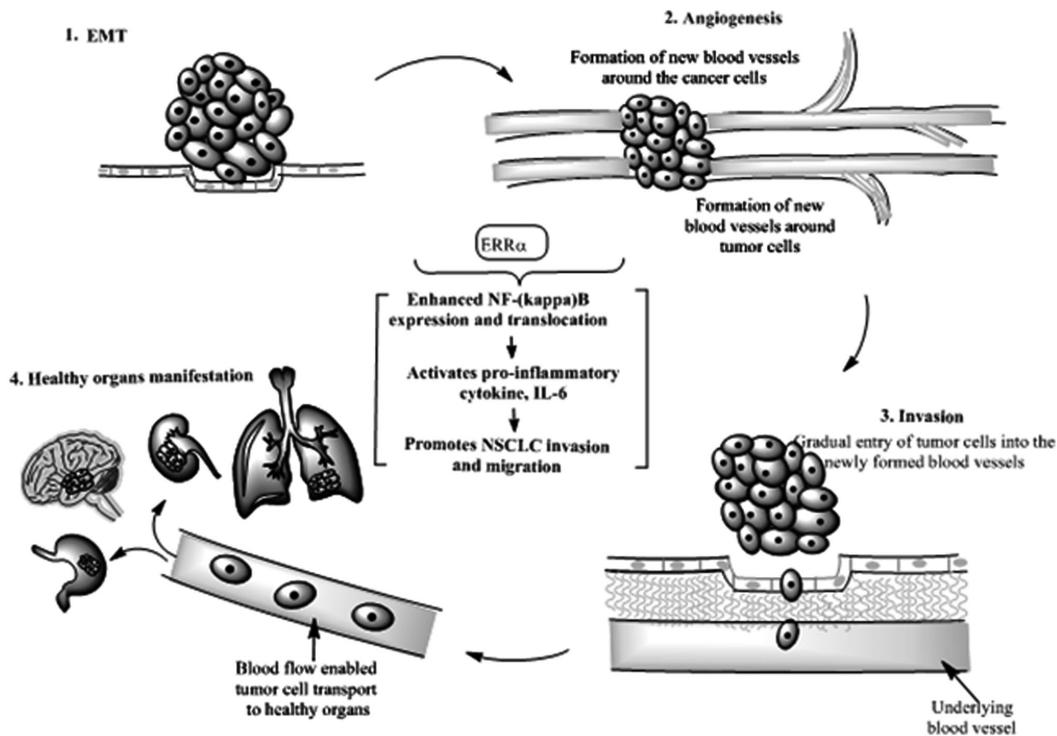


Figure 5. An overview of metastasis mechanism used by primary tumor cells to invade healthy cells in locations other than those of originating tissues. ERR α stimulates metastasis extensively through the NF- κ B mediated pro-inflammatory cytokine IL-6 activation mediated transition from epithelial to mesenchymal regime. Two notable studies from 2014 and 2018 shed light on ERR α aggravated EMT, with the former by Huang *et al* (164) reported treatment of A549 NSCLC cells with ERR α inverse agonist, XCT-790 causing suppressed E-cadherin and zonula occludens-1 (noted epithelial markers) and aggravated fibronectin and vimentin (mesenchymal markers), expression. Zhang *et al* (165) noticed ERR α aggravated NF- κ B expression and translocation which in turn activated the pro-inflammatory cytokine, IL-6 expression. Other studies have reported enhanced IL-6 expression in di (2-ethylhexyl) phthalate (DEHP)-induced NSCLC migration and invasion (166,167). Hence, enhanced ERR α modulates the environment around the tumor by enhanced expression of matrix proteins whereby access of chemotherapeutic drugs to the tumor is prevented, resulting in enhanced tumor growth. ERR, estrogen related receptor; NSCLC, non-small cell lung cancer; EMT, epithelial mesenchymal transition; IL, interleukin.

the efficacy of immune checkpoint blockade (163). However, since EMT is a dynamic and highly fluid process, confirmatory studies are needed to ascertain the therapeutic efficacy of EMT inhibitors on NSCLC complications.

Several studies have now reported ERR α involvement in NSCLC EMT. Huang *et al* (164) treated A549 NSCLC cells with ERR α inverse agonist XCT-790 and examined its effect on markers of epithelial cells, mesenchymal cells and various transcription factors. Analysis revealed ERR α involvement in EMT, as demonstrated by suppression of the epithelial makers, E-cadherin and zonula occludens-1, increased fibronectin, and vimentin (mesenchymal makers), and Slug activation (163). In a subsequent investigation, Zhang *et al* (165) observed ERR α induces pro-inflammatory transcription factor NF- κ B activation and translocation from cytoplasm to nucleus, which in turn led to the expression of the pro-inflammatory cytokine, IL-6 (165). Notably, it was previously demonstrated that IL-6 upregulation is implicated in di (2-ethylhexyl) phthalate (DEHP)-induced NSCLC migration and invasion (166,167). Another recent investigation by Li *et al* (61) involving LUAD cells and using scratch wound healing and transmigration invasion assays demonstrated ERR α involvement in proliferation, invasion and migration. The investigators noted higher ERR α expression in lung cancer tissues in mouse models and advanced lymph node metastasis and tumor stage(s), signifying a positive association between ERR α expression and LUAD complexity (61).

6. Conclusions and future perspective

While the role of ERs in NSCLC is established, that of ERRs in NSCLC is only beginning to be elucidated. A body of literature has recently developed that suggests an important role of ERRs in the development and progression of various cancers including NSCLCs. In particular, ERR α expression by cancer cells has emerged as an important prognostic indicator associated with poor survival in several cancers including NSCLC (129,130,132). In contrast, the role of ERR β and ERR γ in NSCLC remains unknown, due to undetectable low level or null expression of these molecules in adult mammalian lungs (133). A number of antiERR α molecules have been developed, including diethylstilbestrol (DES), that bind to ERR α and inhibit its activity (83). At present, most of the studies of the effects of ERR α modulation in NSCLC are based on *in vitro* cell culture experiments (129-131,162-164). It is now imperative that the molecular mechanisms by which ERR α promotes NSCLC development and progression be examined using *in vivo* models (137,162-164). The implicit involvement of ERR α in NSCLCs could be screened using ERR α antagonists or activating ERR α dependent signaling pathways using specific agonists. In this age of individualized medicine, the effects of antiERR molecules alone or in combination with aromatase inhibitors (e.g. anastrozole), selective estrogen receptor modulators (SERMs e.g. tamoxifen) or selective estrogen receptor down regulators (SERDs e.g. fulvestrant) should be evaluated in specific NSCLC types.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TKM conceptualized the basic theme of the manuscript, prepared the first draft of the manuscript and suggested the contents of figures and tables. PM compiled the information about the physiological functions of estrogen related receptors (ERRs) and the specific role of $ERR\alpha$ in cell cycle regulation, NSCLC proliferation and the role of $ERR\alpha$ in NSCLC and migration after discussion and gaining inputs from TKM. TKM and PM addressed the reviewer's comments. JRH participated in manuscript development, particularly in the writing of the lung cancer statistics in males vs. females and the role of epithelial to mesenchymal transition in lung cancer metastasis. JRH also scrutinized, corrected and approved the finalized manuscript in the initial and revised versions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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