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

TAPAN K. MUKHERJEE[1-3], PARTH MALIK[4] and JOHN R. HOIDAL[1-3]

[1]Division of Respiratory, Critical Care and Occupational Pulmonary Medicine and [2]Department of Internal Medicine, University of Utah; [3]George E. Wahlen Department of Veterans Affairs Medical Centre, Salt Lake City, UT 84132, USA; [4]School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat 382030, India

Received July 6, 2020; Accepted November 18, 2020

DOI: 10.3892/ol.2021.12519

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 (ERRα), 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 ERRα expression is significantly higher compared with healthy individuals. It is well established ERα and ERβ, have 93% and 60% identity in the DNA and ligand binding domains, respectively. ERα and ERRα have 69% (70% with ERRα-1) and 34% (35% with ERRα-1) identity, respectively; ERRα and ERRβ, have 92 and 61% identity, respectively. However, whether there is distinctive ERRα interaction with mammalian estrogens or concurrent involvement in non-ER signalling pathway activation is not known. Relevant to NSCLC, ERRα promotes proliferation, invasion and migration by silencing the tumor suppressor proteins p53 and pRB, and accelerates G_2-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 ERRα activates NSCLC metastasis. Based on these observations, the present article focuses on the feasibility of antiERRα therapy alone and in combination with antiER as a therapeutic strategy for NSCLC complications.

Correspondence to: Dr Tapan K. Mukherjee, Division of Respiratory, Critical Care and Occupational Pulmonary Medicine, Wintrobe Building, University of Utah, Salt Lake City, UT 84132, USA
E-mail: tapan400@gmail.com

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; PD1, 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 receptorα; ESRRB, estrogen related receptorβ; ESRRG, estrogen related receptorγ; 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; PPARγ, 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

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: ERα and ERβ) 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 (ERRα) and estrogen-related receptor β (ERRβ) (51). A third isoform of ERR, ERR-γ (ERRγ) 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 ERRγ.

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 ERRα activity may serve critical roles in disease progression

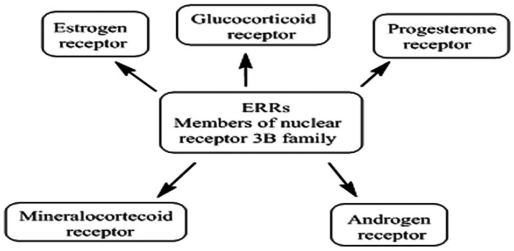

Figure 1. Compositional description of ERRs including estrogen receptors, progesterone receptors, androgen receptors, mineralocorticoid and glucocorticoid receptors. The multiple activities of physiological sustenance infer the significance of ERRs in maintaining homeostasis and regulating the normal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

as well as homeostasis (62). No endogenous ligand for ERRα 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 ERRα 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, ERRα and ERRβ, using the ERα 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, ERRγ. 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*, ERRα), ESRRB (*NR3B2*, ERRβ) and G (*NR3B3*, ERRγ) (70). Several ERRβ and ERRγ 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 ERRα and ERα (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 ERRα, 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 sumolyation 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 hetrodimers 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 PPARα/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 ERRα 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 ERRα 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 ERRα and ERRγ 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 ERRα 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 PPARγ co-activator-1α peptide (84). Of note, PPARγ 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 ERRγ and of ~100 cubic Å in ERRα, allowing transcriptional intervention by synthetic molecules (85-89).

ERs (ERα and ERβ) 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 17β-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-κB, 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

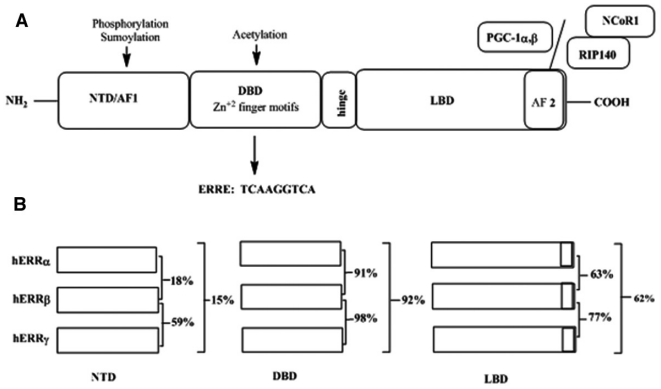

Figure 2. Structural and compositional profile of ERRs. (A) Constitutional binding domains of ERRs. It is notable to observe that DBD and LBD are intervened by a distinctive hinge region, unlike NTD and DBD which interact with each other to a greater extent. Sumoylation refers to post-translational protein 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 CH_3-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 ERRβ and ERRγ share greater sequence conservation compared with ERRα and ERRβ, 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 ERα, ERRα binds to the classical ERE of estrogen responsive genes, characterized by 5'-AGGTCANNNTGA CCT-3' sequence (N denoting a typical nucleotide) (106). ERRα 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, ERRα can affect ERα transcriptional activity. Although ERR dimers can bind to the ERE, ERα dimers (not those of ERβ) 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).

ERRα 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 ERRα, ERRβ and ERRγ expression is much more restricted, with heart and kidney being the major sites (125,126). Expression of both ERRα and ERRγ 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, ERRβ and ERRγ are expressed during early embryonic development (129-131).

Specific roles for each ERR were demonstrated using ERR specific knockout (KO) mice (132-134). ERRα 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). ERRα 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). ERRα KO mice also exhibit a loss of normal mitochondrial biogenesis (134). In contrast, ERRβ KO mice are lethal due to impaired placenta formation (130). ERRγ 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 ERRα is detected in the lung, the exact physiologic role of ERRα in the lung is not known. ERRβ and ERRγ, have not yet been detected in lung tissues (136).

3. ERRs in NSCLCs

In recent years, several studies have reported a close association between ERRα 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 ERRα 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 ERRα expression was a hallmark of metabolically active organs, such as the heart, liver and brain (128,132,134). Low ERRα expression was detected in several other organs including lung (51). Subsequently, using embryonic and adult

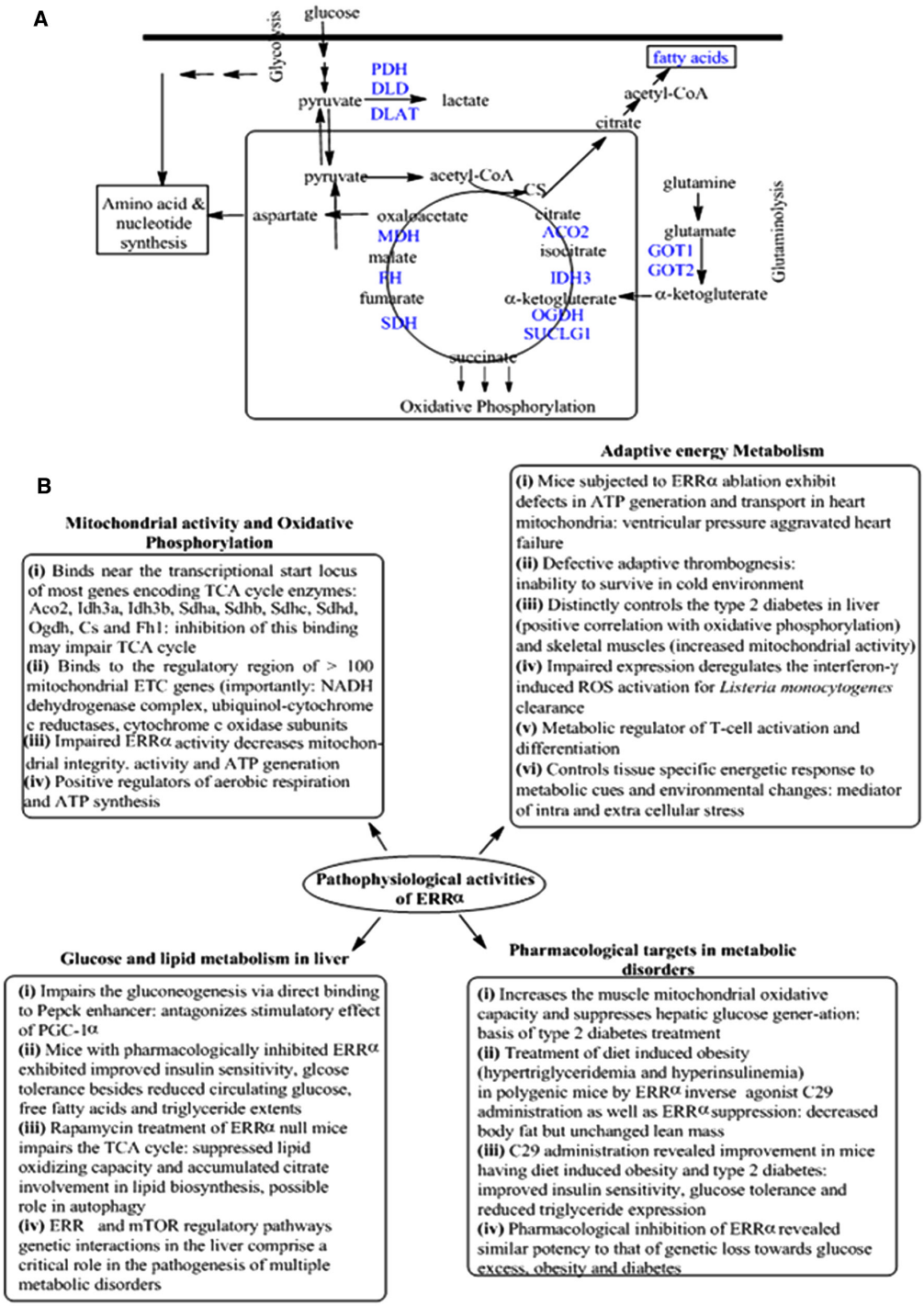

Figure 3. Pathological and physiological significance of ERRα. (A) Regulation of mitochondrial energy production and oxidative phosphorylation, hepatic metabolism of glucose and lipids, distinctive control of type 2 diabetes in liver and skeletal muscles and implication as potential therapeutic target 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, oxaglutarate.

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

First author, year	ERRα	ERRβ	ERRγ	(Refs.)
Deblois and Giguere, 2013; Gravel, 2018	• 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	• 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	• Affects the tumor growth *via* 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

First author, year	ERRα	ERRβ	ERRγ	(Refs.)
Audet-Walsh *et al*, 2015	• Enhanced expression promotes the tumor development: Serves as a vital prognostic factor	• 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	• 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.

C, Ovarian cancer

First author, year	ERRα	ERRβ	ERRγ	(Refs.)
Sun *et al*, 2005	• 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	• 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	• 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	ERRα	ERRβ	ERRγ	(Refs.)
Kang *et al*, 2018	• No significant observation reported to date	• No significant observation reported to date	• 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	ERRα	ERRβ	ERRγ	(Refs.)
Kim *et al*, 2016; Pons *et al*, 2005	• No significant correlation with tumor growth was noticed	• No significant correlation with tumor growth was noticed	• Aggravating factor for advanced tumor node metastasis and Barcelona Clinic Liver Cancer Stages	(120,121)

Table I. Continued.

E, Hepatocellular carcinoma				
First author, year	ERRα	ERRβ	ERRγ	(Refs.)
			• Treatment with siRNA or inverse agonist (GSK5182) inhibited the cell cycle proliferation *via* G_1 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	ERRα	ERRβ	ERRγ	(Refs.)
Zhou *et al*, 2019	• Interaction with ovarian tumor domain comprising OTUB1 promoter • Promotes metastasis *via* inducing vimentin expression • OTUB1 could therefore be used as a novel ERRα target	• No significant involvement was noticed	• 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 I; ER, estrogen; PGC, peroxisome proliferator-activated receptor-γ; CK1, cyclin-dependent kinase inhibitor.

samples, indicating possible diagnostic or post-therapeutic prognostic roles of ERRα in NSCLC (91,138-140). One study elucidated a cell-specific ERRα transactivator functioning though SFRE sequence, wherein ERRα 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 ERRα functioning were due to the osteopontin gene promoter as a transcription regulating target for ERRα (138). Pettersson *et al* (139) obbserved the expression of nuclear receptors in embryonal carcinoma stem cells. This study found that adequate homodimerization and DNA binding of mERRβ 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 mERRβ 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 ERRα via studying the effect of administered XCT-790, an ERRα 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 ERRα regulated cell cycle mechanisms could modulate tumour suppressor activities and arrest the cell cycle (140). The specific role of ERRα 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 ERRα involvement in regulating cell proliferation as well as subsequent invasion/migration (metastasis). The mechanism by which ERRα regulates NSCLC cell division and migration is discussed in the following sections.

4. Role of ERRα in cell cycle regulation and NSCLC proliferation

Continuous cell cycling without a G_0 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 ERRα 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 ERRα 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, ERRα 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 ERRα 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 ERRα knock down. Following ERRα knock down, cell cycle phase (G_1-S-G_2-M) specific distribution of LUAD and LSCC cells were monitored using fluorescence-activated cell sorting (61). The results demonstrated that ERRα knockdown in LUAD leads to cell synchronization at the G_2-M phase transition, but the LSCC cells continued with cell cycle progression (61). These observations infer that ERRα is essential for LUAD cells G_2-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 ERRα 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-κB (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

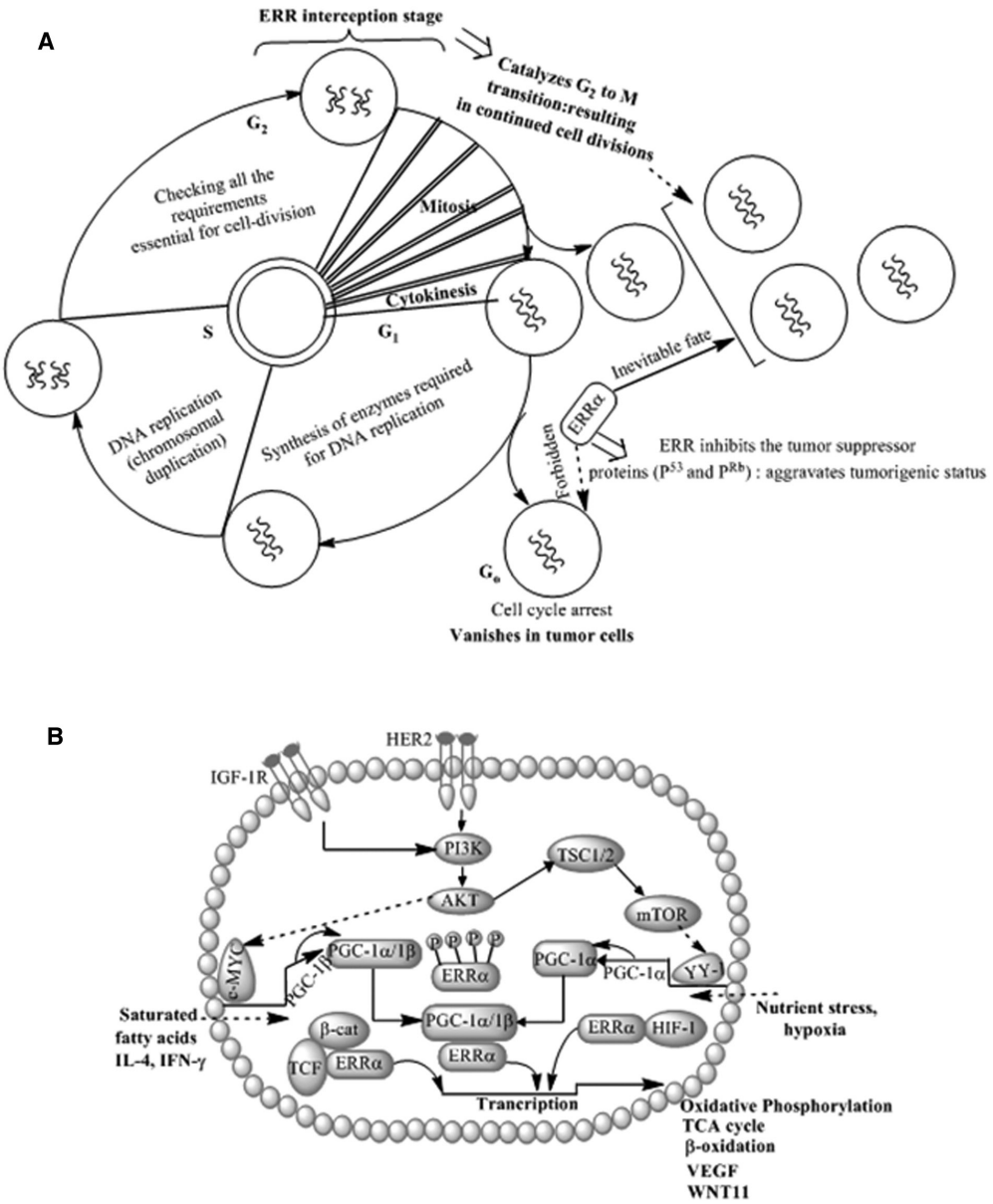

Figure 4. ERR interception of the cell cycle and ERRα/PGC-1 influence on cancer signaling pathways. (A) Prominent ERR effects on cell cycle involve accelerated G_2 to M (mitosis) progression. ERRs dislodge the resting stage (G_0) by stimulating the action of positive factors, culminating in continued cell-divisions. (B) The ERRα/PGC-1 axis (complex) is a prominent suppressor of multiple tumor signaling pathways. PGC-1α and β are the vital ERRα co-activators and simultaneously function as converging centres for multiple signaling pathways relevant to cancer pathogenesis. Topical research attempts have inferred enhanced PGC-1β 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-1α expression. Other than cMYC induction and mTOR/YY-1 pathway activation, hypoxia and nutritive stress also function as potential sources of PGC-1α, while saturated fatty acids and cytokines promote PGC-1β expression under physiological conditions. The resultant ERRα/PGC-1α/1β complex, thereafter, activates the expression of genes corresponding to the TCA cycle, oxidative phosphorylation and numerous other metabolic processes. ERRα 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. ERRα 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

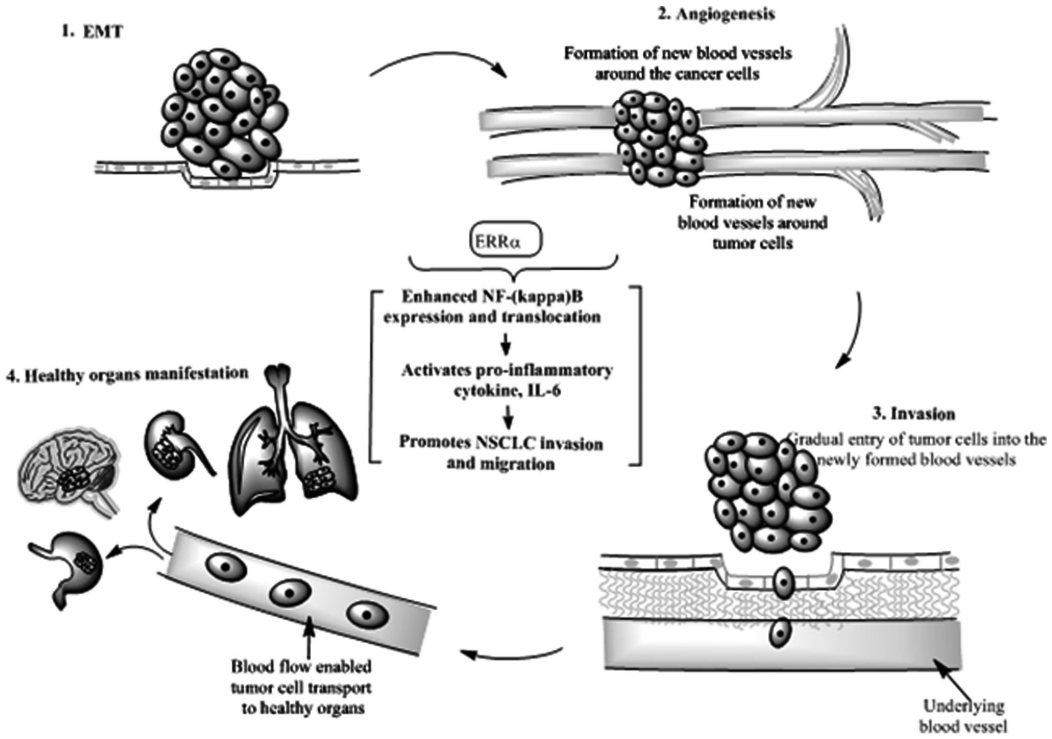

Figure 5. An overview of metastasis mechanism used by primary tumor cells to invade healthy cells in locations other than those of originating tissues. ERRα stimulates metastasis extensively through the NF-κB mediated pro-inflammatory cytokine IL-6 activation mediated transition from epithelial to mesenchymal regime. Two notable studies from 2014 and 2018 shed light on ERRα aggravated EMT, with the former by Huang *et al* (164) reported treatment of A549 NSCLC cells with ERRα 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 ERRα aggravated NF-κB 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 ERRα 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 ERRα involvement in NSCLC EMT. Huang *et al* (164) treated A549 NSCLC cells with ERRα inverse agonist XCT-790 and examined its effect on markers of epithelial cells, mesenchymal cells and various transcription factors. Analysis revealed ERRα 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 ERRα induces pro-inflammatory transcription factor NF-κB 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 ERRα involvement in proliferation, invasion and migration. The investigators noted higher ERRα expression in lung cancer tissues in mouse models and advanced lymph node metastasis and tumor stage(s), signifying a positive association between ERRα 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, ERRα 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 ERRβ and ERRγ in NSCLC remains unknown, due to undetectable low level or null expression of these molecules in adult mammalian lungs (133). A number of antiERRα molecules have been developed, including diethylstilbestrol (DES), that bind to ERRα and inhibit its activity (83). At present, most of the studies of the effects of ERRα 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 ERRα promotes NSCLC development and progression be examined using *in vivo* models (137,162-164). The implicit involvement of ERRα in NSCLCs could be screened using ERRα antagonists or activating ERRα 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. anastrazole), 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.

Acknowledgements

Not applicable.

Funding

The present study was supported by a grant from the Renzetti Presidential Endowed Chair, Department of Internal Medicine, University of Utah, USA.

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 ERRα in cell cycle regulation, NSCLC proliferation and the role of ERRα 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.

References

1. International Agency for Research on Cancer (IARC): GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide, 2013.
2. Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C and Negri E: European cancer mortality predictions for the year 2017, with focus on lung cancer. Ann Oncol 28: 1117-1123, 2017.
3. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, Mariotto A, Lake AJ, Wilson R, Sherman RL, *et al*: Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst 109: djx030, 2017.
4. Herbst RS, Morgensztern D and Boshoff C: The biology and management of non-small cell lung cancer. Nature 553: 446-454, 2018.
5. Morgensztern D, Ng SH, Gao F and Govindan R: Trends in stage distribution for patients with non-small cell lung cancer: A National cancer database survey. J Thorac Oncol 5: 29-33, 2010.
6. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69: 7-34, 2019.
7. Jemal A, Miller KD, Ma J, Siegel RL, Fedewa SA, Farhad I, Devesa SS and Thun MJ: Higher lung cancer incidence in young women than young men in the United States. N Engl J Med 378: 1999-2009, 2018.
8. Ragavan MV and Patel MI: Understanding sex disparities in lung cancer incidence: Ar women more at risk? Lung Cancer Manag 9: LMY34, 2020.
9. Yuan Y, Liu L, Chen H, Wang Y, Xu Y, Mao H, Li J, Mills GB, Shu Y, Li L and Liang H: Comprehensive characterization of molecular differences in cancer between male and female patients. Cancer Cell 29: 711-722, 2016.
10. Xia B, Feldman R, Cozen W, Kang I, Raez LE, Borghaei H, Kim C, Nagasaka M, Mamdani H, Vanderwalde AM, *et al*: Sex disparities in hormone positive lung cancer. J Clin Oncol 38 (15_suppl): e21552, 2020.
11. Fidler-Benaoudia MM, Torre LA, Bray F, Ferlay J and Jemal A: Lung cancer incidence in young women vs. young men: A systematic analysis in 40 countries. Int J Cancer 147: 811-819, 2020.
12. Skov BG, Fischer BM and Pappot H: Oestrogen receptor beta over expression in males with non-small cell lung cancer is associated with better survival. Lung Cancer 59: 88-94, 2008.
13. Greiser CM, Greiser EM and Dören M: Menopausal hormone therapy and risk of lung cancer: Systematic review and meta-analysis. Maturitas 65: 198-204, 2010.
14. Adami HO, Persson I, Hoover R, Schairer C and Bergkvist L: Risk of cancer in women receiving hormone replacement therapy. Int J Cancer 44: 833-839, 1989.
15. Risch HA, Howe GR, Jain M, Burch JD, Holowaty EJ and Miller AB: Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. Am J Epidemiol 138: 281-293, 1993.
16. Mollerup S, Berge G, Baera R, Skaug V, Hewer A, Phillips DH, Stangeland L and Haugen A: Sex differences in risk of lung cancer: Expression of genes in the PAH bioactivation pathway in relation to smoking and bulky DNA adducts. Int J Cancer 119: 741-744, 2006.
17. Klugman M, Xue X and Hosgood HD III: Race/ethnicity and lung cancer survival in the United States: A meta-analysis. Cancer Causes Control 30: 1231-1241, 2019.
18. Schabath MB, Cress D and Muñoz-Antonia T: Racial and ethnic differences in the epidemiology and genomics of lung cancer. Cancer Control 23: 338-346, 2016.
19. Izbicka E, Streeper RT, Michalek JE, Louden CL, Diaz A III and Campos DR: Plasma biomarkers distinguish non-small cell lung cancer from asthma and differ in men and women. Cancer Genomics Proteomics 9: 27-35, 2012.
20. Hastings RH, Laux AM, Casillas A, Xu R, Lukas Z, Ernstrom K and Deftos LJ: Sex-specific survival advantage with parathyroid hormone-related protein in non-small cell lung carcinoma patients. Clin Cancer Res 12: 499-506, 2006.
21. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, Yang ZY, Mao C and Tang JL: The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. Oncotarget 7: 78985-78993, 2016.
22. Kim HR, Shim HS, Chung JH, Lee YJ, Hong YK, Rha SY, Kim SH, Ha SJ, Kim SK, Chung KY, *et al*: Distinct clinical features and outcomes in never-smokers with nonsmall cell lung cancer who harbor EGFR or KRAS mutations or ALK rearrangement. Cancer 118: 729-739, 2012.
23. Patel MI, McKinley M, Cheng I, Haile R, Wakelee H and Gomez SL: Lung cancer incidence trends in California by race/ethnicity, histology, sex and neighbourhood socioeconomic status: An analysis spanning 28 years. Lung Cancer 108: 140-149, 2017.
24. Chang CH, Lee CH, Ho CC, Wang JY and Yu CJ: Sex-based impact of epidermal growth factor receptor mutation in patients with non-small cell lung cancer and previous tuberculosis. Medicine (Baltimore) 94: e444, 2015.
25. Wang C, Qiao W, Jiang Y, Zhu M, Shao J, Ren P, Liu D and Li W: Effect of sex on the efficacy of patients receiving immune checkpoint inhibitors in advanced non-small cell lung cancer. Cancer Med 8: 4023-4031, 2019.
26. Pinto JA, Vallejos CS, Raez LE, Mas LA, Ruiz R, Torres-Roman JS, Morante Z, Araujo JM, Gomez HL, Aguilar A, *et al*: Sex and outcomes in non-small cell lung cancer: An old prognostic variable comes back for targeted therapy and immunotherapy? ESMO Open 3: e000344, 2018.
27. Nelson R: ALK inhibitors: Possible new treatment for lung cancer. Medscape Medical News AACR-IASLC Joint Conference on Molecular Origins of Lung Cancer, Jan 15, 2010.

28. Wang WC, Shiao HY, Lee CC, Fung KS and Hsieh HP: Anaplastic lymphnoma kinase (ALK) inhibitors: A review of deign and discovery. Med Chem Comm 5: 1266-1279, 2014.
29. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, *et al*: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353: 123-132, 2005.
30. Yim SH and Chung YJ: Molecular epidemiology of female lung cancer. Cancers (Basel) 3: 1861-1876, 2011.
31. Guinee DG Jr, Travis WD, Trivers GE, De Benedetti VM, Cawley H, Welsh JA, Bennett WP, Jett J, Colby TV, Tazelaar H, *et al*: Sex comparisons in human lung cancer: Analysis of p53 mutations, anti-p53 serum antibodies and C-erbB-2 expression. Carcinogenesis 16: 993-1002, 1995.
32. Kure EH, Ryberg D, Hewer A, Phillips DH, Skaug V, Baera R and Haugen A: p53 mutations in lung tumours: Relationship to sex and lung DNA adduct levels. Carcinogenesis 17: 2201-2205, 1996.
33. Rivlin N, Brosh R, Oren M and Rotter V: Mutations in the p53 tumor suppressor gene. Genes Cancers 2: 466-474, 2011.
34. Rivera MP: Lung cancer in women: Differences in epidemiology, biology, histology and treatment outcomes. Semin Respir. Crit Care Med 34: 792-801, 2013.
35. Stocco C: Tissue physiology and pathology of aromatase. Steroids 77: 27-35, 2012.
36. Barakat R, Oakley O, Kim H, Jin J and Ko CJ: Extra-gonadal sites of estrogen biosynthesis and function. BMV Rep 49: 488-496, 2016.
37. Hammes SR and Levin ER: Impact of estrogens in males and androgens in females. J Clin Invest 129: 1818-1826, 2019.
38. Reckelhoff JF: Sex differences in the regulation of blood pressure. Hypertension 37: 1199-1208, 2001.
39. Blenck CL, Harvey PA, Reckelhoff JF and Leinwand LA: The importance of biological sex and estrogen in rodent models of cardiovascular health and disease. Circ Res 118: 1294-1312, 2016.
40. Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, Speed C and Jones M: Aromatase-A brief Overview. Ann Rev Physiol 64: 93-127, 2002.
41. Weinberg OK, Marquez-Garban DC, Fishbein MJ, Goodglick L, Garban HJ, Dubinett SM and Pietras RJ: Aromatase inhibitors in human lung cancer therapy. Cancer Res 65: 11287-11291, 2005.
42. Mollerup S, Jørgensen K, Berge G and Haugen A: Expression of estrogen receptors alpha and beta in human lung tissue and cell lines. Lung Cancer 37: 153159, 2002.
43. Stabile LP, Davis AL, Gubish CT, Hopkins TM, Luketich JD, Christie N, Finkelstein S and Siegfried JM: Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. Cancer Res 62: 2141-2150, 2002.
44. Carey MA, Card JW, Voltz JW, Germolec DR, Korach KS and Zeldin DC: The impact of sex and sex hormones on lung physiology and disease: Lessons from animal studies. Am J Physiol Lung Cell Mol Physiol 293: L272-L278, 2007.
45. Brandenberger AW, Tee MK, Lee JY, Chao V and Jaffe RB: Tissue distribution of estrogen receptors alpha (ER-alpha) and beta (ER-beta) mRNA in the midgestational human fetus. J Clin Endocrinol Metab 82: 3509-3512, 1997.
46. Márquez-Garbán DC, Chen HW, Fishbein MC, Goodglick L and Pietras RJ: Estrogen receptor signaling pathways in human non-small cell lung cancer. Steroids 72: 135-143, 2007.
47. Baik CS and Eaton KD: Estrogensignaling in lung cancer: An opportunity for novel therapy. Cancers (Basel) 4: 969-988, 2012.
48. Hsu LH, Liu KJ, Tsai MF, Wu CR, Feng AC, Chu NM and Kao SH: Estrogen adversely affects the prognosis of patients with lung adenocarcinoma. Cancer Sci 106: 51-59, 2015.
49. Heilbroner SP, Xanthopoulos EP, Buono D, Huang Y, Carrier D, Shah A, Kim J, Corradetti M, Wright JD, Neugut AI, *et al*: Impact of estrogen monotherapy on survival in women with stage III-IV non-small cell lung cancer. Lung Cancer 129: 8-15, 2019.
50. Garon EB, Siegfried JM, Stabile LP, Young PA, Marquez-Garban DC, Park DJ, Patel R, Hu EH, Sadeghi S, Parikh RJ, *et al*: Randomized phase II study of fulvestrant and erlotinib compared with erlotinib alone in patients with advanced or metastatic non-small cell lung cancer. Lung Cancer 123: 91-98, 2018.
51. Giguere V, Yang N, Segui P and Evans RM: Identification of a new class of steroid hormone receptors. Nature 331: 91-94, 1988.
52. Eudy JD, Yao S, Weston MD, Ma-Edmonds M, Talmadge CB, Cheng JJ, Kimberling WJ and Sumegi J: Isolation of a gene encoding a novel member of the nuclear receptor superfamily from the critical region of Usher syndrome type IIa at 1q41. Genomics 50: 382-384, 1998.
53. Hong H, Yang L and Stallcup MR: Hormone-independent transcriptional activation and coactivator binding by novel orphan nuclear receptor ERR3. J Biol Chem 274: 22618-22626, 1999.
54. Lata K and Mukherjee TK: Knockdown of receptor for advanced glycation end products attenuate 17α-ethinyl-estradiol dependent proliferation and survival of MCF-7 breast cancer cells. Biochim Biophys Acta 1840: 1083-1091, 2014.
55. Riggins RB, Lan JP, Zhu Y, Klimach U, Zwart A, Cavalli LR, Haddad BR, Chen L, Gong T, Xuan J, *et al*: ERRgamma mediates tamoxifen resistance in novel models of invasive lobular breast cancer. Cancer Res 68: 8908-8917, 2008.
56. Manna S, Bostner J, Sun Y, Miller LD, Alayev A, Schwartz NS, Lager E, Fornander T, Nordenskjöld B, Yu JJ, *et al*: ERRα is a marker of tamoxifen response and survival in triple-negative breast cancer. Clin Cancer Res 22: 1421-1431, 2016.
57. Lam SS, Mak AS, Yam JW, Cheung AN, Ngan HY and Wong AS: Targeting estrogen-related receptor alpha inhibits epithelial-to-mesenchymal transition and stem cell properties of ovarian cancer cells. Mol Ther 22: 743-751, 2014.
58. Yoriki K, Mori T, Kokabu T, Matsushima H, Umemura S, Tarumi Y and Kitawaki J: Estrogen-related receptor alpha induces epithelial-mesenchymal transition through cancer-stromal interactions in endometrial cancer. Sci Rep 9: 6697, 2019.
59. Fujimura T, Takahashi S, Urano T, Ijichi N, Ikeda K, Kumagai J, Murata T, Takayama K, Horie-Inoue K, Ouchi Y, *et al*: Differential expression of estrogen-related receptors beta and gamma (ERRbeta and ERRgamma) and their clinical significance in human prostate cancer. Cancer Sci 101: 646-651, 2010.
60. Liang R, Lin Y, Yuan CL, Liu ZH, Li YQ, Luo XL, Ye JZ and Ye HH: High expression of estrogen-related receptor α is significantly associated with poor prognosis in patients with colorectal cancer. Oncol Lett 15: 5933-5935, 2018.
61. Li P, Wang J, Wu D, Ren X, Wu W, Zuo R, Zeng Q, Wang B, He X, Yuan J and Xie N: ERRα is an aggressive factor in lung adenocarcinoma indicating poor prognostic outcomes. Cancer Manag Res 11: 8111-8123, 2019.
62. Ariazi EA and Jordan VC: Estrogen-related receptors as emerging targets in cancer and metabolic disorders. Curr Top Med Chem 6: 203-215, 2006.
63. Busch BB, Stevens WC Jr, Martin R, Ordentlich P, Zhou S, Sapp DW, Horlick RA and Mohan R: Identification of a selective inverse agonist for the orphan nuclear receptor estrogen-related receptor alpha. J Med Chem 47: 5593-5596, 2004.
64. Willey PJ, Murray IR, Qian J, Busch BB, Stevens WC Jr, Martin R, Mohan R, Zhou S, Ordentlich P, Wei P, *et al*: Regulation of PPARgamma coactivator 1alpha (PGC-1alpha) signaling by an estrogen-related receptor alpha (ERRalpha) ligand. Proc Natl Acad Sci USA 101: 8912-8917, 2004.
65. Chisamore MJ, Cunningham ME, Flores O, Wilkinson HA and Chen JD: Characterization of a novel small molecule subtype specific estrogen-related receptor alpha antagonist in MCF-7 breast cancer cells. PLoS One 4: e5624, 2009.
66. Teng CT, Beames B, Merrick BA, Martin N, Romeo C and Jetten AM: Development of a stable cell line with an intact PGC-1α/ERRα axis for screening environmental chemicals. Biochem Biophys Res Commun 444: 177-181, 2014.
67. Teng CT, Hsieh JH, Zhao J, Huang R, Xia M, Martin N, Gao X, Dixon D, Auerbach SS, Witt KL and Merick BA: Development of novel cell lines for high-throughput screening to detect estrogen-related receptor alpha modulators. SLAS Discov 22: 720-731, 2017.
68. Wei W, Schwaid AG, Wang X, Wang X, Chen S, Chu Q, Saghatelian A and Wan Y: Ligand activation of ERRα by cholesterol mediates statin and bisphosphonate effects. Cell Metab 23: 479-491, 2016.
69. Nuclear Receptors Nomenclature Committee: A unified nomenclature system for the nuclear receptor superfamily. Cell 97: 161-163, 1999.
70. Tremblay AM and Giguere V: The NR3B subgroup: An ovERRview. Nucl Recept Signal 5: e009, 2007.
71. Heard DJ, Norby PL, Holloway J and Vissing H: Human ERRgamma, a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: Tissue-specific isoforms are expressed during development and in the adult. Mol Endocrinol 14: 382-392, 2000.
72. Laudet V, Hänni C, Coll J, Catzeflis F and Stéhelin D: Evolution of the nuclear receptor gene superfamily. EMBO J 11: 1003-1013, 1992.

73. Huss JM, Garbacz W and Xie W: Constitutive activities of estrogen related receptors: Transcriptional regulation of metabolism by the ERR pathways in health and disease. Biochim Biophys Acta 1852: 1912-1927, 2015.
74. Tremblay AM, Wilson BJ, Yang XJ and Giguere V: Phosphorylation-dependent sumoylation regulates estrogen-related receptor-alpha and-gamma transcriptional activity through a synergy control motif. Mol Endocrinol 22: 570-584, 2008.
75. Vu EH, Kraus RJ and Mertz JE: Phosphorylation-dependent sumoylation of estrogen-related receptor-alpha1. Biochemistry 46: 9795-9804, 2007.
76. Gearhart MD, Hombeck SM, Evans RM, Dyson HJ and Wright PE: Monomeric complex of human orphan estrogen related receptor-2 with DNA: A pseudo-dimer interface mediates extended half-site recognition. J Mol Biol 327: 819-832, 2003.
77. Huppunen J and Aarnisalo P: Dimerisation modulates the activity of the orphan nuclear receptor ERRgamma. Biochem. Biophys Res Commun 314: 964-970, 2004.
78. Oka SI, Zhai P, Alcendor R, Park JY and Sadoshima J: Suppression of ERR targets by a PPARα/Sirt1 complex in the failing heart. Cell Cycle 11: 856-864, 2012.
79. Onofrio ND, Servillo L and Balestrieri ML: SIRT1 and SIRt6 signaling pathways in cardiovascular diseases protection. Antioxid Redox Signal 28: 711-732, 2018.
80. Wang C, Fu M and Pestell RG: Estrogen receptor acetylation and phosphorylation in hormone responses. Br Cancer Online 8: e46, 2005.
81. Wilson BJ, Tremblay AM, Deblois G, Sylvain-Drolet G and Giguere V: An acetylation switch modulates the transcriptional activity of estrogen-related receptor alpha. Mol Endocrinol 24: 1349-1358, 2010.
82. Chen S, Zhou D, Yang C and Sherman M: Molecular basis for the constitutive activity of estrogen-related receptor alpha-1. J Biol Chem 276: 28465-28470, 2001.
83. Xie W, Hong H, Yang NN, Lin RJ, Simon CM, Stallcup MR and Evans RM: Constitutive activation of transcription and binding of coactivator by estrogen-related receptors 1 and 2. Mol Endocrinol 13: 2151-2162, 1999.
84. Kallen J, Schlaeppi JM, Bitsch F, Filipuzzi I, Schib A, Riou V, Graham A, Strauss A, Geiser M and Foumier B: Evidence for ligand-independent transcriptional activation of the human estrogen-related receptor alpha (ERRalpha): Crystal structure of ERRalpha ligand binding domain in complex with peroxisome proliferator-activated receptor coactivator-1alpha. J Biol Chem 279: 49330-49337, 2004.
85. Greschik H, Flaig R, Renaud JP and Moras D: Structural basis for the deactivation of the estrogen-related receptor gamma by diethylstilbestrol or 4-hydroxytamoxifen and determinants of selectivity. J Biol Chem 279: 33639-33646, 2004.
86. Greschik H, Wurtz JM, Sanglier S, Borguet W, van Dorsselaer A, Moras D and Renaud JP: Structural and functional evidence for ligand-independent transcriptional activation by the estrogen-related receptor 3. Mol Cell 9: 303-313, 2002.
87. Kallen J, Lattmann R, Beerli R, Blechschmidt A, Blommers MJ, Geiser M, Ottl J, Schlaeppi JM, Strauss A and Fournier B: Crystal structure of human estrogen-related receptor alpha in complex with a synthetic inverse agonist reveals its novel molecular mechanism. J Biol Chem 282: 23231-23239, 2007.
88. Wang L, Zuercher WJ, Consler TG, Lambert MH, Miller AB, Orband-Miller LA, McKee DD, Wilson TM and Nolte RT: X-ray crystal structures of the estrogen-related receptor gamma ligand binding domain in three functional states reveal the molecular basis of small molecule regulation. J Biol Chem 281: 37773-37781, 2006.
89. Jin KS, Park JK, Yoon J, Rho Y, Kim JH, Kim EE and Ree M: Small-angle X-ray scattering studies on structures of an estrogen-related receptor α ligand binding domain and its complexes with ligands and coactivators. J Phys Chem B 112: 9603-9612, 2008.
90. Yaşar P, Ayaz G, User SD, Güpür G and Muyan M: Molecular mechanism of estrogen-estrogen receptor signaling. Reprod Med Biol 16: 4-20, 2017.
91. Couse JF and Korach KS: Estrogen receptor null mice: What have we learned and where will they lead us? Endocr Rev 20: 358-417, 1999.
92. Klinge CM, BrollyCL, Bambara RA and Hilf R: Hsp70 is not required for high affinity binding of purified calf uterine estrogen receptor to estrogen response element DNA in vitro. J Steroid Biochem Mol Biol 63: 283-301, 1997.
93. Devin-Leclerc J, Meng X, Delahaye F, Leclerc P, Baulieu EE and Catelli MG: Interaction and dissociation by ligands of estrogen receptor and Hsp90: The antiestrogen RU 58668 induces a protein synthesis-dependent clustering of the receptor in the cytoplasm. Mol Endocrinol 12: 842-854, 1998.
94. Kumar S, Lata K, Mukhopadhyay S and Mukherjee TK: Role of estrogen receptors in pro-oxidative and anti-oxidative actions of estrogens: A perspective. Biochim Biophys Acta 1800: 1127-1135, 2010.
95. Klinge CM: Estrogen receptor interaction with co-activators and co-repressors. Steroids 65: 227-251, 2000.
96. Klein-Hitpass L, Ryffel GU, Heitlinger E and Cato AC: A 13 bp palindrome is a functional estrogen responsive element and interacts specifically with estrogen receptor. Nucleic Acids Res 16: 647-663, 1988.
97. Cheung E and Kraus WL: Genomic analyses of hormone signaling and gene regulation. Annu Rev Physiol 72: 191-218, 2010.
98. Carroll JS, Meyer CA, Song J, Li W, Geistlinger TR, Eeckhoute J, Brodsky AS, Keeton EK, Fertuck KC, Hall GF, *et al*: Genome-wide analysis of estrogen receptor binding sites. Nat Genet 38: 1289-1297, 2006.
99. Hall JM, Couse JF and Korach KS: The multifaceted mechanisms of estradiol and estrogen receptor signaling. J Biol Chem 276: 36869-36872, 2001.
100. Li C, Briggs MR, Ahlborn TE, Kraemer FB and Liu J: Requirement of Sp1 and estrogen receptor alpha interaction in 17β-estradiol-mediated transcriptional activation of the low density lipoprotein receptor gene expression. Endocrinol 142: 1546-1553, 2001.
101. Safe S: Transcriptional activation of genes by 17 beta-estradiol through estrogen receptor Sp1 interactions. Vitam Horm 62: 231-252, 2001.
102. Paech K, Webb P, Kuiper GG, Nilsson S, Gustafsson J, Kushner PJ and Scanlan TS: Differential ligand activation of estrogen receptors ERalpha and ERbeta at AP1 sites. Science 277: 1508-1510, 1997.
103. Webb P, Nguyen P, Valentine C, Lopez GN, Kwok GR, McInerney E, Katzenellenbogen BS, Enmark E, Gustafsson JA, Nilsson S and Kushner PJ: The estrogen receptor enhances AP-1 activity by two distinct mechanisms with different requirements for receptor transactivation functions. Mol Endocrinol 13: 1672-1685, 1999.
104. Kushner PJ, Agard DA, Greene GL, Scanlan TS, Shiau AK, Uht RM and Webb P: Estrogen receptor pathways toAP-1. J Steroid Biochem Mol Biol 74: 311-317, 2000.
105. Marino M, Galluzzo P and Ascenzi P: Estrogen signaling multiple pathways to impact gene transcription. Curr Genomics 7: 497-508, 2006.
106. Klinge CM: Estrogen receptor interaction with estrogen response elements. Nucleic Acids Res 29: 2905-2919, 2001.
107. Johnston SD, Liu XD, Zuo F, Eisenbraun TL, Wiley SR, Kraus RJ and Mertz JE: Estrogen-related receptor alpha 1 functionally binds as a monomer to extended half-site sequences including ones contained within estrogen-response elements. Mol Endocrinol 11: 342-352, 1997.
108. Zhang Z and Teng CT: Estrogen receptor-related receptor alpha 1 interacts with coactivator and constitutively activates the estrogen response elements of the human lactoferrin gene. J Biol Chem 275: 20837-20846, 2000.
109. Vanacker JM, Petterson K, Gustafsson JA and Laudet V: Transcriptional targets shared by estrogen receptor-related receptors (ERRs) and estrogen receptor (ER) alpha, but not by ER beta. EMBO J 18: 4270-4279, 1999.
110. Mullen EM, Gu P and Cooney AJ: Nuclear receptors in regulation of mouse ES cell pluripotency and differentiation. PPAR Res 2007: 61563, 2007.
111. Deblois G and Giguere V: Oestrogen-related receptors in breast cancer: Control of cellular metabolism and beyond. Nat Rev Cancer 13: 27-36, 2013.
112. Gravel SP: Deciphering the dichotomous effects of PGC-1α on tumorigenesis and metastasis. Front Oncol 8: 75, 2018.
113. LeBleu VS, O'Connell JT, Gonzalez Herrera KN, Wikman H, Pantel K, Haigis MC, de Carvalho FM, Damascena A, Domingos Chinen LT, Rocha RM, *et al*: PGC-1α mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis. Nat Cell Biol 16: 992-1003, 1-15, 2014.
114. Tan Z, Luo X, Xiao L, Tang M, Bode AM, Dong Z and Cao Y: The role of PGC-1α in cancer metabolism and its therapeutic implications. Mol Cancer Ther 15: 774-782, 2016.

115. Torrano V, Valcarcel-Jimenez L, Cortazar AR, Liu X, Urosevic J, Castillo-Martin M, Fernandez-Ruiz S, Morciano G, Caro-Maldonado A, Guiu M, *et al*: The metabolic co-regulator PGC1α suppresses prostate cancer metastasis. Nat Cell Biol 18: 645-656, 2016.
116. Deblois G, St-Pierre J and Giguere V: The PGC-1/ERR signaling axis in cancer. Oncogene 32: 3483-3490, 2013.
117. Audet-Walsh É, Yee T, McGuirk S, Vernier M, Ouellet C, St-Pierre J and Giguère V: Androgen-dependent repression of ERRγ reprograms metabolism in prostate cancer. Cancer Res 77: 378-389, 2017.
118. Sun P, Sehouli J, Denkert C, Mustea A, Kongsen D, Koch I, Wei L and Lichtenegger W: Expression of estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor biomarkers in ovarian cancer cells. J Mol Med 83: 457-467, 2005.
119. Kang MH, Choi H, Oshima M, Cheong JH, Kim S, Lee JH, Park YS, Choi HS, Kweon MN, Pack CG, *et al*: Estrogen-related receptor gamma functions as a tumor suppressor in gastric cancer. Nat Commun 9: 1920, 2018.
120. Kim JH, Choi YK, Byun JK, Kim MK, Kang YN, Kim SH, Lee S, Jang BK and Park KG: 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 48: e213, 2016.
121. Pons F, Varela M and Llovet JM: Sensing systems in hepatocellular carcinoma. HPB (Oxford) 7: 35-41, 2005.
122. Zhou Y, Jia Q, Meng X, Chen D and Zhu B: ERRα regulates OTUB1 expression to promote colorectal cancer cell migration. J Cancer 10: 5812-5819, 2019.
123. Luo C, Balsa E, Thomas A, Hatting M, Jedrychowski M, Gygi SP, Widlung HR and Puigserver P: ERRα maintains mitochondrial oxidative metabolism and constitutes an actionable target in PGC1α-elevated melanomas. Mol Cancer Res 15: 1366-1375, 2017.
124. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM and Mangelsdorf DJ: Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. Cell 126: 789-799, 2006.
125. Ranhotra HS: The orphan estrogen-related receptor alpha and metabolic regulation: New frontiers. J Recept Signal Transduct Res 35: 565-568, 2015.
126. Giguère V: Transcriptional control of energy homeostasis by the estrogen-related receptors. Endocr Rev 29: 677-696, 2008.
127. Ijichi N, Ikeda K, Horie-Inoue K, Yagi K, Okazaki Y and Inoue S: Estrogen-related receptor alpha modulates the expression of adipogenesis-related genes during adipocyte differentiation. Biochem Biophys Res Commun 358: 813-818, 2007.
128. Kubo M, Ijichi N, Ikeda K, Horie-Inoue K, Takeda S and Inoue S: Modulation of adipogenesis-related gene expression by estrogen-related receptor gamma during adipocytic differentiation. Biochim Biophys Acta 1789:71-77, 2009.
129. Lorke DE, Susens U, Borgmeyer U and Hermans-Borgmeyer I: Differential expression of the estrogen receptor related receptor gamma in the mouse brain. Brain Res Mol Brain Res 77: 277-280, 2000.
130. Luo J, Sladek R, Bader JA, Matthyssen A, Rossant J and Giguère V: Placental abnormalities in mouse embryos lacking the orphan nuclear receptor ERR-beta. Nature 388: 778-782, 1997.
131. Borgmeyer-Hermans I, Süsens U and Borgmeyer U: Developmental expression of the estrogen receptor-related receptor gamma in the nervous system during mouse embryogenesis. Mech Dev 97: 197-199, 2000.
132. Luo J, Sladek R, Carrier J, Bader JA, Richard D and Giguère V: Reduced fat mass in mice lacking orphan nuclear receptor estrogen-related receptor alpha. Mol Cell Biol 23: 7947-7956, 2003.
133. Huss JM, Imahashi K, Dufour CR, Weinheimer CJ, Courtois M, Kovacs A, Giguère V, Murphy E and Kelly DP: The nuclear receptor ERRalpha is required for the bioenergetic and functional adaptation to cardiac pressure overload. Cell Metab 6: 25-37, 2007.
134. Villena JA and Kralli A: ERRalpha: A metabolic function for the oldest orphan. Trends Endocrinol Metab 19: 269-276, 2008.
135. Alaynick WA, Kondo RP, Xie W, He W, Dufour CR, Downes M, Jonker JW, Giles W, Naviaux RK, Giguere V and Evans RM: ERRgamma directs and maintains the transition to oxidative metabolism in the postnatal heart. Cell Metab 6: 13-24, 2007.
136. Zhou W, Liu Z, Wu J, Liu JH, Hyder SM, Antoniou E and Lubahn DB: Identification and characterization of two novel splicing isoforms of human estrogen-related receptor beta. Clin Endocrinol Metab 91: 569-579, 2006.
137. Xu Z, Wang Y, Xiao ZG, Zou C, Zhang X, Wang Z, Wu D, Yu S and Chan FL: Nuclear receptor ERRα and transcription factor ERG form a reciprocal loop in the regulation of TMPRSS2: ERGfusion gene in prostate cancer. Oncogene 37: 6259-6274, 2018.
138. Bonnelye E, Vanacker JM, Dittmar T, Begue A, Desbiens X, Denhardt DT, Aubin JE, Laudet V and Fournier B: The ERR-1 orphan receptor is a transcriptional activator expressed during bone development. Mol Endocrinol 11: 905-916, 1997.
139. Pettersson K, Svensson K, Mattsson R, Carlsson B, Ohlsson R and Berkenstam A: Expression of a novel member of estrogen response element-binding nuclear receptors is restricted to the early stages of chorion formation during mouse embryogenesis. Mech Dev 54: 211-223, 1996.
140. Wang J, Wang Y and Wong C: Oestrogen-related receptor alpha inverse agonist XCT-790 arrests A549 lung cancer cell population growth by inducing mitochondrial reactive oxygen species production. Cell Prolif 43: 103-113, 2010.
141. Fouad YF and Aanei C: Revisiting the hallmarks of cancer. Am. J Cancer Res 7: 1016-1036, 2017.
142. Pardee AB: G1 events and regulation of cell proliferation. Science 246: 603-608, 1989.
143. Harper JV: Synchronization of cell populations in G1/S and G2/M phases of the cell cycle. Methods Mol Biol 296: 157-166, 2005.
144. Makowiecki C, Nolte A, Sutaj B, Keller T, Avci-Adali M, Stoll H, Schlensak C, Wendel HP and Walker T: New basic approach to treat non-small cell lung cancer based on RNA-interference. Thorac Cancer 5: 112-120, 2014.
145. Martin TA, Ye L, Sanders AJ, Lane J and Jiang WG: Cancer invasion and metastasis: Molecular and cellular perspective. Mad Curie Bioscience Database, Landes Bioscience, 2000-2013.
146. Polyak K and Weinberg RA: Transitions between epithelial and mesenchymal states: Acquisition of malignant and stem cell traits. Nat Rev Cancer 9: 265-273, 2009.
147. Craene BD and Berx G: Regulatory networks defining EMT during cancer initiation and progression. Nat Rev Cancer 13: 97-110, 2013.
148. Singh A and Settleman J: EMT, Cancer stem cells and drug resistance: An emerging axis of evil in the war on cancer. Oncogene 29: 4741-4751, 2010.
149. Tiwari N, Gheldof A, Tatari M and Christofori G: EMT as the ultimate survival mechanism of cancer cells. Semin Cancer Biol 22: 194-207, 2012.
150. Krebs MG, Sloane R, Priest L, Lancashire L, Hou JM, Greystoke A, Ward TH, Ferraldeschi R, Hughes A, Clack G, *et al*: Evaluation and prognostic significance of circulating tumor cells in patients with non-small cell lung cancer. J Clin Oncol 29: 1556-1563, 2011.
151. Jakobsen KR, Demuth C, Sorensen BS and Nielsen AL: The role of epithelial to mesenchymal transition in resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. Transl Lung Cancer Res 5: 172-182, 2016.
152. Li L, Gu X, Yue J, Zhao Q, Lv D, Chen H and Xu L: Acquisition of EGFR TKI resistance and EMT phenotype is linked with activation of IGF1R/NF-κB pathway in EGFR-mutant NSCLC. Oncotarget 8: 92240-92253, 2017.
153. Byers LA, Diao L, Wang J, Saintigny P, Girard L, Peyton M, Shen L, Fan Y, Giri U, Tumula PK, *et al*: An epithelial-mesenchymal transition gene signature predicts resistance to EGFR and PI3K inhibitors and identifies Axl as a therapeutic target for overcoming EGFR inhibitor resistance. Clin Can Res 19: 279-290, 2013.
154. Aguilera TA and Giaccia AJ: Molecular Pathways: Oncologic pathways and their role in T-cell exclusion and immune evasion-A new role for the AXL receptor tyrosine kinase. Clin Cancer Res 23: 2928-2933, 2017.
155. Datar I and Schalper KA: Epithelial-Mesenchymal transition and immune evasion during lung cancer progression: The chicken or the egg? Clin Cancer Res 22: 3422-3424, 2016.
156. Lou Y, Diao L, Cuentas ER, Denning WL, Chen L, Fan YH, Byers LA, Wang J, Papadimitrakopoulou VA, Behrens C, *et al*: Epithelial-mesenchymal transition is associated with a distinct tumor microenvironment including elevation of inflammatory signals and multiple immune checkpoints in lung adenocarcinoma. Clin Can Res 22: 3630-3642, 2016.
157. Chen L, Gibbons DL, Goswami S, Cortez MA, Ahn YH, Byers LA, Zhang X, Yi X, Dwyer D, Lin W, *et al*: Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. Nat Commun 5: 5241, 2014.

158. Chae YK, Chang S, Ko T, Anker J, Agte S, Iams W, Choi WM, Lee K and Cruz M: Epithelial-mesenchymal transition (EMT) signature is inversely associated with T-cell infiltration in non-small cell lung cancer (NSCLC). Sci Rep 8: 2918, 2018.
159. Kwaśniak K, Czarnik-Kwaśniak J, Maziarz A, Aebisher D, Zielińska K, Karczmarek-Borowska B and Tabarkiewicz J: Scientific reports concerning the impact of interleukin 4, interleukin 10 and transforming growth factor β on cancer cells. Cent Eur J Immunol 44: 190-220, 2019.
160. Steen EH, Wang X, Balaji S, Butte MJ, Bollyky PL and Keswani SG: The role of the anti-inflammatory cytokine Interleukn-10 in tissue fibrosis. Adv Wound Care (New Rochelle) 9: 184-198, 2020.
161. Tsoukalas N, Aravantinou-Fatorou A, Tolia M, Giaginis C, Galanapoulos M, Kiakou M, Kostakis ID, Dana E, Vamvakaris I, Korogiannos A, *et al*: Epithelial-mesenchymal transition in non small-cell lung cancer. Anticancer Res 37: 1773-1778, 2017.
162. Mahmood MQ, Ward C, Muller HK, Sohal SS and Walters EH: Epithelial mesenchymal transition (EMT) and non-small cell lung cancer (NSCLC): A mutual association with airway disease. Med Oncol 34: 45, 2017.
163. Thompson JC, Hwang WT, Davis C, Deshpande C, Jeffries S, Rajpurohit Y, Krishna V, Smirnov D, Verona R, Lorenzi MV, *et al*: Gene signatures of tumor inflammation and epithelial-to-mesenchymal transition (EMT) predict responses to immune checkpoint blockade in lung cancer with high accuracy. Lung Cancer 139: 1-8, 2020.
164. Huang JW, Guan BZ, Yin LH, Liu FN, Hu B, Zheng QY, Li FL, Zhong YX and Chen Y: Effects of estrogen-related receptor alpha (ERRα) on proliferation and metastasis of human lung cancer A549 cells. J Huazhong Univ Sci Technolog Med Sci 34: 875-881, 2014.
165. Zhang J, Guan X, Liang N and Li S: Estrogen-related receptor alpha triggers the proliferation and migration of human non-small cell lung cancer via interleukin-6. Cell Biochem Funct 36: 255-262, 2018.
166. Wang Y, Zhao M, Liu J, Ni J, Jiao Y and Bai C: Up regulation of IL-6 is involved in di (2-ethylhexyl) phthalate (DEHP) induced migration and invasion of non-small cell lung cancer (NSCLC) cells. Biomed. Pharmacother 89: 1037-1044, 2017.
167. Kim JH: Di(2-ethylhexyl) phthalate promotes lung cancer cell line A549 progression via Wnt/β-catenin signaling. J Toxicol Sci 44: 237-244, 2019.