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MINI-REVIEW

Women's Health Research and Novel Perspectives on Sex as an Investigative Variable

The role of estrogen receptors in lung diseases

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Abstract

Lung diseases are major global causes of morbidity and mortality, yet the molecular basis of their observed sex differences remains unclear. Beyond their roles in reproductive biology, estrogens are central regulators of pulmonary homeostasis through three principal receptors: *1*) estrogen receptor α (ERα), *2*) estrogen receptor β (ERβ), and *3*) the G-protein-coupled estrogen receptor 1 (GPER1). These receptors are widely expressed across the airway epithelium, smooth muscle, fibroblasts, lung endothelium, and immune cells, where they integrate slow, genomic transcriptional programs and rapid, membrane-initiated signaling cascades to regulate inflammation, oxidative balance, and tissue remodeling. ERβ, often the dominant pulmonary isoform, tends to preserve extracellular matrix integrity and attenuate maladaptive inflammation, whereas ERα frequently amplifies proinflammatory transcriptional programs. GPER1 mediates rapid nongenomic responses that modulate vascular tone, airway smooth-muscle reactivity, and innate immune function, and is both an important regulator of allergic inflammation and a modulator of oncogenic signaling. Together, estrogen receptor subtype balance, subcellular localization, and ligand context determine whether estrogenic signaling is protective or pathogenic. Clinically, this framework helps explain life course and sex differences, such as postpubertal female predominance of asthma, menstrual and pregnancy-related exacerbations, and enhanced chronic obstructive pulmonary disease (COPD) susceptibility in women at lower tobacco exposure. In this review, we synthesize mechanistic and clinical evidence across lung diseases; delineate areas where data remain incomplete or contradictory; and outline opportunities for experimental and translational innovation. These include development of receptor-selective or biased ligands, inhaled or localized delivery, and implementation of sex-aware clinical trial designs to leverage estrogen-receptor biology for precision respiratory therapeutics.

asthma; COPD; estrogen receptors; lung cancer; sex differences

INTRODUCTION

Chronic respiratory diseases remain a global health challenge, accounting for nearly 10% of all deaths and affecting more than 485 million individuals (1). Despite decades of research, the molecular mechanisms that underlie the striking sex differences in these conditions remain incompletely understood. Women are more likely to develop severe, corticosteroid-resistant asthma, display accelerated chronic obstructive pulmonary disease (COPD) progression at lower levels of smoke exposure, and exhibit distinct lung-cancer phenotypes and outcomes (2, 3). These epidemiologic trends highlight the influence of sex hormones, particularly estrogens, on lung structure and function.

Estrogens exert pleiotropic effects far beyond reproduction, influencing vascular tone, metabolism, immune surveillance, and wound repair (4). Their biological actions are mediated by three principal receptors: *1*) estrogen receptor α (ERα; *ESR1*), *2*) estrogen receptor β (ERβ; *ESR2*), and *3*) the G-protein-coupled estrogen receptor 1 (GPER1; *GPR30*). These receptors are expressed in multiple lung cell lineages, including the airway epithelium, smooth muscle, fibroblasts, endothelial cells, and alveolar macrophages (5). Acting as ligand-dependent transcription factors or membrane-associated signal transducers, estrogen receptors (ERs) integrate endocrine cues with environmental and inflammatory stimuli (6). This integration provides a molecular basis for sex-specific modulation of airway responsiveness, oxidative balance, and tissue remodeling (7).

At the genomic level, ERα and ERβ regulate transcription of genes controlling cytokine production, extracellular matrix (ECM) turnover, and mitochondrial antioxidant defense (8). ERβ generally promotes anti-inflammatory and cytoprotective outcomes, whereas ERα tends to amplify nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-driven inflammation and fibroblast activation (9). Membrane-initiated estrogen signaling, primarily through GPER1, engages rapid second-messenger cascades, cyclic adenosine monophosphate (cAMP), Ca^{2+}, and phosphoinositide 3-kinase (PI3K)/AKT that influence airway

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smooth-muscle contractility and innate immune responses (10). Together, these mechanisms position ERs as dynamic regulators of lung physiology capable of mediating both protective and pathogenic effects depending on cellular context and hormonal milieu.

Recognizing the central role of estrogen signaling in lung homeostasis reframes our understanding of respiratory disease pathogenesis. The interplay between systemic hormone levels, receptor subtype balance, and downstream transcriptional or kinase signaling may explain why disease trajectories differ between sexes and across life stages such as puberty, pregnancy, and menopause. This review synthesizes emerging evidence on the multifaceted roles of ERα, ERβ, and GPER1 in lung biology, delineates receptor-specific mechanisms in asthma, COPD, fibrosis, and lung cancer, and explores the translational potential of receptor-biased therapeutics for sex-aware precision medicine.

SEX DIFFERENCES IN LUNG DISEASES

Sex-related differences in the prevalence, severity, and progression of lung diseases are well documented and reflect the complex interaction between hormonal fluctuations, receptor signaling, and immune regulation rather than mere genetic or environmental variation. Across the life course, hormonal transitions such as puberty, pregnancy, and menopause reshape the expression and activation of ERs contributing to marked variability in airway physiology and disease outcomes. Epidemiologically, asthma occurs more frequently in boys during childhood but shifts to higher prevalence and greater severity in adult women after puberty, coinciding with rising systemic estrogen levels and cyclical hormonal changes throughout the reproductive years (2, 3, 7, 11, 12). In contrast, women experience a steeper decline in lung function and earlier onset of COPD despite lower cumulative tobacco exposure, suggesting that estrogen and its receptors sensitize the female lung to oxidative injury and inflammation (2, 3, 12, 13). These clinical observations underscore that sex hormones, particularly estrogens, serve as key modulators of pulmonary immune tone, airway remodeling, and vascular function.

Mechanistically, ERα, ERβ, and GPER1 exhibit cell- and context-dependent actions that drive sex-specific responses. ERβ and GPER1 generally exert anti-inflammatory and cytoprotective effects by dampening NF-κB-dependent cytokine production, reducing oxidative stress, and promoting IL-10-mediated immunoregulation (6, 9, 10, 14–16). These protective pathways are typically more pronounced in females, contributing not only to greater resistance to acute injury but also to exaggerated allergic inflammation when estrogen levels fluctuate. By contrast, ERα amplifies Th2 cytokine production (IL-4, IL-5, and IL-13) and can promote airway hyperresponsiveness and fibroblast activation, mechanisms that may account for the higher prevalence of severe, steroid-resistant asthma among women (6, 11, 17, 18). Estrogen-driven regulation of mitochondrial metabolism and antioxidant enzymes further contributes to sex differences in oxidative injury and repair capacity, with ERβ localization to mitochondria enhancing oxidative phosphorylation and reactive oxygen species detoxification in female lung cells (16, 19). These receptor-level distinctions integrate endocrine signals with immune and metabolic control, explaining why identical exposures can produce divergent outcomes across sexes.

At the translational level, recognition of sex differences in receptor expression and signaling offers opportunities for personalized therapy. Preclinical and clinical data suggest that ERβ-selective agonists and GPER1 modulators may provide anti-inflammatory and antifibrotic benefits preferentially in females, whereas modulation of ERα signaling could be beneficial in males or in postmenopausal women with low endogenous estrogen activity (6, 14, 20, 21). Life-stage-specific hormonal states, such as puberty, pregnancy, menopause, must therefore be considered when designing and interpreting studies of ER-targeted interventions. Incorporating sex as a biological variable in experimental design and early-phase clinical trials will be essential for optimizing the safety and efficacy of emerging estrogen receptor-based therapies in pulmonary disease (3, 12, 21).

MECHANISMS OF ESTROGEN RECEPTOR SIGNALING IN THE LUNG

Estrogen Receptors as Multimodal Signaling Platforms

ERs (ERα, ERβ, and GPER1) operate as a multilayered signaling network in the lung (6, 10, 22). Although ERα and ERβ classically regulate gene expression by binding estrogen response elements and interacting with core transcription factors (23), GPER1 and membrane-associated ER pools elicit rapid second-messenger responses (cAMP, intracellular Ca^{2+}, PI3K/AKT, and MAPK) that modulate ion channels, cytoskeletal dynamics, and kinase signaling (14, 24). This dual architecture permits immediate physiological modulation (e.g., bronchodilation or rapid changes in cytokine release) while also enabling longer-term transcriptional reprogramming that can alter remodeling and repair.

Genomic (Nuclear) Signaling

Ligand-activated ERα and ERβ regulate transcription of cytokines, ECM regulators [MMPs/tissue inhibitor of metalloproteinases (TIMPs)], antioxidant enzymes, and cell-cycle genes. In many pulmonary contexts, ERβ is associated with anti-inflammatory and cytoprotective transcriptional programs that upregulate antioxidant defenses (SOD2, catalase) and restrain fibroblast-to-myofibroblast differentiation, whereas ERα tends to potentiate NF-κB-dependent inflammatory gene expression and coactivator recruitment (p300/CBP, SRC family) (23). Chromatin state and cofactor availability therefore determine receptor-specific transcriptional outputs; sustained estrogen exposure or disturbed coactivator balance may produce long-lasting epigenetic changes that contribute to sex-biased disease susceptibility (25).

Nongenomic (Membrane-Initiated) Signaling and GPER1

Membrane-localized ERs and GPER1 drive rapid signaling that modulates airway tone, vascular reactivity, and immediate immune responses. GPER1 activates adenylyl cyclase (increasing cAMP), mobilizes intracellular Ca^{2+}, and triggers PI3K/AKT and extracellular signal-regulated kinase (ERK)

cascades; in airway smooth muscle (ASM) and endothelium, these actions modulate contractility and nitric oxide pathways, and in macrophages/epithelium, they can promote anti-inflammatory IL-10 production (15, 26). Since membrane-initiated signaling acts within seconds to minutes, it is particularly relevant to acute exacerbations and rapid functional modulation.

Isoforms, Splice Variants, and Localization

Alternative splicing creates receptor isoforms (e.g., ERα36 and ERα46) with distinct localization and signaling properties (27, 28). ERα36 frequently localizes to the membrane and cytoplasm and can activate epidermal growth factor receptor (EGFR)/Src-PI3K/AKT pathways in a ligand-dependent or ligand-independent manner, promoting proliferation and survival signals implicated in repair and tumor progression (28); ERα46 can antagonize full-length ERα transcriptional activity (29). The ratio of full-length to truncated isoforms is dynamic and responsive to inflammatory cytokines and oxidative stress, providing a mechanistic basis for context-dependent receptor functions (30).

Mitochondrial and Redox Control

ERβ and GPER1 influence mitochondrial function and cellular redox homeostasis. Mitochondrial ERβ interacts with mitochondrial DNA to promote the expression of oxidative phosphorylation genes and ROS-detoxifying enzymes, thereby preserving ATP production and limiting oxidative damage. GPER1 signals can enhance mitochondrial biogenesis through AKT-dependent modulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and nuclear respiratory factor 1 (NRF1) (20). Together, these pathways couple hormone signaling to metabolism and antioxidant defenses, key determinants of tissue resilience against pollutants, allergens, and infection (31).

Cross Talk and Contextual Modulation

ER signaling interfaces with glucocorticoid receptors (GRs), progesterone receptors, and growth-factor receptors including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) and is modulated by posttranslational modifications (phosphorylation, SUMOylation), ligand bias, and environmental endocrine disruptors (32). These interactions amplify context dependence: the same ligand can yield different outcomes across cell types and disease states depending on receptor composition, localization, cofactor availability, and the inflammatory/redox milieu (32, 33).

Integration with Cellular Microenvironments

Beyond their direct effects within individual cells, ERs also influence communication between different lung cell types. ER signaling modifies the release and molecular content of extracellular vesicles, including microRNAs that are transferred between epithelial, immune, and mesenchymal cells. Through these vesicle-mediated signals, ERβ and GPER1 can suppress proinflammatory macrophage activation, limit fibroblast proliferation, and promote epithelial repair (17). These paracrine interactions integrate immune regulation with tissue remodeling, highlighting how ER signaling coordinates multicellular responses in the lung.

Experimental Considerations and Methodological Advances

Addressing unresolved questions requires improved specificity in reagents and models. Recommended approaches include using highly selective agonists/antagonists alongside genetic manipulation (CRISPR) and expression regulation (siRNA) to deconvolve receptor subtype function; using membrane-impermeable estrogen conjugates [estrogen-bovine serum albumin (BSA) conjugate] to isolate membrane effects; combining single cell and spatial transcriptomics with quantitative proteomics and phosphoproteomics to map receptor expression and signaling in situ; and adopting physiologic hormone concentrations and life-stage models (puberty, pregnancy, and menopause) in preclinical studies (34, 35). Key experimental priorities include defining spatiotemporal ER signaling during injury/repair, quantifying isoform ratios across disease states, elucidating ligand bias and posttranslational modulation, and mapping ER cross talk with VEGFR and EGFR to inform combinatorial therapies (36).

The interplay between genomic, nongenomic, and mitochondrial signaling pathways is summarized schematically in Fig. 1, which illustrates how ERα, ERβ, and GPER1 coordinate estrogenic regulation of inflammation, oxidative balance, and airway remodeling in the lung.

ERs exhibit distinct expression patterns across pulmonary structural and immune cell populations, determining the magnitude and specificity of estrogenic responses in the lung. Single cell and targeted expression analyses demonstrate that ERα, ERβ, and GPER1 are not uniformly distributed, but instead show cell-type-specific enrichment that aligns with their functional diversity. For instance, ERβ and GPER1 predominate in the airway epithelium (6–8, 19), smooth muscle (2, 11, 15), fibroblasts (18, 37, 38), and macrophages (9, 10, 17, 26), where they mediate anti-inflammatory, antioxidant, and antifibrotic effects, whereas ERα is relatively enriched in epithelial and lymphoid compartments (17, 39–41), where it can drive proinflammatory signaling. The relative expression of these receptors across major pulmonary cell types is summarized in Fig. 2, providing a spatial and functional framework for interpreting receptor-specific mechanisms discussed in the subsequent disease sections.

ESTROGENIC REGULATION OF LUNG DEVELOPMENT

Beyond its roles in the mature lung, estrogen signaling also contributes to pulmonary development. Both ERα and ERβ are expressed during fetal and neonatal stages, where they regulate alveolar septation, surfactant synthesis, and epithelial differentiation (6, 7, 19). Estrogen enhances type II alveolar cell function and surfactant protein expression, supporting lung compliance and postnatal respiratory adaptation. Mitochondrial ERβ facilitates energy metabolism required for alveolarization, whereas GPER1 contributes to vascular and airway morphogenesis through rapid Ca^{2+} and PI3K/AKT signaling (6, 15, 19). Disruption of these

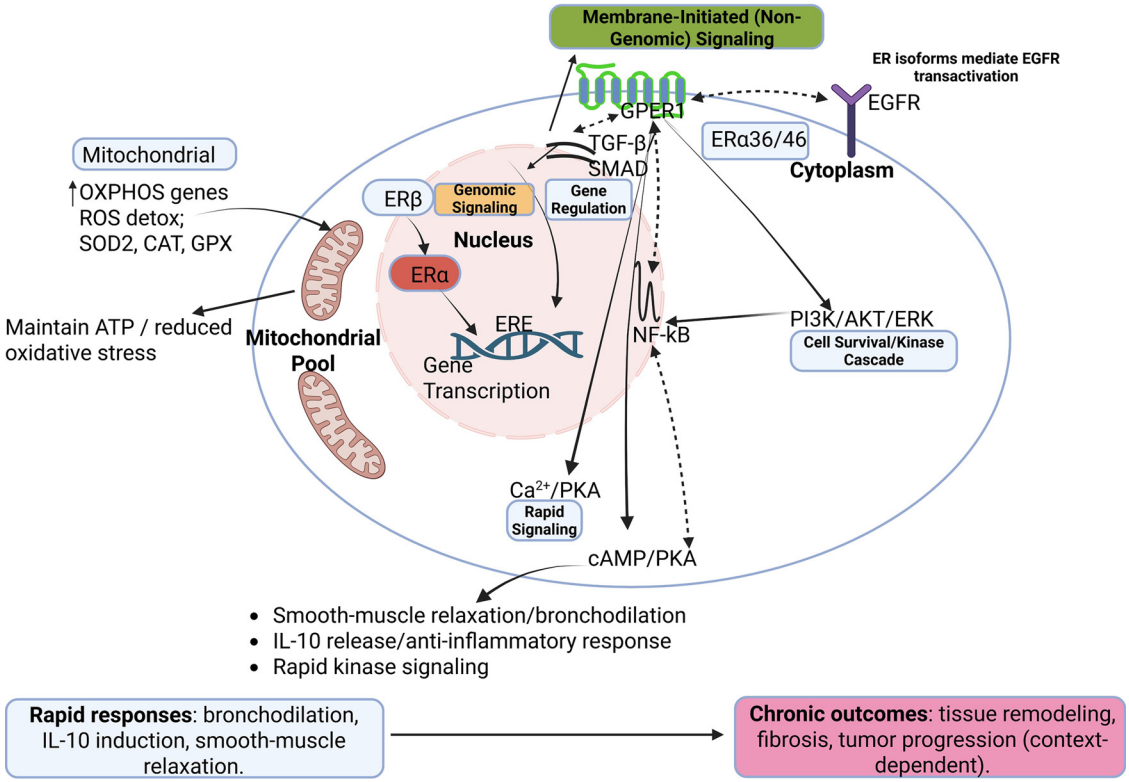

Figure 1. Estrogen-receptor signaling in lung cells. Nuclear (genomic) estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) signaling regulate gene transcription through estrogen-response elements (ERE). Membrane-initiated (nongenomic) signaling through the G-protein-coupled estrogen receptor 1 (GPER1) and ERα splice variants (ERα36/46) activates cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA), calcium (Ca^{2+})/PKA, and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/extracellular signal-regulated kinase (ERK) cascades. Mitochondrial ERβ supports oxidative phosphorylation (OXPHOS) and reactive oxygen species (ROS) detoxification. Cross talk with epidermal growth factor receptor (EGFR), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and transforming growth factor-beta (TGF-β)/mothers against decapentaplegic homolog (SMAD) integrates these pathways to determine protective vs. pathogenic outcomes. Membrane ERα36/46 isoforms are shown near the plasma membrane, where they mediate rapid cross talk (transactivation) with EGFR to propagate PI3K/AKT/ERK signaling.

developmental pathways may underlie sex-related differences in neonatal respiratory distress and long-term airway structure (3, 39).

DISEASE-SPECIFIC ROLES OF ESTROGEN RECEPTORS

In Fig. 3, we summarize how receptor subtype, localization, and signaling bias map onto disease mechanisms and clinical patterns for major pulmonary disorders. Each subsection links mechanistic findings to translational implications and highlights gaps for future work.

Asthma

Asthma illustrates estrogenic regulation of both immune and structural disease axes. Epidemiologically, postpubertal female predominance, cyclical exacerbations with the menstrual cycle, and pregnancy-associated changes indicate hormone-dependent modulation of disease (39, 43, 44). Mechanistically, ERα promotes Th2 polarization and enhances production of IL-4, IL-5, and IL-13, thereby supporting eosinophilic inflammation, whereas ERβ restrains Th2 and Th17 differentiation and reduces IL-17α production, actions that are especially relevant to neutrophilic, steroid-resistant phenotypes (40, 41, 45). In airway smooth muscle, ERβ activation increases cAMP and decreases Ras homolog family member A (RhoA) activity, leading to relaxation and reduced proliferation; in contrast, ERα and membrane variants (ERα36) can potentiate growth-factor-driven proliferation and extracellular-matrix deposition (11). Live-cell imaging by Ambhore et al. (12) demonstrated that ERα and ERβ differentially regulate lamellipodial protrusion and focal-adhesion dynamics in airway-smooth-muscle migration, with ERβ suppressing and ERα promoting remodeling.

Therapeutically, these findings identify ERβ and GPER1 as complementary targets for controlling airway inflammation and remodeling. ERβ-selective agonists (e.g., diarylpropionitrile and LY500307) reproduce estrogen's anti-inflammatory and bronchodilatory effects while avoiding ERα-mediated proliferation, making them promising treatments for chronic and steroid-resistant asthma (16, 46). GPER1 activation (e.g., the agonist G-1) produces rapid, nongenomic bronchodilation and suppresses Th2 cytokines through cAMP/PKA and PI3K/AKT signaling while enhancing IL-10-dependent immunoregulation (13, 47, 48). Together, ERβ-selective and GPER1-targeted agonists provide a dual-pathway approach, ERβ agonists addressing chronic remodeling, and GPER1 agonists mitigating acute inflammatory exacerbations, with careful modulation of ERα activity to minimize proinflammatory effects (46).

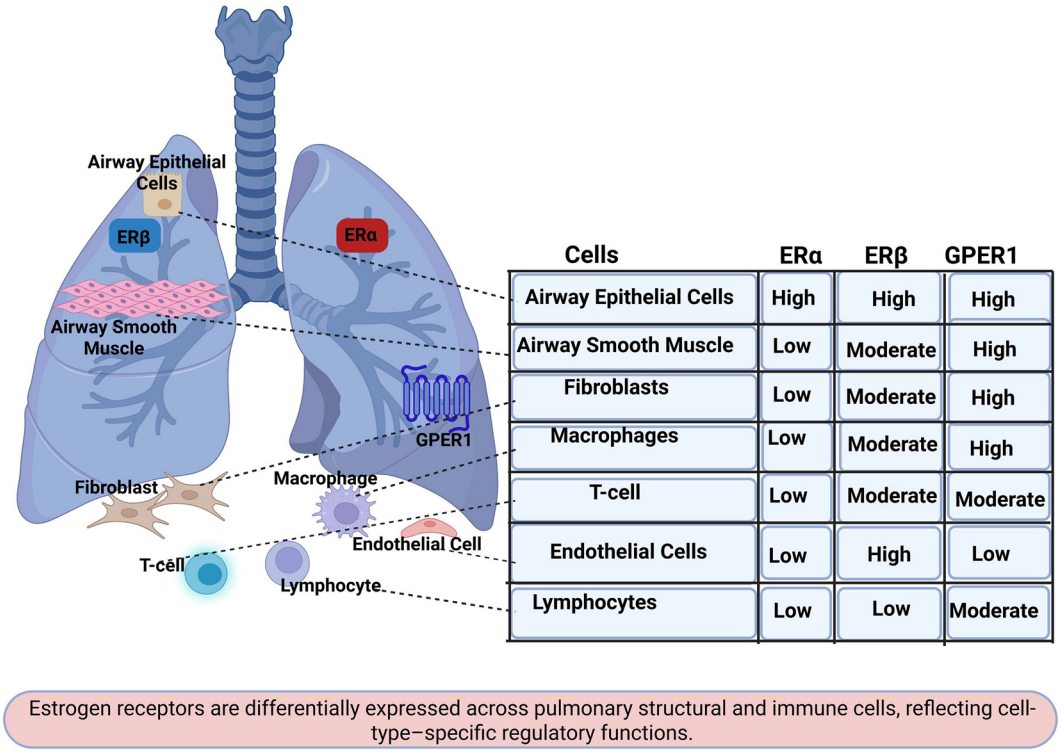

Figure 2. Distribution of estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G-protein-coupled estrogen receptor 1 (GPER1) across major pulmonary cell types. Expression levels (high/moderate/low) are derived from published single cell and targeted studies (6, 7, 9–12, 15, 16, 18, 42). Estrogen receptors are differentially expressed across pulmonary structural and immune cells, reflecting cell-type-specific regulatory functions.

Chronic Obstructive Pulmonary Disease

COPD demonstrates notable sex differences: women develop clinically significant disease with lower cumulative smoke exposure and show faster decline in lung function in some cohorts (49). ERβ expression is downregulated in COPD epithelium and fibroblasts; ERβ activation restores antioxidant enzyme expression (SOD, catalase) and attenuates

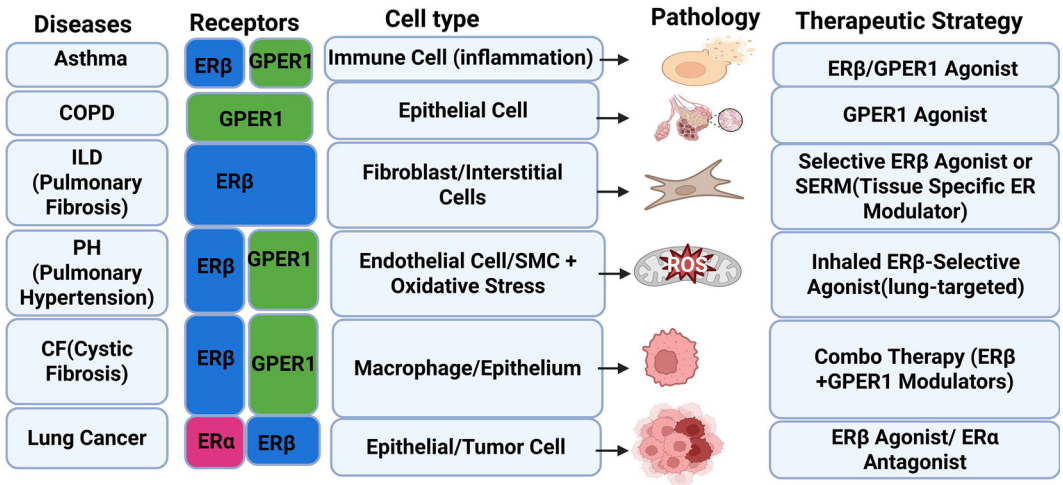

Figure 3. Disease-specific mapping of estrogen receptor biology to cellular pathology and candidate therapeutic approaches. Protective signaling mediated by estrogen receptor beta (ERβ) and the G-protein-coupled estrogen receptor 1 (GPER1) counteracts inflammation, oxidative stress, and tissue remodeling, whereas estrogen receptor alpha (ERα) contributes to proliferative or pathogenic signaling, particularly in lung cancer. Although both ERβ and GPER1 contribute to endothelial protection and vasodilation in pulmonary hypertension, current therapeutic development focuses primarily on inhaled ERβ-selective agonists for targeted pulmonary delivery. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ECM, extracellular matrix; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER1, G-protein-coupled estrogen receptor 1; ILD, interstitial lung disease; NSCLC, non-small-cell lung cancer; PH, pulmonary hypertension; SERM, selective estrogen receptor modulator (a synthetic ligand that acts as a tissue-specific estrogen receptor agonist or antagonist); SMC, smooth muscle cells; TGF-β/SMAD, transforming growth factor-beta/mothers against decapentaplegic homolog signaling pathway.

transforming growth factor-beta/suppressor of mothers against decapentaplegic (TGF-β/SMAD)-driven fibroblast proliferation in vitro (42). ERα signaling enhances NF-κB-mediated IL-8 and TNF-α production and may amplify neutrophilic inflammation (50). Preclinical smoke exposure models suggest that GPER1 agonism can reduce oxidative injury and vascular dysfunction (46). These data support testing ERβ- and GPER1-targeted approaches for halting progression and improving antioxidant defenses in COPD, with stratification by sex and smoking history.

Pulmonary Fibrosis and Interstitial Lung Disease

Fibrotic progression involves sustained fibroblast activation, extracellular-matrix deposition, and aberrant repair (37). ERβ agonism inhibits myofibroblast differentiation and collagen synthesis by antagonizing transforming growth factor-β (TGF-β)/SMAD signaling and enhancing mitochondrial antioxidant defenses (38, 51). Conversely, ERα activation under high-estrogen conditions can promote fibroblast proliferation (18). Selective estrogen receptor modulators (SERMs) synthetic compounds that bind ERs and act as tissue-specific agonists or antagonists can therefore be leveraged to selectively activate ERβ signaling in the lung while minimizing systemic estrogenic effects. Together, ERβ-selective agonists and SERMs represent potential antifibrotic therapeutic strategies for interstitial lung disease (ILD), though lung-specific efficacy and long-term safety remain to be validated.

Pulmonary Hypertension

Pulmonary arterial hypertension presents an "estrogen paradox," with higher incidence in women but comparatively better survival than men (52). Mechanistically, ERβ and GPER1 promote endothelial nitric oxide synthase (eNOS) activation and inhibit vascular smooth muscle proliferation through PI3K/AKT signaling, whereas ERα and certain estrogen metabolites foster vascular remodeling (53). Activation of ERβ, particularly through inhaled or lung-targeted agonists, has shown promise in preclinical models by improving pulmonary vascular relaxation, reducing right ventricular pressure, and limiting vascular remodeling (54–56).

The rationale for using an inhaled ERβ agonist parallel, yet differs from, the approaches described for asthma and COPD. Like ERβ-selective agents used in airway disease, inhaled ERβ agonists exploit the receptor's antiproliferative and vasodilatory effects, but their delivery route is optimized to achieve direct pulmonary vascular exposure while minimizing systemic hormonal effects. In contrast, GPER1 agonists used in asthma and COPD primarily target rapid, nongenomic bronchodilation and epithelial protection, whereas ERβ agonism in pulmonary hypertension (PH) focuses on sustained modulation of vascular tone and remodeling. Collectively, these findings identify ERβ as a vasoprotective receptor and highlight inhaled ERβ agonists as a feasible, tissue-specific therapeutic strategy for PH.

Cystic Fibrosis

Women with cystic fibrosis (CF) often experience earlier lung function decline and worse infection outcomes than men (57, 58). Estrogenic regulation of CFTR expression and epithelial ion transport involves both ERβ and GPER1. ERβ supports antioxidant defense and epithelial repair, whereas GPER1 modulates mucin secretion and ciliary function. Combination therapies targeting both receptors could restore epithelial transport and immune balance, mitigating infection-driven exacerbations in females.

Lung Cancer

In non-small-cell lung cancer (NSCLC), ERβ predominance often correlates with better prognosis through transcriptional repression of proliferation genes and promotion of apoptosis. However, recent evidence also suggests a context-dependent protumorigenic role of ERβ. Liu et al. (59) demonstrated that ERβ can enhance tumor invasion by upregulating CXCR4 expression, thereby promoting migration and epithelial-mesenchymal transition in NSCLC. Membrane ER variants (ERα36) and GPER1 activate PI3K/AKT and yes-associated protein (YAP) signaling that favor invasion and therapy resistance (21). Estrogen also modulates tumor immunology: ERα increases PD-L1 expression and may affect responses to immune checkpoint therapy (60). Combinatorial targeting of ERα36/GPER1 with EGFR or PI3K inhibitors represents a promising translational strategy but must be balanced against potential systemic and tumorigenic risks.

THERAPEUTIC AND TRANSLATIONAL IMPLICATIONS

The mechanistic clarity summarized above enables a translational pivot from descriptive endocrinology to receptor-targeted pulmonary therapeutics. Multiple strategic paths converge: receptor-selective targeting, ligand biasing, combinatorial approaches, and localized (inhaled) delivery systems designed to achieve high pulmonary concentrations while minimizing systemic estrogenic exposure and off-target effects. Such delivery methods are especially valuable for ERβ-selective agonists intended to treat airway inflammation and vascular remodeling, where direct deposition in the lung allows efficient receptor engagement and reduced hormonal side effects (54–56).

Table 1 summarizes these translational strategies, outlining experimental approaches, biomarkers, and model systems that can validate receptor-specific mechanisms and optimize delivery routes for ER-targeted interventions. Table 1 highlights how single-cell mapping, receptor fractionation, ex vivo functional assays, and in vivo life-stage models together form an integrated pipeline for translating mechanistic discoveries into safe, receptor-selective therapies.

First, ERβ-selective agonists (e.g., LY500307, WAY-200070, and diarylpropionitrile) recapitulate anti-inflammatory and antifibrotic effects in preclinical models without engaging ERα-driven proliferation, supporting further translational exploration (16). Second, GPER1 agonists such as G-1 produce rapid bronchodilation and suppress inflammatory cytokines through cAMP/PKA and PI3K/AKT and may be useful in treating acute exacerbations or as adjuncts to slow disease progression (47, 62). Third, ERα antagonists and selective estrogen-receptor modulators (SERMs) can repress NF-κB-driven inflammation and potentially restore glucocorticoid sensitivity in steroid-

Table 1. *Priority experimental approaches and biomarkers to validate receptor-specific mechanisms and support translational progress*

Experiment	Rationale	Key Readouts/Biomarkers	Suggested Models/Samples	References
Single-cell and spatial transcriptomic/proteomic mapping	Define ERα, ERβ, and GPER1 expression across lung compartments; identify sex- and disease-specific receptor localization	ER isoform transcripts (ERα36/46), coexpression with IL-10, IL-17, and TGF-β/SMAD markers; ERβ/GPER1-high cell clusters	Human airway biopsies, resected lung tissue, single-cell suspensions for scRNA-seq + spatial transcriptomics	(6–8, 19)
Receptor fractionation and isoform quantification (nuclear, membrane, mitochondrial)	Distinguish genomic vs. non-genomic receptor pools and quantify truncated isoforms; assess posttranslational modifications	ER isoform ratios (full-length/ERα36/46), phosphorylation or SUMOylation status, p-AKT activation	Primary airway epithelial cells, fibroblasts, macrophages; fractionated lung biopsies	(19, 28–30)
Airway smooth muscle (ASM) contractility and calcium dynamics assays	Evaluate nongenomic (GPER1-mediated) bronchodilation and ERβ effects on contractility and proliferation	Intracellular Ca^{2+} flux, cAMP levels, p-MLC, RhoA activity, relaxation response to ERβ/GPER1 agonists (G-1, DPN)	Primary human ASM cells, tracheal rings, allergen-challenged mice	(2, 11, 12, 15, 16)
Ex vivo airway biopsy or air-liquid interface (ALI) epithelial models	Assess receptor-dependent epithelial barrier and inflammatory responses under physiologic estrogen exposure	TEER, MUC5AC expression, IL-8, IL-6, IL-10 release, epithelial repair rate postinjury	Human ALI cultures (male/female), bronchial explants ± ER agonists	(6, 7, 42)
Mitochondrial functional assays (Seahorse XF, mtDNA expression)	Quantify ERβ/GPER1 regulation of oxidative phosphorylation and redox balance	Basal/maximal OCR, ROS, SOD2, CAT, GPX expression, mitochondrial *OXPHOS* gene upregulation	Primary epithelial cells, fibroblasts, macrophages; isolated mitochondria	(15, 19, 61)
Ligand-bias pharmacologic profiling	Identify ligands that favor ERβ/GPER1 protective signaling while minimizing ERα/mTOR proliferative signaling	p-AKT/p-mTOR ratio, coactivator recruitment (SRC-1, PGC-1α), NF-κB inhibition, transcriptional reporter assays	Isoform-specific cell lines, high-throughput ligand screens, primary-cell validation	(14, 27, 62)
Life-stage and hormonal exposure models (ovariectomy ± HRT, allergen, smoke, fibrosis)	Explore life-course-dependent receptor shifts and hormonal modulation under stress or disease exposure	Disease phenotype (AHR, fibrosis, vascular remodeling), tissue ER expression, cytokine profiles, mitochondrial activity	Ovariectomized mice ± estradiol/HRT; HDM or OVA allergy, cigarette-smoke or bleomycin fibrosis models	(3, 49, 56)
3-D organoid/coculture models (epithelium-immune-fibroblast)	Investigate paracrine signaling, EV exchange, and receptor-targeted therapeutic effects in multicellular contexts	EV miRNA cargo, macrophage polarization (M1/M2), fibroblast α-SMA, collagen production, drug response to ERβ/GPER1 agonists	Human airway organoids or cocultures (male/female donors); patient-derived lung explants	(9, 10, 17, 48)

AHR, airway hyperresponsiveness; ER, estrogen receptor; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; EV, extracellular vesicle; GPER1, G-protein-coupled estrogen receptor 1; HDM, house dust mite; HRT, hormone replacement therapy; MLC, myosin light chain; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OCR, oxygen consumption rate; OVA, ovalbumin; RhoA, Ras homolog family member A; SMA, smooth muscle actin (α-SMA); TEER, transepithelial electrical resistance.

resistant asthma, but their systemic effects require careful assessment (63). The emergent class of biased ligands offers the opportunity to stabilize receptor conformations that favor anti-inflammatory coactivator recruitment (e.g., SRC-1 and PGC-1α) while avoiding proliferative cofactor engagement (61).

Combined therapies that account for pathway cross talk will likely be most effective. For example, pairing ERβ agonists or GPER1 activators with corticosteroids or anti-IL-5/IL-13 biologics in asthma and COPD may synergize anti-inflammatory responses; combining ERβ activation with antifibrotic agents (nintedanib and pirfenidone) merits study in ILD; and coinhibition of ERα36/GPER1 with EGFR/PI3K inhibitors could overcome resistance in ER-positive lung cancers. Importantly, sex, hormonal stage, and receptor expression should be integrated into trial design (64, 65). Biomarkers such as circulating estradiol, tissue ER isoform ratios, receptor localization, and phospho-signatures can enable patient stratification and pharmacodynamic monitoring. Noninvasive imaging (ER-targeted PET) and exhaled-breath metabolomics are promising avenues for real-time assessment.

Finally, inhaled formulations or nanocarrier-based delivery systems could maximize local lung exposure while minimizing systemic estrogenic effects and off-target risks. Drug development priorities include GPER1-biased ligands that preferentially activate anti-inflammatory PI3K/AKT arms without engaging mTOR-driven proliferation, dual ERβ/GPER1 agonists that combine genomic and nongenomic benefits, and computational/structural approaches to design ligands with desired signaling bias.

CONCLUSIONS

ERs form an integrated, context-sensitive signaling network that controls inflammation, redox homeostasis, and structural remodeling in the lung. ERβ and GPER1 often confer cytoprotective, anti-inflammatory, and antifibrotic effects, whereas ERα and certain membrane/splice variants can amplify inflammation, proliferation, and remodeling. The balance among receptor subtypes, splice forms, subcellular localization, and microenvironmental context explains the dual, and sometimes paradoxical, roles of estrogen in pulmonary disease and

underlies important sex differences in clinical patterns. Advancing the field requires precise mechanistic dissection, receptor-selective pharmacology, sex-aware clinical designs, and long-term safety evaluation. With these tools, receptor-targeted precision medicine for lung disease is an achievable goal.

Key Points

1) ERα, Erβ, and GPER1 exert distinct but interacting genomic, nongenomic, and mitochondrial effects in airway, vascular, and immune cells.
2) ERβ and GPER1 largely mediate protective anti-inflammatory and antifibrotic signaling; ERα commonly promotes proinflammatory and proliferative programs.
3) Sex-related disease variability arises from differences in receptor subtype activity and localization: ERα-driven inflammation predominates in female asthma and COPD, whereas ERβ and GPER1 signaling confer antifibrotic and vasoprotective effects in ILD and PH; altered ERα36 and ERβ distribution contribute to sex differences in lung cancer.
4) Therapeutic strategies should emphasize receptor selectivity, ligand bias, local (inhaled) delivery, and sex/hormone stratification in trials.
5) Critical next steps include mapping receptor topology at single-cell resolution, developing biased ligands, and integrating receptor biomarkers into clinical studies.

Outstanding Questions

1) What molecular determinants convert ER signaling from protective to profibrotic in chronic injury?
2) How do ER splice variants (ERα36/46) and GPER1 interact within single cells to drive divergent outcomes?
3) Can pharmacologic amplification of mitochondrial ERβ be achieved safely to mitigate oxidative stress in COPD and fibrosis?
4) How should sex, hormonal status, and receptor biomarkers be operationalized in clinical trial design and regulatory pathways?
5) What are the long-term oncogenic and systemic safety implications of chronic ERβ or GPER1 activation?

DISCLOSURES

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AUTHOR CONTRIBUTIONS

C.D.E. prepared figures; C.D.E. drafted manuscript; C.D.E. and P.S. edited and revised manuscript; C.D.E. and P.S. approved final version of manuscript.

REFERENCES

1. **Cao Z**, **He L**, **Luo Y**, **Tong X**, **Zhao J**, **Huang K**, **Chen Q**, **Jiao L**, **Liu Y**, **Geldsetzer P**, **Yang T**, **Wang C**, **Bärnighausen TW**, **Chen S.** Burden of chronic respiratory diseases and their attributable risk factors in 204 countries and territories, 1990–2021: results from the global burden of disease study 2021. *Chin Med J Pulm Crit Care Med* 3: 100–110, 2025. doi:10.1016/j.pccm.2025.05.005.
2. **Barnes PJ.** Sex differences in chronic obstructive pulmonary disease mechanisms. *Am J Respir Crit Care Med* 193: 813–814, 2016. doi:10.1164/rccm.201512-2379ED.
3. **Silveyra P**, **Babayev M**, **Ekpruke CD.** Sex, hormones, and lung health. *Physiol Rev* 106: 53–86, 2026. doi:10.1152/physrev.00026.2024.
4. **Hou H**, **Adzika GK.** Estrogen and estrogen receptors in cardioimmunology: implications in physiology, pathophysiology, and therapeutic strategies. *Acta Physiol (Oxf)* 241: e70124, 2025. doi:10.1111/apha.70124.
5. **Barnes PJ.** The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 118: 3546–3556, 2008. doi:10.1172/JCI36130.
6. **Chen P**, **Li B**, **Ou-Yang L.** Role of estrogen receptors in health and disease. *Front Endocrinol (Lausanne)* 13: 839005, 2022. doi:10.3389/fendo.2022.839005.
7. **Ekpruke CD**, **Silveyra P.** Sex differences in airway remodeling and inflammation: clinical and biological factors. *Front Allergy* 3: 875295, 2022. doi:10.3389/falgy.2022.875295.
8. **Gong P**, **Madak-Erdogan Z**, **Li J**, **Cheng J**, **Greenlief CM**, **Helferich W**, **Katzenellenbogen JA**, **Katzenellenbogen BS.** Transcriptomic analysis identifies gene networks regulated by estrogen receptor α (ERα) and ERβ that control distinct effects of different botanical estrogens. *Nucl Recept Signal* 12: e001, 2014. doi:10.1621/nrs.12001.
9. **Kovats S.** Estrogen receptors regulate innate immune cells and signaling pathways. *Cell Immunol* 294: 63–69, 2015. doi:10.1016/j.cellimm.2015.01.018.
10. **Notas G**, **Kampa M**, **Castanas E.** G protein-coupled estrogen receptor in immune cells and its role in immune-related diseases. *Front Endocrinol (Lausanne)* 11: 579420, 2020. doi:10.3389/fendo.2020.579420.
11. **Ambhore N**, **Bhallamudi S**, **Kalidhindi RSR**, **Saladi S**, **Pabelick CM**, **Prakash YS**, **Satish V.** Role of estrogen metabolites in regulating intracellular calcium in human airway smooth muscle cell. *Am J Respir Crit Care Med* 201: A1237–A1237, 2020. doi:10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A1237.
12. **Ambhore NS**, **Balraj P**, **Pabelick CM**, **Prakash YS**, **Sathish V.** Estrogen receptors differentially modifies lamellipodial and focal adhesion dynamics in airway smooth muscle cell migration. *Mol Cell Endocrinol* 579: 112087, 2024. doi:10.1016/j.mce.2023.112087.
13. **Clements L**, **Alexander A**, **Hamilton K**, **Irving A**, **Harvey J.** G-protein coupled estrogen receptor (GPER1) activation promotes synaptic insertion of AMPA receptors and induction of chemical LTP at hippocampal temporoammonic-CA1 synapses. *Mol Brain* 16: 16, 2023. doi:10.1186/s13041-023-01003-3.
14. **Prossnitz ER**, **Barton M.** The G-protein-coupled estrogen receptor GPER in health and disease. *Nat Rev Endocrinol* 7: 715–726, 2011. doi:10.1038/nrendo.2011.122.
15. **Xu F**, **Ma J**, **Wang X**, **Wang X**, **Fang W**, **Sun J**, **Li Z**, **Liu J.** The role of G protein-coupled estrogen receptor (GPER) in vascular pathology and physiology. *Biomolecules* 13: 1410, 2023. doi:10.3390/biom13091410.
16. **Weiser MJ**, **Wu TJ**, **Handa RJ.** Estrogen receptor-beta agonist diarylpropionitrile: biological activities of R- and S-enantiomers on behavior and hormonal response to stress. *Endocrinology* 150: 1817–1825, 2009. doi:10.1210/en.2008-1355.
17. **Keselman A**, **Fang X**, **White PB**, **Heller NM.** Estrogen signaling contributes to sex differences in macrophage polarization during asthma. *J Immunol* 199: 1573–1583, 2017. doi:10.4049/jimmunol.1601975.
18. **Tzouvelekis A**, **Bouros D.** Estrogen signaling and MicroRNAs in lung fibrosis. sex, hormones, and rock scars. *Am J Respir Crit Care Med* 200: 1199–1200, 2019. doi:10.1164/rccm.201908-1535ED.
19. **Chen JQ**, **Russo PA**, **Cooke C**, **Russo IH**, **Russo J.** ERbeta shifts from mitochondria to nucleus during estrogen-induced neoplastic transformation of human breast epithelial cells and is involved in estrogen-induced synthesis of mitochondrial respiratory chain proteins. *Biochim Biophys Acta* 1773: 1732–1746, 2007. doi:10.1016/j.bbamcr.2007.05.008.
20. **Prossnitz ER**, **Barton M.** Estrogen biology: new insights into GPER function and clinical opportunities. *Mol Cell Endocrinol* 389: 71–83, 2014. doi:10.1016/j.mce.2014.02.002.
21. **Gao X**, **Cai Y**, **Wang Z**, **He W**, **Cao S**, **Xu R**, **Chen H.** Estrogen receptors promote NSCLC progression by modulating the membrane

receptor signaling network: a systems biology perspective. *J Transl Med* 17: 308, 2019. doi:10.1186/s12967-019-2056-3.
22. **Siegfried JM**, **Stabile LP.** Estrongenic steroid hormones in lung cancer. *Semin Oncol* 41: 5–16, 2014. doi:10.1053/j.seminoncol.2013.12.009.
23. **Song D**, **He H**, **Indukuri R**, **Huang Z**, **Stepanauskaite L**, **Sinha I**, **Haldosén L-A**, **Zhao C**, **Williams C.** ERα and ERβ homodimers in the same cellular context regulate distinct transcriptomes and functions. *Front Endocrinol (Lausanne)* 13: 930227, 2022. doi:10.3389/fendo.2022.930227.
24. **DeLeon C**, **Wang DQ**, **Arnatt CK.** G protein-coupled estrogen receptor, GPER1, offers a novel target for the treatment of digestive diseases. *Front Endocrinol (Lausanne)* 11: 578536, 2020. doi:10.3389/fendo.2020.578536.
25. **Chlamydas S**, **Markouli M**, **Strepkos D**, **Piperi C.** Epigenetic mechanisms regulate sex-specific bias in disease manifestations. *J Mol Med (Berl)* 100: 1111–1123, 2022. doi:10.1007/s00109-022-02227-x.
26. **Son SE**, **Im DS.** Activation of G protein-coupled estrogen receptor 1 (GPER) attenuates obesity-induced asthma by switching M1 macrophages to M2 macrophages. *Int J Mol Sci* 25: 9532, 2024. doi:10.3390/ijms25179532.
27. **Pagano MT**, **Ortona E**, **Dupuis ML.** A role for estrogen receptor alpha36 in cancer progression. *Front Endocrinol (Lausanne)* 11: 506, 2020. doi:10.3389/fendo.2020.00506.
28. **Sołtysik K**, **Czekaj P.** ERα36—another piece of the estrogen puzzle. *Eur J Cell Biol* 94: 611–625, 2015. doi:10.1016/j.ejcb.2015.10.001.
29. **Saito K**, **Cui H.** Estrogen receptor alpha splice variants, post-translational modifications, and their physiological functions. *Cells* 12: 895, 2023. doi:10.3390/cells12060895.
30. **Figtree GA**, **McDonald D**, **Watkins H**, **Channon KM.** Truncated estrogen receptor alpha 46-kDa isoform in human endothelial cells: relationship to acute activation of nitric oxide synthase. *Circulation* 107: 120–126, 2003. doi:10.1161/01.cir.0000043805.11780.f5.
31. **Novelle MG**, **Camacho-Morales A**, **Martínez De Morentin PB.** Editorial: role of estrogens as key regulators of energy homeostasis. *Front Endocrinol (Lausanne)* 14: 1279619, 2023. doi:10.3389/fendo.2023.1279619.
32. **Shanle EK**, **Xu W.** Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. *Chem Res Toxicol* 24: 6–19, 2011. doi:10.1021/tx100231n.
33. **Mukherjee TK**, **Malik P**, **Hoidal JR.** The emerging role of estrogen related receptorα in complications of non-small cell lung cancers. *Oncol Lett* 21: 258, 2021. doi:10.3892/ol.2021.12519.
34. **Guerrero-Limón G**, **Muller M.** Exploring estrogen antagonism using CRISPR/Cas9 to generate specific mutants for each of the receptors. *Chemosphere* 364: 143100, 2024. doi:10.1016/j.chemosphere.2024.143100.
35. **Ciallella HL**, **Russo DP**, **Aleksunes LM**, **Grimm FA**, **Zhu H.** Predictive modeling of estrogen receptor agonism, antagonism, and binding activities using machine- and deep-learning approaches. *Lab Invest* 101: 490–502, 2021. doi:10.1038/s41374-020-00477-2.
36. **Kovalski JR**, **Kuzuoglu-Ozturk D**, **Ruggero D.** Protein synthesis control in cancer: selectivity and therapeutic targeting. *EMBO J* 41: e109823, 2022. doi:10.15252/embj.2021109823.
37. **Wang J**, **Li K**, **Hao D**, **Li X**, **Zhu Y**, **Yu H**, **Chen H.** Pulmonary fibrosis: pathogenesis and therapeutic strategies. *MedComm (2020)* 5: e744, 2024. doi:10.1002/mco2.744.
38. **Pedram A**, **Razandi M**, **O'Mahony F**, **Lubahn D**, **Levin ER.** Estrogen receptor-beta prevents cardiac fibrosis. *Mol Endocrinol* 24: 2152–2165, 2010. doi:10.1210/me.2010-0154.
39. **Yung JA**, **Fuseini H**, **Newcomb DC.** Hormones, sex, and asthma. *Ann Allergy Asthma Immunol* 120: 488–494, 2018. doi:10.1016/j.anai.2018.01.016.
40. **Jacobsen EA**, **Doyle AD**, **Colbert DC**, **Zellner KR**, **Protheroe CA**, **LeSuer WE**, **Lee NA**, **Lee JJ.** Differential activation of airway eosinophils induces IL-13-mediated allergic Th2 pulmonary responses in mice. *Allergy* 70: 1148–1159, 2015. doi:10.1111/all.12655.
41. **Na H**, **Lim H**, **Choi G**, **Kim BK**, **Kim SH**, **Chang YS**, **Nurieva R**, **Dong C**, **Chang SH**, **Chung Y.** Concomitant suppression of T_H2 and T_H17 cell responses in allergic asthma by targeting retinoic acid receptor-related orphan receptor γt. *J Allergy Clin Immunol* 141: 2061–2073.e5, 2018. doi:10.1016/j.jaci.2017.07.050.
42. **Kortekaas RK**, **Geillinger-Kästle KE**, **Fuentes-Mateos R**, **van Orsoy R**, **Al-Alyan N**, **Burgess JK**, **Gosens R.** The disruptive effects of COPD exacerbation-associated factors on epithelial repair responses. *Front Immunol* 15: 1346491, 2024. doi:10.3389/fimmu.2024.1346491.
43. **Wasti B**, **Chen Z**, **He Y**, **Duan WT**, **Liu SK**, **Xiang XD.** Role of sex hormones at different physiobiological conditions and therapeutic potential in MBD2 mediated severe asthma. *Oxid Med Cell Longev* 2021: 7097797, 2021. doi:10.1155/2021/7097797.
44. **Gutiérrez-Brito JA**, **Lomelí-Nieto JÁ**, **Muñoz-Valle JF**, **Oregon-Romero E**, **Corona-Angeles JA**, **Hernández-Bello J.** Sex hormones and allergies: exploring the gender differences in immune responses. *Front Allergy* 5: 1483919, 2025. doi:10.3389/falgy.2024.1483919.
45. **Nakagome K**, **Nagata M.** The possible roles of IL-4/IL-13 in the development of eosinophil-predominant severe asthma. *Biomolecules* 14: 546, 2024. doi:10.3390/biom14050546.
46. **Sharma G**, **Hu C**, **Staquicini DI**, **Brigman JL**, **Liu M**, **Mauvais-Jarvis F**, **Pasqualini R**, **Arap W**, **Arterburn JB**, **Hathaway HJ**, **Prossnitz ER.** Preclinical efficacy of the GPER-selective agonist G-1 in mouse models of obesity and diabetes. *Sci Transl Med* 12: eaau5956, 2020 [Erratum in *Sci Transl Med* 14: eadc9803, 2022]. doi:10.1126/scitranslmed.aau5956.
47. **Chen J**, **Zhao R**, **Wang Y**, **Xiao H**, **Lin W**, **Diao M**, **He S**, **Mei P**, **Liao Y.** G protein-coupled estrogen receptor activates PI3K/AKT/mTOR signaling to suppress ferroptosis via SREBP1/SCD1-mediated lipogenesis. *Mol Med* 30: 28, 2024. doi:10.1186/s10020-023-00763-x.
48. **Itoga M**, **Ishioka Y**, **Makiguchi T**, **Tanaka H**, **Taima K**, **Saito N**, **Tomita H**, **Tasaka S.** Role of G-protein-coupled estrogen receptor in the pathogenesis of chronic asthma. *Immunol Lett* 265: 16–22, 2024 [Erratum in *Immunol Lett*. 267:106868, 2024]. doi:10.1016/j.imlet.2023.12.001.
49. **Pinkerton KE**, **Harbaugh M**, **Han MK**, **Jourdan Le Saux C**, **Van Winkle LS**, **Martin WJ**, **Kosgei RJ**, **Carter EJ**, **Sitkin N**, **Smiley-Jewell SM**, **George M.** Women and lung disease. Sex differences and global health disparities. *Am J Respir Crit Care Med* 192: 11–16, 2015. doi:10.1164/rccm.201409-1740PP.
50. **Guo Q**, **Jin Y**, **Chen X**, **Ye X**, **Shen X**, **Lin M**, **Zeng C**, **Zhou T**, **Zhang J.** NF-κB in biology and targeted therapy: new insights and translational implications. *Signal Transduct Target Ther* 9: 53, 2024. doi:10.1038/s41392-024-01757-9.
51. **Jiang M**, **Bu W**, **Wang X**, **Ruan J**, **Shi W**, **Yu S**, **Huang L**, **Xue P**, **Tang J**, **Zhao X**, **Su L**, **Cheng D.** Pulmonary fibrosis: from mechanisms to therapies. *J Transl Med* 23: 515, 2025. doi:10.1186/s12967-025-06514-2.
52. **Sun Y**, **Sangam S**, **Guo Q**, **Wang J**, **Tang H**, **Black SM**, **Desai AA.** Sex differences, estrogen metabolism and signaling in the development of pulmonary arterial hypertension. *Front Cardiovasc Med* 8: 719058, 2021. doi:10.3389/fcvm.2021.719058.
53. **You Q**, **Song H**, **Zhu Z**, **Wang J**, **Wang R**, **Du M**, **Fu Y**, **Yuan J**, **Tan R.** Decoding the enigmatic estrogen paradox in pulmonary hypertension: delving into estrogen metabolites and metabolic enzymes. *Cell Mol Biol Lett* 29: 155, 2024. doi:10.1186/s11658-024-00671-w.
54. **Chaudhary KR**, **Deng Y**, **Yang A**, **Cober ND**, **Stewart DJ.** Penetrance of severe pulmonary arterial hypertension in response to vascular endothelial growth factor receptor 2 blockade in a genetically prone rat model is reduced by female sex. *J Am Heart Assoc* 10: e019488, 2021. doi:10.1161/JAHA.120.019488.
55. **Boucherat O**, **Agrawal V**, **Lawrie A**, **Bonnet S.** The latest in animal models of pulmonary hypertension and right ventricular failure. *Circ Res* 130: 1466–1486, 2022. doi:10.1161/CIRCRESAHA.121.319971.
56. **Frump AL**, **Goss KN**, **Vayl A**, **Albrecht M**, **Fisher A**, **Tursunova R**, **Fierst J**, **Whitson J**, **Cucci AR**, **Brown MB**, **Lahm T.** Estradiol improves right ventricular function in rats with severe angioproliferative pulmonary hypertension: effects of endogenous and exogenous sex hormones. *Am J Physiol Lung Cell Mol Physiol* 308: L873–L890, 2015. doi:10.1152/ajplung.00006.2015.
57. **Lam GY**, **Goodwin J**, **Wilcox PG**, **Quon BS.** Sex disparities in cystic fibrosis: review on the effect of female sex hormones on lung pathophysiology and outcomes. *ERJ Open Res* 7: 00475–02020, 2021. doi:10.1183/23120541.00475-2020.
58. **Saint-Criq V**, **Harvey BJ.** Estrogen and the cystic fibrosis gender gap. *Steroids* 81: 4–8, 2014. doi:10.1016/j.steroids.2013.11.023.
59. **Liu S**, **Hu C**, **Li M**, **An J**, **Zhou W**, **Guo J**, **Xiao Y.** Estrogen receptor beta promotes lung cancer invasion via increasing CXCR4 expression. *Cell Death Dis* 13: 70, 2022. doi:10.1038/s41419-022-04514-4.

60. **Maitra R**, **Malik P**, **Mukherjee TK.** Targeting estrogens and various estrogen-related receptors against non-small cell lung cancers: a perspective. *Cancers (Basel)* 14: 80, 2021. doi:10.3390/cancers14010080.
61. **Rius-Pérez S**, **Torres-Cuevas I**, **Millán I**, **Ortega ÁL**, **Pérez S.** PGC-1α, inflammation, and oxidative stress: an integrative view in metabolism. *Oxid Med Cell Longev* 2020: 1452696, 2020. doi:10.1155/2020/1452696.
62. **Arterburn JB**, **Prossnitz ER.** G protein-coupled estrogen receptor GPER: molecular pharmacology and therapeutic applications. *Annu Rev Pharmacol Toxicol* 63: 295–320, 2023. doi:10.1146/annurev-pharmtox-031122-121944.
63. **Jin P**, **Duan X**, **Huang Z**, **Dong Y**, **Zhu J**, **Guo H**, **Tian H**, **Zou CG**, **Xie K.** Nuclear receptors in health and disease: signaling pathways, biological functions and pharmaceutical interventions. *Signal Transduct Target Ther* 10: 228, 2025. doi:10.1038/s41392-025-02270-3.
64. **Carriera L**, **Fantò M**, **Martini A**, **D'Abramo A**, **Puzio G**, **Scaramozzino MU**, **Coppola A.** Combination of biological therapy in severe asthma: where we are? *J Pers Med* 13: 1594, 2023. doi:10.3390/jpm13111594.
65. **Chen Y**, **Wang L**, **Xie J.** Combining dual biologics therapy for severe asthma: a series of ten cases. *J Asthma Allergy* 18: 507–517, 2025. doi:10.2147/JAA.S507008.