Journal of Steroid Biochemistry & Molecular Biology 127 (2011) 216–222

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Sex steroid receptors in human lung diseases

Mohit K. Verma, Yasuhiro Miki, Hironobu Sasano*

Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan

ARTICLE INFO

Article history:
Received 29 July 2011
Accepted 30 July 2011

Keywords:
Steroid receptor
Estrogen
Progesterone
Androgen
Lung disease

ABSTRACT

Several epidemiological studies have reported that gender differences exist in clinical and biological manifestations of human lung diseases. In particular, women are far more likely to develop both neoplastic and non-neoplastic lung diseases than men. This gender difference above suggests that sex steroid may be involved in the pathogenesis of various lung diseases. These sex steroids mediate their effects through sex steroid receptors including estrogen receptors (ER) i.e. ERα and ERβ progesterone receptors (PR) i.e. PR-A and PR-B and androgen receptors (ARs), all of which have been reported to be expressed in lung tissue. Therefore it becomes important to clarify the potential roles of sex steroid receptor in both neoplastic and non-neoplastic lung diseases toward improved treatment options for the patients. In this review, we summarized a number of studies in humans and experimental animals that have identified possible roles of sex steroids in respiratory physiology and pathology.

Contents

1. Sex differences in human lung diseases

Roles of sex steroids receptors in sexual development have been postulated for many years [1] but their effects beyond the reproductive system have remained relatively unknown. However, recently the biological and clinical significance of the sex steroids receptors (and, by association, sex hormones) in pathogenesis and development of numerous disorders have been proposed in many studies [2]. The sex steroids receptors are composed of estrogen receptors (ER) i.e. ERα and ERβ, progesterone receptors (PR) i.e. PR-A and PR-B and androgen receptors (ARs), all of which are present in rats [3], mouse [4], and humans [5]. ERα, ERβ, PR-A and PR-B expression have been identified not only in the mammalian female and male reproductive tracts, but also in the female mammary glands, bone, cardiovascular tissues, lung, and the brain [1,6] while AR has been reported to be expressed primarily in mammalian reproductive tissues [7]. In addition, increasing number of investigators has paid attentions to gender differences of various non-reproductive disorders. All the sex steroid receptors have been reported to be expressed in lung tissues of various mammalian species [6,8]. Therefore, sex hormones may reasonably be postulated to play important roles in the lung under both physiological and pathophysiological conditions via sex steroid hormone pathway, Fig. 1.

The potential contributions of sex hormones to formation of gender disparities in lung diseases have been proposed by some investigators. For instance, clinical course or responses to therapeutic modes of chronic obstructive pulmonary disease (COPD), asthma, lung fibrosis, lung cancer, and other respiratory ailments have been reported to be influenced in some way by gender

* Corresponding author at: Department of Pathology, Tohoku University Graduate School of Medicine, 2-1 Seriyo-machi, Aoba-ku, Sendai, Miyagi-ken 980-8575, Japan. Tel.: +81 22 717 8050; fax: +81 22 717 8051.
E-mail address: hsasano@patholo2.med.tohoku.ac.jp (H. Sasano).

0960-0760/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2011.07.013

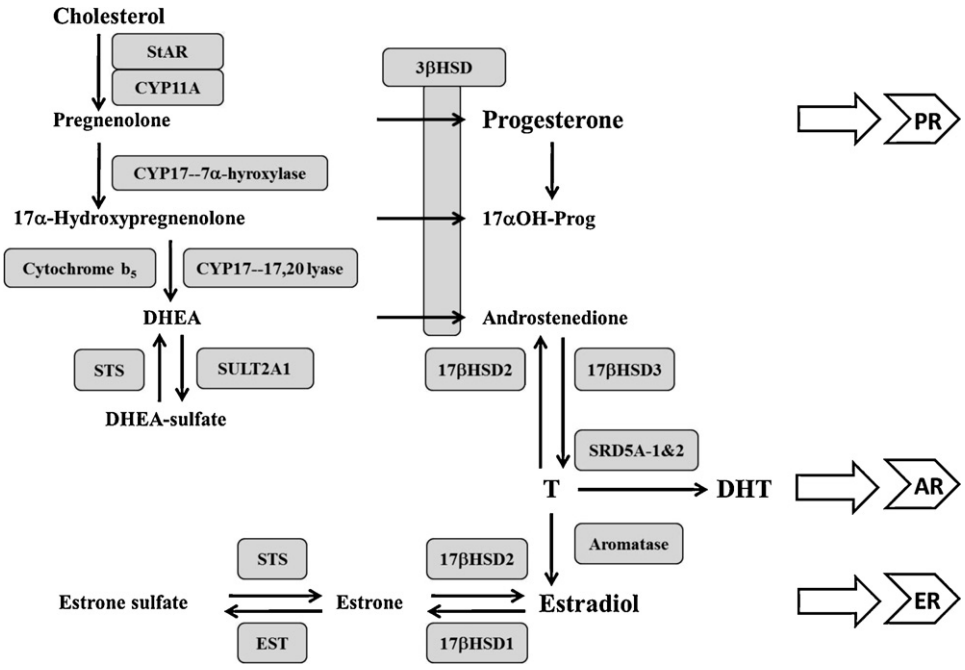

Fig. 1. Overview of the sex steroid hormone biosynthetic pathway and associated nuclear receptors. StAR, steroidogenic acute regulatory protein; CYP, cytochrome P450; STS, steroid sulfatase; SULT2A1, hydroxysteroid sulfotransferase; 3βHSD, 3β-hydroxysteroid dehydrogenase; 17βHSD, 17β-hydroxysteroid dehydrogenase; SRD5A, steroid 5-alpha-reductase; EST, estrogen sulfotransferase; T, testosterone; DHT, dihydrotestosterone; PR, progesterone receptor, AR, androgen receptor; ER, estrogen receptor.

differences [9–11]. In particular, an increased morbidity and mortality from these pulmonary disorders has been observed in women. For instance, in 2000, for the first time the number of women dying of COPD surpassed the number of men despite lower incidence of smoking [12]. In addition, women are more likely to develop COPD after smoking less number of cigarettes per lifetime than men [13] and also have a 50% increment in the risks of mortality compared to men among the patients with severe COPD with oxygen dependence [14]. Women are also approximately 20% more likely than men to ever have been diagnosed with asthma and have 40% higher asthma prevalence and 45% higher asthma death rate than men [15]. It is also well known that the patients with pulmonary exacerbations are more likely to be females than males among the patients with COPD [16] and female cystic fibrosis patients are associated with adverse clinical outcome than their male counterparts [17]. There has been a marked increment in the incidence of lung cancer development in females over the last decade as well. Among non-smoking-associated lung carcinoma patients, women are more likely than men to develop lung carcinomas, especially adenocarcinomas [18,19]. In addition, overall survival was significantly higher in women with no hormonal replacement therapy (HRT) compared with those who received HRT [20,21]. Women have been also reported to be more susceptible to carcinogenic actions in lung cancer development as high concentrations of heavy metals such as Cd or Ni resulted in a significant increment in lung cancer mortality in women, but not in men [22].

Genetic and environmental factors are considered to clearly play important roles but these gender disparities in both neoplastic and non-neoplastic lung disease development may also depend partly upon hormonal actions in lung epithelial cells. The activation of the hormonal pathway in either neoplastic or non-neoplastic lung epithelial cells may further depend upon the types and degrees of steroid receptor expression. Therefore, in this brief review, we will summarize what are known on the expression of sex steroid receptors and their potential roles in the pathogenesis of both neoplastic and non-neoplastic diseases in lung patients.

2. Estrogen receptors in non-neoplastic human lung diseases

The most convincing unifying hypothesis for explaining the gender differences in pathogenesis of non-neoplastic diseases in lung patients is that estrogen is indeed involved in lung disease development. The exact mechanism by which estrogens may be involved is not necessarily clear at this juncture, but some investigators have reported that they may act as ligands for ERs expressed in lung epithelial cells. ERs have been reported to be expressed in variety of tissues including ovary, breast, CNS, bone and kidney [1,6,23]. Earlier studies demonstrated that ERs were expressed only in lung tumor tissues but not in normal counterparts with a much higher frequency in female patients [24,25]. However, ERs, particularly ERβ, was subsequently demonstrated to be relatively widely expressed and to be functional both in normal and cancerous lung tissues of both genders with both nuclear and extra-nuclear localizations [26–29]. In addition, the study using ER-deficient (ERKO) mice revealed that both ERα and ERβ are required for the formation of a full functional and morphological development of alveoli structures in female mice, but have a much smaller effect on alveolar dimensions in male mice [30,31]. This result above also suggested that ER pathway may contribute more significantly to pathophysiology of female lung when compared to male lung. Therefore, various experimental animal models have been employed in order to examine potential sex-related differences in the risk of inflammatory lung diseases to clarify these gender differences of pulmonary disorders, Table 1.

Chronic exposure of mice to cigarette smoke has led to the development of emphysematous-like changes in alveolar structure and related alterations of pulmonary functions more rapidly in females than in males [32]. After inhalation, chemicals in cigarette smoke are metabolized largely by cytochrome P450 (CYP) enzymes, which are a family of xenobiotic enzymes responsible for detoxifying cigarette smoke. CYP-based metabolites are then conjugated by Phase II enzymes and excreted. However, if there is underexpression of Phase II enzymes or complete saturation of their binding

Table 1
Summary of previous studies on ERs in non-neoplastic lung disease.

References	Methodology	No. of cases	Principal finding
[30]	*In vivo* (mouse)	–	Both ERα and ERβ are required for the development of alveoli structures in female mice, but have much smaller effect in male mice
[37]	*In vivo* (mouse)	–	Female mice demonstrated an increased airway inflammation when challenged with an allergen compared to male
[38]	*In vivo* (mouse)	–	Either ovariectomy or anti-estrogen therapy in female mice prevented this increased airway inflammation caused by the allergen
[39]	*In vivo* (rat)	–	E2* up-regulated pro-inflammatory cytokines, i.e. IL-1β and TNFα and down-regulated anti-inflammatory cytokines, i.e. IL-10
[43]	*In vitro* (NHNE*)		E2 up-regulated MUC5B (a mucin) via MAPK activation which was abrogated by ER blocker
[45]	*In vivo* (human) and *in vitro* (HBEC*)	CF* = 10 and non-CF = 12	E2 inhibited Ca^{2+} activated and uridine triphosphate mediated Cl^- secretion I either CF or non-CF patients which subsequently caused mucus plugging

* E2, estradiol; NHNE, normal human nasal epithelial cells; HBEC, human bronchial epithelial cells; CF, cystic fibrosis.

sites, CYP-based toxic metabolites accumulate in the lung and lungs may suffer oxidant damages through a process of bio-activation. Estradiol up-regulates these CYP enzymes without necessarily altering the expression of Phase II enzymes, which may make Phase II enzymes to get completely saturated of their binding sites and thereby makes female lungs more susceptible to oxidant damage in response to cigarette smoking. For instance, lungs of female mice are reported to be associated with higher expression of CYP enzymes and demonstrated increased accumulation of potent oxidants from naphthalene metabolites, a typical component of side stream cigarette smoke, compared to male mice [33]. In humans, cigarette smoking increases expression of CYP enzymes i.e. CYP1A1 and CYP1B1, which are regulated by ERα [34]. ER activation in the lungs increases protein expression of CYP1A1 as well [35]. The increased CYP expression was also reported to be related to increased levels of estradiol [36] and increased metabolism of cigarette smoke to generate oxidants/oxidizers [10]. These results all suggest that female sex hormone, estrogen, contribute to the development of oxidative stresses and thus may make female more susceptible to greater airway injuries or COPD than male.

Female mice demonstrated an increased airway inflammation when challenged with an allergen compared to male counterparts [37]. In addition, ovariectomized rats are protected from increased airway inflammation related to allergens and estrogen replacement in these ovariectomized rats reestablishes airway inflammation to levels detected in intact females [38]. In addition, treatment of female rats with the selective estrogen receptor modulator, tamoxifen, also blunted the development of allergic airway diseases [38]. These findings all suggest that female hormones augment airway inflammation in the presence of allergens. Estradiol may up-regulate early phase pro-inflammatory cytokines such as IL-1β and TNFα and down-regulate anti-inflammatory cytokines such as IL-10 [39]. One potential mechanism for this response could be estrogen-mediated deviation in helper T cells towards a TH2 phenotype. For example when male mice were given estradiol, the ratio of IL-2/IFN-Y to IL-4-producing cells became nearly equal, suggesting that estrogen promotes a TH2 response [40]. In addition to animal models, there are data suggesting that estrogen can stimulate secretion of IL-4, -5, -6, and -10 by TH2 lymphocytes, in humans [40]. All of these reported findings suggest that female sex hormone, estrogen, may modulate overall inflammatory response to allergen and thus make female more susceptible to incidence of asthma than male.

Accumulation of thick, tenacious mucus plays a pivotal role in pulmonary symptoms of cystic fibrosis (CF) pathophysiology [41]. Excess sputum production in the lung may contribute greatly to the morbidity and mortality in CF and other inflammatory lung diseases [42]. MUC5B is one of the major mucins in the human airway sub-mucosal glands and was reported to be upregulated by female sex hormone estrogen in human airway epithelial cells [43]. In addition, high circulating levels of estradiol are reported to reduce Ca^{2+}-activated Cl^- secretion from airway epithelial cells in culture, thereby disrupting ion and water balance and resulting in thick and tenacious mucus formation [44]. In humans, estrogen also inhibits both Ca^{2+}-activated and uridine triphosphate-mediated Cl^- secretion in both non-CF and CF airway epithelia [45]. These data above suggest that female sex hormone, estrogen, may enhance mucus production and result in worsening of airflow limitation in CF more significantly in female than male patients.

3. Estrogen receptors in neoplastic human lung diseases

Lung cancer remains the leading cause of cancer mortality worldwide. It is true that tobacco smoking still remains its prime cause among both men and women [46,47]. However, among non-smoking-associated lung cancer patients, it is also true that females are more likely than males to develop lung carcinomas, especially adenocarcinomas [18,19]. In addition, both estrogen receptors (ERs) and aromatase were reported to be expressed very frequently in human lung epithelial neoplasms [48]. These findings all suggest that sex steroids may contribute to the pathogenesis and development of lung carcinoma which may further lead to gender differences in lung cancer mortality. Earlier studies on the presence of ERs in lung tumor focused only on the classical ERα, then termed simply as ER. After the discovery of ERβ, human lung carcinoma has been studied by various laboratories for the patterns of both ERα and ERβ expression in NSCLCs using immunohistochemistry but results reported in these studies were highly inconsistent varying from "0% to 100% for ERα" and "30% to 100% for ERβ" [24,25,27,48–58]. ERβ immunoreactivity was associated with better clinical outcome especially in male NSCLC patients [52,54]. In addition, the presence of ERα and the absence of ERβ expression in lung tumor tissues were also reported to be associated with poor prognosis in NSCLC patients [55]. In addition, EGFR mutations were also reported to be associated with ERα expression [58] whereas ERβ expression was associated with aromatase expression in NSCLC patients [48]. These reports all suggest a possible functional correlation between ER expression with either aromatase expression or/and EGFR mutations in NSCLC patients.

A number of researchers have investigated the mechanisms involved in lung cancer progression via ER activation, Table 2. Estrogens stimulated cell proliferation in non-small cell lung carcinoma (NSCLC) cell lines to a far greater extent than in non-neoplastic lung fibroblasts [59]. Estrogens also promoted the transcription of estrogen-responsive (ERE) genes in NSCLC cells expressing endogenous ERs [62]. Many NSCLC cell lines lacking ERα but expressing ERβ demonstrated tumor promoting features [26,60–64]. These results are in contrast to the previously reported results of clinical studies in NSCLC patients which suggest that ERβ was associated with better clinical outcome in NSCLC patients [52,54,55].

Table 2
Summary of previous studies on ERs in neoplastic lung disease.

References	Methodology	No. of cases	Principal finding
[48]	IHC* (human)	105	ERβ expression was associated with aromatase expression in NSCLC*
[52,54,55]	IHC (human)	278/301/104	ERβ expression was associated with better clinical outcome in NSCLC
[56]	IHC/HPLC* (human)	59	Aromatase expression was associated with intratumoral E2 conc. in NSCLC
[58]	IHC (human)	317	ERα expression was associated with EGFR mutations in NSCLCs
[60–62]	*In vitro* (NSCLC cell lines)	–	ERβ demonstrated tumor promoting features in the absence of ERα
[26,62,63]	*In vivo* (mouse)	–	E2* stimulated the growth of lung carcinoma xenografts
[76]	IHC (human)	442	Lower levels of aromatase predicted a better survival in females above 65
[77,78]	*In vitro* and *in vivo*	–	Aromatase inhibitor (AI) suppressed the lung tumor growth
[79]	Southern blot (human)	46	Patients with a history of smoking had a significantly lower incidence of ER promoter methylation than non-smokers in lung tumors

* IHC, immunohistochemistry; NSCLC, non-small cell lung carcinomas; HPLC, high pressure liquid chromatography.

However, it is also important to note that results of recent studies have demonstrated that ERβ can function as a tumor promoter in the absence of ERα expression in other hormone-dependent cancer as well [65–69]. In NSCLC cell lines, genomic actions of estrogen were demonstrated to be induced only by ligands specific to ERβ and not by ligands specific to ERα [63]. These results all suggested that estrogenic actions in NSCLC cell lines are conveyed primarily through ERβ. In addition to these genomic actions of estrogens, some researchers have also demonstrated that estrogenic actions may occur at the cell surface in NSCLC cells involving mainly membrane/cytoplasmic pools of ERs [26,49,60,62,70,71]. In breast carcinoma cells, ERs utilize the membrane epidermal growth factor receptor (EGFR) to rapidly signal through various kinase cascades, i.e. mitogen activated protein kinase (MAPK) and/or protein kinase B (PKB/Akt) [72]. NSCLC cells demonstrated similar transactivation of EGFR on administration of exogenous estrogens which ultimately resulted in MAPK activation [26]. Many other investigators also reported a similar activation of MAPK and/or Akt on 17β-estradiol treatment in NSCLC cells, but without the transactivation of EGFR [49,60,61,70,71]. Whether estrogen exerts its effects in NSCLC primarily through genomic or non-genomic signaling pathway has, however, still remained in dispute. In addition to *in vivo* studies, 17β-estradiol exposure was demonstrated to stimulate the growth of lung carcinoma xenografts as well [26,62,63]. These data suggest that at this juncture, NSCLC could reasonably be considered as a novel estrogen target tissue.

In normal men and women, between 40% and 65% of circulating testosterone (T) and between 20% and 40% of circulating estradiol (E2) is bound to sex hormone binding globulin SHBG [73]. SHBG regulates tissue delivery of sex hormones by binding them and retaining them in the circulatory pool, where they are relatively inert. However, once the sex hormones dissociate from SHBG, they can escape the blood stream, and bind with the intracellular androgen or estrogen receptors. However, a large proportion of estrogens in women (approximately 75% before menopause, and close to 100% after menopause) are produced in peripheral hormone-target tissues through aromatase from abundantly present circulating precursor adrenal androgens [74]. Aromatase was reported to be expressed frequently in both male and female patients with human lung carcinoma [48,49,56,75]. Aromatase expression was also significantly associated with intra-tumoral estrogen concentration in NSCLCs [56]. A lower expression of aromatase was associated with better prognosis of NSCLC patients especially among post-menopausal female [76]. Preclinical studies further demonstrated that aromatase inhibitor (AI) suppressed the lung tumor growth both *in vitro* and *in vivo*. For example, exemestane, an irreversible steroidal inactivator in combination with cisplatin, a standard chemotherapy in NSCLC patients, demonstrated significant anti-tumor effects [77]. Both letrozole and anastrozole, reversible steroidal inactivators, demonstrated similar anti-tumor activity in NSCLCs [56,78]. These findings all indicated the possible importance of elevated *in situ* estrogen concentrations through aromatase in NSCLC patients.

In addition, cigarette smoke may also modulate ER pathway in lung cancer patients. Patients with a history of smoking had a significantly lower incidence of ER promoter methylation (20%) than non-smokers (36%) [79]. ER promoter methylation leads to gene silencing, thus provides an indirect evidence for the synergistic activity of cigarette smoke and the ER pathway in the development of lung cancer. However, the possible mechanisms by which smoking could modulate the possible cancer-promoting effects of estrogen should be examined by further analysis.

4. Progesterone receptors in non-neoplastic human lung diseases

Progesterone receptors (PRs) mediate the effects of progesterone i.e. progestin, and were reported to be expressed more frequently in non-neoplastic lung tissues compared to malignant lung tissue samples [80]. Both nuclear and extra-nuclear localization of PRs have been reported in lung [80]. Progestin has been demonstrated to regulate the breathing in animals, where a combined administration of a synthetic potent progestin and estradiol for 5 days significantly increased tidal volume and minute expiratory ventilation reduced arterial PCO_2, and enhanced the ventilatory response to CO_2 inhalation [81]. While estrogen is necessary to induce the PR expression, the PR activation generally promotes differentiation and inhibits cellular proliferation in contrast to estrogenic effects [82]. The existence of such dual hormone effects leading towards a delicate balance between estradiol and progesterone effects has been detected in pathogenesis of non-neoplastic lung disease as well as above. Many researchers have investigated the potential role of PRs in lung diseases, Table 3.

Estrogen down-regulate anti-inflammatory cytokines such as IL-10 and up-regulates in inflammatory cytokines such as IL-4 in male mice [39,40] as described in the previous chapter. Progesterone, on the other hand, significantly increases the expression of IL-10, IL-β and TNF-α in the lungs, and augments the release of IL-4 by bone marrow cells in male mice, which may result in systemic eosinophilia [39]. The exact mechanism is not necessarily known but nitric oxide (NO) concentration, a biomarker for airway inflammation in asthma, were reported to be positively associated with serum progesterone ($p < 0.05$) but inversely related to serum estradiol levels [83]. In addition, exhaled NO concentrations were also reported to be highest in the luteal phase (when serum progesterone levels are expected to reach their peak) [84]. Suppression of the menstrual cycle with the use of oral contraceptives, on the other hand, completely abolished these associations above. In addition, progesterone and environmental tobacco smoke were reported to act synergistically to exacerbate allergic airway disease in mice [85]. Taken together, these data all suggest that progesterone may be a very important regulator of airway inflammation in asthmatics.

Table 3
Summary of previous studies on PRs in non-neoplastic lung disease.

References	Methodology	No. of cases	Principal finding
[39]	*In vivo* (mouse)	–	Progesterone up regulated anti-inflammatory cytokines i.e. IL-10 in lung and augmented the release of IL-4 by bone marrow
[83,84]	ELISA (human)	17	NO* conc., a biomarker for airway inflammation in asthma, was positively associated with serum progesterone
[85]	*In vivo* (mouse)	–	Allergic asthmatic exacerbation caused by increased serum progesterone was further enhanced by tobacco smoke

* NO, nitrous oxide.

Table 4
Summary of previous studies on PRs in neoplastic lung disease.

References	Methodology	No. of cases	Principal finding
[80]	*In vitro* (NSCLC cell lines)	–	E2 and progestin cooperated in stimulating VEGF* secretion
[86,88]	IHC (human)	228/121	Low PR expression was a prognostic factor for poor clinical outcome in NSCLC patients
[87]	*In vivo* (mouse)	–	Progesterone supplementation inhibited the growth of PR-positive lung tumors
[89]	*In vivo* (mouse)	–	PR antagonist improved survival of mice with spontaneous lung cancer

* VEGF, vascular endothelial growth factor.

5. Progesterone receptors in neoplastic human lung diseases

Reported results of PR expression or status in human lung tumors are enormously inconsistent reporting a high expression frequency of 39–63% [86–88] and others showing little or no expression at all [48,55]. Progesterone is mainly secreted into circulation from the ovary or placenta in premenopausal females. However, as in estrogen, progesterone has also been reported to be synthesized *in situ* by NSCLC cells [86]. In addition, several studies reported that low PR expression is a prognostic factor for poor clinical outcome in NSCLC patients [86,88] while other studies failed to demonstrate such a correlation [58]. Similar contrasting findings have also been reported in animal models, Table 4. Progesterone supplementation has been reported to inhibit the growth of PR-positive lung tumors in mice with a decrement of Ki-67, cyclin A and E and an increment of p21 and p27 levels [87]. On the other hand, mice treated with an antiprogestin (i.e. mifepristone) also inhibited the progression of spontaneous lung tumors [89]. However, it is also true that estrogen and progestins in NSCLC cells may cooperate in promoting expression of vascular endothelial growth factor (VEGF) which is essential for the progression of lung carcinoma, largely by increasing proliferation of endothelial cells from neighboring blood vessels [80]. These results all suggest that progesterone in co-operation with estrogen may play important roles in lung carcinogenesis but it awaits further examinations for clarification.

6. Androgen receptors in neoplastic and non-neoplastic human lung diseases

Roles of androgens in lung maturation have drawn much attention. Lung maturation, as measured by surfactant production, is delayed in male fetuses compared with female counterparts. However, administration of the anti-androgen flutamide abolishes the gender difference in lung maturation by increasing male surfactant levels to those of females [90]. Androgens mediate their effects via androgen receptors (ARs). AR immunoreactivity was detected during a critical time period in fetal lung branching morphogenesis in the epithelia of the budding component [91,92]. AR expression was also reported in both normal and malignant human lung cells from adults [93].

A less severe bronchial-bronchiolar inflammation was detected in allergic male mice compared with allergic female mice [37]. This reduced level of inflammation was not evident when males were castrated, suggesting a protective role of androgens in allergic lung inflammation [37]. Airway inflammatory and lung functional responses of male C57BL/6 mice to airway administration of Bacterial lipopolysaccharide (LPS), a ubiquitous airborne contaminant which causes airway inflammation and hyperresponsiveness, were however reported to be more marked than those of female. Castration prevented this exaggerated LPS-induced inflammation suggesting that androgens promote non-allergic lung inflammation [94]. In addition, an enhanced susceptibility to lung and airway fibrosis, as a measure of collagen content, was detected only in male mice expressing AR compared to either in age matched female or in mice deficient of AR [95]. Androgens have also been reported to promote the production of IL-2 by TH1 cells, thus modulates the overall inflammatory response in conjugation with estrogens in lung tissue [96].

The role of androgen receptor has not been investigated effectively in pathogenesis of lung cancer. However, a recent report demonstrated that ARs are expressed frequently in NSCLC tissues and cell lines [93]. A human alveolar carcinoma-derived cell line with PTII-like properties, A549, not only contains AR but also exhibits androgen-dependent gene expression [93]. Some of the androgen-responsive genes in these cells belong to interesting categories with regard to survival of malignant cells, such as oxygen utilization and apoptosis, thus makes the roles of androgens in lung cancer biology worthy of further inquiry.

7. Future perspectives

Increasing evidence suggest that sex steroids play pivotal roles in lung which could lead to considerable gender differences in respiratory physiology and pathology. This recognition of the potential of sex steroid actions in lung diseases presentation is important to the design of future experimental studies and gender specific effective therapeutic options for their treatment. In particular, the importance of ERs in NSCLC provided a strong rationale to evaluate anti-tumor activities of ER blocker in lung cancer. Therefore, a Phase II clinical trial for combination therapy with erotinib, an EGFR-TKI, and fulvestant, an ER blocker, versus erlotinib alone in NSCLC patients is underway (ClinicalTrails.gov Identifier: NCT00100854 and NCT00592007). Similarly, a phase II randomized trial of fluvestrant and anastrozole (aromatase inhibitors) as consolidation therapy in postmenopausal women with advanced NSCLC is to be scheduled (ClinicalTrial.gov Identifier: NCT00932152). Similar efforts need to be undertaken in understanding roles of sex steroid actions in variety of lung diseases which could ultimately identify

an improved treatment options for the patients being suffered with pulmonary disorders.

Competing interests

The authors declare that they have no competing interests.

References

[1] K.F. Koehler, L.A. Helguero, L.A. Haldosen, M. Warner, J.A. Gustafsson, Reflections on the discovery and significance of estrogen receptor beta, Endocr. Rev. 26 (2005) 465–478.
[2] A.A. Bardin, N. Boulle, G. Lazennec, F. Vignon, P. Pujol, Loss of ERβ expression as a common step in estrogen-dependent tumor progression, Endocr. Relat. Cancer 11 (2004) 537–551.
[3] G.G. Kuiper, E. Enmark, M. Pelto-Huikko, S. Nilsson, J.A. Gustafsson, Cloning of a novel receptor expressed in rat prostate and ovary, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 5925–5930.
[4] G.B. Tremblay, A. Tremblay, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, F. Labrie, V. Giguere, Cloning, chromosomal localization, and functional analysis of the murine estrogen receptor beta, Mol. Endocrinol. 11 (1997) 353–365.
[5] S. Mosselman, J. Polman, R. Dijkema, ER beta, identification and characterization of a novel human estrogen receptor, FEBS Lett. 392 (1996) 49–53.
[6] J.F. Couse, J. Lindzey, K. Grandien, J.A. Gustafsson, K.S. Korach, Tissue distribution and quantitative analysis of estrogen receptor-alpha (ERalpha) and estrogen receptor-beta (ERbeta) messenger ribonucleic acid in the wild-type and ERalpha-knockout mouse, Endocrinology 138 (1997) 4613–4621.
[7] Z. Culig, Role of the androgen receptor axis in prostate cancer, Urology 62 (2003) 21–26.
[8] G. Giannopoulos, S.K. Smith, Androgen receptors in fetal rabbit lung and the effect of fetal sex on the levels of circulating hormones and pulmonary hormone receptors, J. Steroid Biochem. 17 (1982) 461–465.
[9] C.F. Caracta, Gender differences in pulmonary disease, Mt. Sinai J. Med. 70 (2003) 215–224.
[10] D.D. Sin, S.B. Cohen, A. Day, H. Coxson, P.D. Pare, Understanding the biological differences in susceptibility to chronic obstructive pulmonary disease between men and women, Proc. Am. Thorac. Soc. 4 (2007) 671–674.
[11] J.W. McCallister, J.G. Mastronarde, Sex differences in asthma, J. Asthma 45 (2008) 853–861.
[12] M.K. Han, D. Postma, D.M. Mannino, N.D. Giardino, S. Buist, J.L. Curtis, F.J. Martinez, Gender and chronic obstructive pulmonary disease: why it matters, Am. J. Respir. Crit. Care Med. 176 (2007) 1179–1184.
[13] R.F. Gillum, Frequency of attendance at religious services and cigarette smoking in American women and men: the Third National Health and Nutrition Examination Survey, Prev. Med. 41 (2005) 607–613.
[14] M.C. Machado, J.A. Krishnan, S.A. Buist, A.L. Bilderback, G.P. Fazolo, M.G. Santarosa, F. Queiroga Jr., W.M. Vollmer, Sex differences in survival of oxygen-dependent patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 174 (2006) 524–529.
[15] L. Akinbami, Centers for Disease Control and Prevention, Asthma Prevalence, Health Care Use and Mortality: United States 2003–05, http://www.cdc.gov/nchs/data/hestat/asthma03-05/asthma03-05.htm.
[16] K. De Boer, K.L. Vandemheen, E. Tullis, S. Doucette, D. Fergusson, A. Freitag, N. Paterson, M. Jackson, M.D. Lougheed, V. Kumar, S.D. Aaron, Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis, Thorax (2011) (Epub ahead of print).
[17] M. Corey, J. Farewell, Determinants of mortality from cystic fibrosis in Canada 1970–1989, Am. J. Epidemiol. 143 (1996) 1007–1017.
[18] M.J. Thun, S.J. Henley, D. Burns, A. Jemal, T.G. Shanks, E.E. Calle, Lung cancer death rates in lifelong nonsmokers, J. Natl. Cancer Inst. 98 (2006) 691–699.
[19] H.A. Wakelee, E.T. Chang, S.L. Gomez, T.H. Keegan, D. Feskanich, C.A. Clarke, L. Holmberg, L.C. Yong, L.N. Kolonel, M.K. Gould, D.W. West, Lung cancer incidence in never smokers, J. Clin. Oncol. 25 (2007) 472–478.
[20] A.K. Ganti, A.E. Sahmoun, A.W. Panwalkar, K.K. Tendulkar, A. Potti, Hormone replacement therapy is associated with decreased survival in women with lung cancer, J. Clin. Oncol. 24 (2006) 59–63.
[21] R.T. Chlebowski, A.G. Schwartz, H. Wakelee, G.L. Anderson, M.L. Stefanick, J.E. Manson, R.J. Rodabough, J.W. Chien, J. Wactawski-Wende, M. Gass, J.M. Kotchen, K.C. Johnson, M.J. O'Sullivan, J.K. Ockene, C. Chen, F.A. Hubbell, Women's Health Initiative Investigators: oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomized controlled trial, Lancet 374 (2009) 1243–1251.
[22] S. Parodi, R. Baldi, C. Benco, M. Franchini, E. Garrone, M. Vercelli, F. Pensa, R. Puntoni, V. Fontana, Lung cancer mortality in a district of La Spezia (Italy) exposed to air pollution from industrial plants, Tumori 90 (2004) 81–85.
[23] J.A. Gustafsson, Estrogen receptor beta—a new dimension in estrogen mechanism of action, J. Endocrinol. 163 (1999) 379–383.
[24] C.C. Canver, V.A. Memoli, P.L. Vanderveer, C.A. Dingivan, R.M. Mentzer Jr., Sex hormone receptors in non-small-cell lung cancer in human beings, J. Thorac. Cardiovasc. Surg. 108 (1994) 153–157.
[25] U. Kaiser, J. Hofmann, M. Schilli, B. Wegmann, U. Klotz, S. Wedel, A.K. Virmani, E. Wollmer, D. Branscheid, A.F. Gazdar, K. Havemann, Steroid-hormone receptors in cell lines and tumor biopsies of human lung cancer, Int. J. Cancer 67 (1996) 357–364.
[26] L.P. Stabile, J.S. Lyker, C.T. Gubish, W. Zhang, J.R. Grandis, J.M. Siegfried, Combined targeting of the estrogen receptor and the epidermal growth factor receptor in non-small cell lung cancer shows enhanced antiproliferative effects, Cancer Res. 65 (2005) 1459–1470.
[27] Y. Omoto, Y. Kobayashi, K. Nishida, E. Tsuchiya, H. Eguchi, K. Nakagawa, Y. Ishikawa, T. Yamori, H. Iwase, Y. Fujii, M. Warner, J.A. Gustafsson, S.I. Hayashi, Expression, function, and clinical implications of the estrogen receptor beta in human lung cancers, Biochem. Biophys. Res. Commun. 285 (2001) 340–347.
[28] C. Patrone, T.N. Cassel, K. Pettersson, Y.S. Piao, G. Cheng, P. Ciana, A. Maggi, M. Warner, J.A. Gustafsson, M. Nord, Regulation of postnatal lung development and homeostasis by estrogen receptor beta, Mol. Cell. Biol. 23 (2003) 8542–8552.
[29] A.H. Taylor, F. Al-Azzawi, Immunolocalisation of oestrogen receptor beta in human tissues, J. Mol. Endocrinol. 24 (2000) 145–155.
[30] D. Massaro, G.D. Massaro, Estrogen receptor regulation of pulmonary alveolar dimensions: alveolar sexual dimorphism in mice, Am. J. Physiol. Lung Cell. Mol. Physiol. 290 (2006) 866–870.
[31] D. Massaro, G.D. Massaro, Estrogen regulates pulmonary alveolar formation, loss, and regeneration in mice, Am. J. Physiol. Lung Cell. Mol. Physiol. 287 (2004) 1154–1159.
[32] T.H. March, J.A. Wilder, D.C. Esparza, P.Y. Cossey, L.F. Blair, L.K. Herrera, J.D. McDonald, M.J. Campen, J.L. Mauderly, J. Seagrave, Modulators of cigarette smoke-induced pulmonary emphysema in A/J mice, Toxicol. Sci. 92 (2006) 545–559.
[33] C.H. Chichester, A.R. Buckpitt, A. Chang, C.G. Plopper, Metabolism and cytotoxicity of naphthalene and its metabolites in isolated murine Clara cells, Mol. Pharmacol. 45 (1994) 664–672.
[34] W. Han, B.T. Pentecost, R.L. Pietropaolo, M.J. Fasco, S.D. Spivack, Estrogen receptor alpha increases basal and cigarette smoke extract-induced expression of CYP1A1 and CYP1B1, but not GSTP1, in normal human bronchial epithelial cells, Mol. Carcinog. 44 (2005) 202–211.
[35] S. Mollerup, D. Ryberg, A. Hewer, D.H. Phillips, A. Haugen, Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients, Cancer Res. 59 (1999) 3317–3320.
[36] S.D. Spivack, G.J. Hurteau, M.J. Fasco, L.S. Kaminsky, Phase I and II carcinogen metabolism gene expression in human lung tissue and tumors, Clin. Cancer Res. 9 (2003) 6002–6011.
[37] T. Hayashi, Y. Adachi, K. Hasegawa, M. Morimoto, Less sensitivity for late airway inflammation in males than females in BALB/c mice, Scand. J. Immunol. 57 (2003) 562–567.
[38] A.P. Ligeiro de Oliveira, R.M. Oliveira-Filho, Z.L. da Silva, P. Borelli, W. Tavares de Lima, Regulation of allergic lung inflammation in rats: interaction between estradiol and corticosterone, Neuroimmunomodulation 11 (2004) 20–27.
[39] A.P. De Oliveira, H.V. Domingos, G. Cavriani, A.S. Damazo, A.L. Dos Santos Franco, S.M. Oliani, R.M. Oliveira-Filho, B.B. Vargaftig, W.T. de Lima, Cellular recruitment and cytokine generation in a rat model of allergic lung inflammation are differentially modulated by progesterone and estradiol, Am. J. Physiol. Cell. Physiol. 293 (2007) C1120–C1128.
[40] L.S. Ackerman, Sex hormones and the genesis of autoimmunity, Arch. Dermatol. 142 (2006) 371–376.
[41] R.C. De Lisle, Pass the bicarb: the importance of HCO_3^- for mucin release, J. Clin. Invest. 119 (2009) 2535–2537.
[42] J.A. Voynow, B.K. Rubin, Mucins, mucus, and sputum, Chest 135 (2009) 505–512.
[43] H.J. Choi, Y.S. Chung, H.J. Kim, U.Y. Moon, Y.H. Choi, I. Van Seuningen, S.J. Baek, H.G. Yoon, J.H. Yoon, Signal pathway of 17beta-estradiol-induced MUC5B expression in human airway epithelial cells, Am. J. Respir. Cell. Mol. Biol. 40 (2009) 168–178.
[44] P.L. Zeitlin, Cystic fibrosis and estrogens: a perfect storm, J. Clin. Invest. 118 (2008) 3841–3844.
[45] R.D. Coakley, H. Sun, L.A. Clunes, J.E. Rasmussen, J.R. Stackhouse, S.F. Okada, I. Fricks, S.L. Young, R. Tarran, 17beta-Estradiol inhibits Ca^{2+}-dependent homeostasis of airway surface liquid volume in human cystic fibrosis airway epithelia, J. Clin. Invest. 118 (2008) 4025–4035.
[46] D.R. Youlden, S.M. Cramb, P.D. Baade, The international epidemiology of lung cancer: geographical distribution and secular trends, J. Thorac. Oncol. 3 (2008) 819–831.
[47] J.D. Patel, P.B. Bach, M.G. Kris, Lung cancer in US women: a contemporary epidemic, JAMA 291 (2004) 1763–1768.
[48] K. Abe, Y. Miki, S. Sugawara, T. Suzuki, H. Sasano, Highly concordant coexpression of aromatase and estrogen receptor β in non-small cell lung cancer, Hum. Pathol. 41 (2010) 190–198.
[49] R.J. Pietras, D.C. Márquez, H.W. Chen, E. Tsai, O. Weinberg, M. Fishbein, Estrogen and growth factor receptor interactions in human breast and non-small cell lung cancer cells, Steroids 70 (2005) 372–381.
[50] D.J. Dabbs, R.J. Landreneau, Y. Liu, S.S. Raab, R.H. Maley, M.Y. Tung, J.F. Silverman, Detection of estrogen receptor by immunohistochemistry in pulmonary adenocarcinoma, Ann. Thorac. Surg. 73 (2002) 403–405.
[51] E. Radzikowska, R. Langfort, D. Giedronowicz, Estrogen and progesterone receptors in non-small cell lung cancer patients, Ann. Thorac. Cardiovasc. Surg. 8 (2002) 69–73.
[52] G. Schwartz, G.M. Prysak, V. Murphy, F. Lonardo, H. Pass, J. Schwartz, S. Brooks, Nuclear estrogen receptor beta in lung cancer: expression and survival differences by sex, Clin. Cancer Res. 11 (2005) 7280–7287.

[53] H. Kawai, A. Ishii, K. Washiya, T. Konno, H. Kon, C. Yamaya, I. Ono, Y. Minamiya, J. Ogawa, Estrogen receptor alpha and beta are prognostic factors in non-small cell lung cancer, Clin. Cancer Res. 11 (2005) 5084–5089.
[54] C.T. Wu, Y.L. Chang, J.Y. Shih, Y.C. Lee, The significance of estrogen receptor beta in 301 surgically treated non-small cell lung cancers, J. Thorac. Cardiovasc. Surg. 130 (2005) 979–986.
[55] B.G. Skov, B.M. Fischer, H. Pappot, Oestrogen receptor beta over expression in males with non-small cell lung cancer is associated with better survival, Lung Cancer 59 (2008) 88–94.
[56] H. Niikawa, T. Suzuki, S. Suzuki, S. Nagasaki, J. Akahira, S. Honma, D.B. Evans, S. Hayashi, T. Kondo, H. Sasano, Intratumoral estrogens and estrogen receptors in non-small cell lung carcinoma, Clin. Cancer Res. 14 (2008) 4417–4426.
[57] N. Nose, K. Sugio, T. Oyama, T. Nozoe, H. Uramoto, T. Iwata, T. Onitsuka, K. Yasumoto, Association between estrogen receptor-beta expression and epidermal growth factor receptor mutation in the postoperative prognosis of adenocarcinoma of the lung, J. Clin. Oncol. 27 (2009) 411–417.
[58] M.G. Raso, C. Behrens, M.H. Herynk, S. Liu, L. Prudkin, N.C. Ozburn, D.M. Woods, X. Tang, R.J. Mehran, C. Moran, J.J. Lee, I.I. Wistuba, Immunohistochemical expression of estrogen and progesterone receptors identifies a subset of NSCLCs and correlates with EGFR mutation, Clin. Cancer Res. 15 (2009) 5359–5568.
[59] L.P. Stabile, A.L. Davis, C.T. Gubish, T.M. Hopkins, J.D. Luketich, N. Christie, S. Finkelstein, J.M. Seigfried, Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor α and β and show biological responses to estrogen, Cancer Res. 62 (2002) 2141–2150.
[60] P.A. Hershberger, A.C. Vasquez, B. Kanterewicz, S. Land, J.M. Siegfried, M. Nichols, Regulation of endogenous gene expression in human non-small cell lung cancer cells by estrogen receptor ligands, Cancer Res. 65 (2005) 1598–1605.
[61] P.A. Hershberger, L.P. Stabile, B. Kanterewicz, M.E. Rothstein, C.T. Gubish, S. Land, Y. Shuai, J.M. Siegfried, M. Nichols, Estrogen receptor beta (ERbeta) subtype-specific ligands increase transcription p44/p42 mitogen activated protein kinase (MAPK) activation and growth in human non-small cell lung cancer cells, J. Steroid Biochem. Mol. Biol. 116 (2009) 102–109.
[62] M.J. Jarzynka, I. Bar-Joseph, B. Hu, S.Y. Cheng, Estradiol and nicotine exposure enhances A549 bronchioloalveolar carcinoma xenograft growth in mice through the stimulation of angiogenesis, Int. J. Oncol. 28 (2006) 337–344.
[63] Z. Hammoud, B. Tan, S. Badve, R.M. Bigsby, Estrogen promotes tumor progression in a genetically defined mouse model of lung adenocarcinoma, Endocr. Relat. Cancer 15 (2008) 475–483.
[64] G. Zhao, S. Zhao, T. Wang, S. Zhang, K. Lu, L. Yu, Y. Hou, Estrogen receptor β signaling regulates the progression of Chinese non-small cell lung cancer, J. Steroid Biochem. Mol. Biol. 124 (2011) 47–57.
[65] G.P. Skliris, E. Leygue, P.H. Watson, L.C. Murphy, Estrogen receptor α negative breast cancer patients: estrogen receptor β as a therapeutic target, J. Steroid Biochem. Mol. Biol. 109 (2008) 1–10.
[66] S.K. Gruvberger-Saal, P.O. Bendahl, L.H. Saal, M. Laakso, C. Hegardt, P. Eden, C. Peterson, P. Malmstrom, J. Isola, A. Borg, M. Ferno, Estrogen receptor β expression is associated with tamoxifen response in ERα-negative breast carcinoma, Clin. Cancer Res. 13 (2007) 1987–1994.
[67] G. Cheng, Z. Weihua, M. Warner, J.A. Gustafsson, Estrogen receptors ERα and ERβ in proliferation in the rodent mammary gland, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 3739–3746.
[68] I. Leav, K.M. Lau, J.Y. Adams, J.E. McNeal, M.E. Taplin, J. Wang, H. Singh, S.M. Ho, Comparative studies of the estrogen receptors β and α and the androgen receptor in normal human prostate glands, dysplasia, and in primary and metastatic carcinoma, Am. J. Pathol. 159 (2001) 79–92.
[69] S. Matsuyama, Y. Ohkura, H. Eguchi, Y. Kobayashi, K. Akagi, K. Uchida, K. Nakachi, J.A. Gustafsson, S. Hayashi, Estrogen receptor β is expressed in human stomach adenocarcinoma, J. Cancer Res. Clin. Oncol. 128 (2002) 319–324.
[70] G.F. Zhang, X. Liu, A.M. Farkas, A.V. Parwani, K.L. Lathrop, D. Lenzner, S.R. Land, H. Srinivas, Estrogen receptor β functions through nongenomic mechanisms in lung cancer cells, Mol. Endocrinol. 24 (2010) 471.
[71] D.C. Márquez-Garbán, H.W. Chen, M.C. Fishbein, L. Goodglick, R.J. Pietras, Estrogen receptor signaling pathways in human non-small cell lung cancer, Steroids 72 (2007) 135–143.
[72] E.R. Levin, Bidirectional signaling between the estrogen receptor and the epidermal growth factor receptor, Mol. Endocrinol. 17 (2003) 309–317.
[73] J.F. Dunn, B.C. Nisula, D. Rodbard, Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in uman plasma, J. Clin. Endocrinol. Metab. 53 (1981) 58–68.
[74] F. Labrie, V. Luu-The, C. Labrie, A. Belanger, J. Simard, S.X. Lin, G. Pelletier, Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone, Endocr. Rev. 24 (2003) 152–182.
[75] M.K. Verma, Y. Miki, H. Sasano, Aromatase in human lung carcinoma, Steroids 76 (2011) 759–764.
[76] V. Mah, D.B. Seligson, A. Li, D.C. Márquez, I.I. Wistuba, Y. Elshimali, M.C. Fishbein, D. Chia, R.J. Pietras, L. Goodglick, Aromatase expression predicts survival in women with early-stage non-small cell lung cancer, Cancer Res. 67 (2007) 10484–10490.
[77] D.C. Márquez-Garbán, H.W. Chen, L. Goodglick, M.C. Fishbein, R.J. Pietras, Targeting aromatase and estrogen signaling in human non-small cell lung cancer, Ann. N. Y. Acad. Sci. 1155 (2009) 194–205.
[78] O.K. Weinberg, D.C. Marquez-Garban, M.C. Fishbein, L. Goodglick, H.J. Garban, S.M. Dubinett, R.J. Pietras, Aromatase inhibitors in human lung cancer therapy, Cancer Res. 65 (2005) 11287–11291.
[79] J.P. Issa, S.B. Baylin, S.A. Belinsky, Methylation of the estrogen receptor CpG island in lung tumors is related to the specific type of carcinogen exposure, Cancer Res. 56 (1996) 3655–3658.
[80] D.C. Marquez-Garban, V. Mah, M. Alavi, E.L. Maresh, H.W. Chen, L. Bagryanova, S. Horvath, D. Chia, E. Garon, L. Goodglick, R.J. Pietras, Progesterone and estrogen receptor expression and activity in human non-small cell lung cancer, Steroids 9 (2011) 910–920.
[81] K. Tatsumi, M. Mikami, T. Kuriyama, Y. Fukuda, Respiratory stimulation by female hormones in awake male rats, J. Appl. Physiol. 71 (1991) 37–42.
[82] C.L. Clarke, R.L. Sutherland, Progestin regulation of cellular proliferation, Endocr. Rev. 11 (1990) 266–301.
[83] P.J. Mandhane, S.E. Hanna, M.D. Inman, J.M. Duncan, J.M. Greene, H.Y. Wang, M.R. Sears, Changes in exhaled nitric oxide related to estrogen and progesterone during the menstrual cycle, Chest 136 (2009) 1301–1307.
[84] S. Farha, K. Asosingh, D. Laskowski, J. Hammel, R.A. Dweik, H.P. Wiedemann, S.C. Erzurum, Effects of the menstrual cycle on lung function variables in women with asthma, Am. J. Respir. Crit. Care Med. 180 (2009) 304–310.
[85] V.L. Mitchell, L.J. Gershwin, Progesterone and environmental tobacco smoke act synergistically to exacerbate the development of allergic asthma in a mouse model, Clin. Exp. Allergy 37 (2007) 276–286.
[86] H. Ishibashi, T. Suzuki, S. Suzuki, H. Niikawa, L. Lu, Y. Miki, T. Moriya, S. Hayashi, M. Handa, T. Kondo, H. Sasano, Progesterone receptor in non-small cell lung cancer—a potent prognostic factor and possible target for endocrine therapy, Cancer Res. 65 (2005) 6450–6458.
[87] J.M. Su, H.K. Hsu, H. Chang, S.L. Lin, H.C. Chang, M.S. Huang, H.H. Tseng, Expression of estrogen and progesterone receptors in non-small cell lung cancer: immunohistochemical study, Anticancer Res. 16 (1996) 3803–3806.
[88] L.P. Stabile, S. Dacic, S.R. Land, D. Lenzner, R. Dhir, M. Aquafondata, R.J. Landreneau, J.R. Grandis, J.M. Siegfried, Combined analysis of estrogen receptor beta-1 and progesterone receptor expression identifies lung cancer patients with poor outcome, Clin. Cancer Res. 17 (2011) 154–164.
[89] J.H. Check, L. Sansoucie, J. Chern, E. Dix, Mifepristone treatment improves length and quality of survival of mice with spontaneous lung cancer, Anticancer Res. 30 (2010) 119–122.
[90] H.C. Nielsen, H.M. Zinman, J.S. Torday, Dihydrotestosterone inhibits fetal rabbit pulmonary surfactant production, J. Clin. Invest. 69 (1982) 611–616.
[91] Y. Kimura, T. Suzuki, C. Kaneko, A.D. Darnel, J. Akahira, M. Ebina, T. Nukiwa, H. Sasano, Expression of androgen receptor and 5α-reductase types 1 and 2 in early gestation fetal lung: a possible correlation with branching morphogenesis, Clin. Sci. (Lond.) 105 (2003) 709–713.
[92] J. Plante, M. Simard, P. Rantakari, M. Côté, P.R. Provost, M. Poutanen, Y. Tremblay, Epithelial cells are the major site of hydroxysteroid (17beta) dehydrogenase 2 and androgen receptor expression in fetal mouse lungs during the period overlapping the surge of surfactant, J. Steroid Biochem. Mol. Biol. 117 (2009) 139–145.
[93] L. Mikkonen, P. Pihlajamaa, B. Sahu, F.P. Zhang, O.A. Jänne, Androgen receptor and androgen-dependent gene expression in lung, Mol. Cell. Endocrinol. 317 (2010) 14–24.
[94] J.W. Card, M.A. Carey, J.A. Bradbury, L.M. DeGraff, D.L. Morgan, M.P. Moorman, G.P. Flake, D.C. Zeldin, Gender differences in murine airway responsiveness and lipopolysaccharide-induced inflammation, J. Immunol. 177 (2006) 621–630.
[95] M.S. Markova, J. Zeskand, B. McEntee, J. Rothstein, S.A. Jimenez, L.D. Siracusa, A role for the androgen receptor in collagen content of the skin, J. Invest. Dermatol. 123 (2004) 1052–1056.
[96] T.R. Mosmann, H. Cherwinski, M.W. Bond, M.A. Giedlin, R.L. Coffman, Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins, J. Immunol. 136 (1986) 2348–2357.