Estrogenic Steroid Hormones in Lung Cancer

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It is becoming increasingly clear that steroid hormones are involved in the biology of many organs outside the reproductive system. Evidence has been accumulating since the mid 1990s that the lung contains receptors for both estrogen and progesterone and that these hormones have some role in lung development, pulmonary inflammation, and lung cancer. The estrogen receptor β (ERβ) is the major ER expressed in lung tissues, while inflammatory cells capable of infiltrating the lung are reported to express both ERα and ERβ. Although there is evidence in animals of preferential effects of ERβ in the lungs of females, human lung tumors from males also contain ERβ-positive cells and express aromatase, the enzyme that converts testosterone to estrogens. This review will discuss current literature findings on the role of the ERs and the progesterone receptor (PR), as well CYP19 (aromatase), the rate-limiting enzyme in the synthesis of estrogen, in lung cancer.
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Estrogen receptors (ERs) are members of the nuclear steroid receptor superfamily, and mediate cellular responses to the hormone estrogen. ERs function either as estrogen-dependent transcription factors or as phosphorylation-dependent transcription factors that are activated by kinase pathways not requiring ligand binding.[1] Two different genes encode the ER proteins ERα and ERβ, which are expressed with different tissue distributions.[2] Both ER subtypes bind β-estradiol, the most active form of estrogen, with high affinity. Multiple isoforms of ERα and ERβ exist, including at least three ERα isoforms[3] and five ERβ isoforms.[4,5] ERβ is thought to be the major functional form of ER in the lung based on two lines of evidence. First, differential expression of ERβ mRNA compared to ERα mRNA was found in human lung tissue during fetal development[6] and in the adult mouse lung.[7] Second, female ERβ knockout (-/-) mice display a lung abnormality: at 3 months of age, they display a decreased number of alveoli and reduction in expression of key regulators of surfactant homeostasis.[7] By age 5 months, both female and male mice show alveolar collapse and alterations in extracellular matrix,[8] suggesting that estrogen does have some role in lung homeostasis in males as well as females. In the ERβ -/- mouse, female but not male offspring were protected against development of lung tumors after in utero exposure to the polycyclic hydrocarbon dibenzochrysene.[9] Confirmation that the lung is an estrogen-responsive tissue was observed in the transgenic ERE-luciferase reporter mouse, where a 15-fold induction of reporter gene expression occurred in the lungs of both males[10] and females[11] after estrogen treatment.

Antibodies that distinguish between ERα and ERβ proteins are now well established, and it is apparent that full-length ERβ protein is expressed in most human non-small cell carcinoma (NSCLC) cell lines, and is frequently present in primary specimens of human NSCLCs from men as well as women.[12–16] ERβ protein is detected in both the nucleus and the cytoplasm and is comprised of mainly full-length protein in addition to some smaller variants.[12] However, the frequency and function of the different ERβ isoforms in lung cancer is not well understood because most studies have not undertaken a comparison of the five known ERβ isoforms, which are the result of alternative splicing of the last coding exon.[17,18] ERβ-1 is the full-length ERβ protein and the only fully functional isoform that can bind ligand. ERβ-2 has been reported to function as a dominant negative of ERβ, whereas isoforms -3, -4, and -5 do not have innate activities but can heterodimerize

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with ERβ-1.[4] Whether there is lung tumor expression of full-length ERα is controversial. ERα staining of lung tumor tissues and cell lines was found primarily in the cytoplasm and on the cell membrane, with rare expression in the nucleus,[12–16] and both mRNA and protein analysis showed ERα messages to be comprised of alternatively spliced variants.[12] These variant isoforms lack the amino-terminus because the proteins are differentially detected by antibodies that recognize the ERα amino- and carboxy-terminal.[12] Immunoblotting failed to detect the expected 66-kd ERα protein, while smaller variants of 42 kd and 54 kd were found.[19,20] Estrogen-mediated RNA transcription, non-genomic signaling that activates tyrosine kinases, and proliferation in lung tumor cell lines can be blocked by the ER inhibitor fulvestrant, providing evidence that ERs found in lung cancer are functional.[12,19,20] Comparisons of ERα- and ERβ-selective agonists show that biological effects are predominantly mediated by ERβ.[20] Although ERα protein may be found in some lung tumors, such as those with EGFR mutation,[21] ERβ appears to be the major ER expressed in lung cancer.

ERs AND LUNG CANCER SURVIVAL

There are now many published reports examining ER status in relation to NSCLC patient survival (Table 1). Recently, high cytoplasmic ERβ-1 staining was identified as a negative prognostic factor for lung cancer, independent of other prognostic factors.[22] Nuclear ERβ positivity was observed in the majority of lung cancer cases[13–16,22] and was found to be a favorable prognostic indicator in some studies. In some reports, the prognostic significance was only observed in male patients or was limited to a subset of patients with a particular mutation.[14–16] However, most studies used antibodies to total ERβ that could not distinguish different ERβ isoforms. The negative effect of ERβ-1 on survival was observed in male and female patients and showed no interaction with sex. Prognostic significance of cytoplasmic ER protein may be related to the importance of non-genomic signaling for ER action in the lung (discussed below). Isoform specificity was also reported in a study demonstrating that ERβ-1, but not ERβ-2, was related to worse prognosis in female stage I lung cancer patients.[23] Nuclear ERβ-1 also correlated with poor survival in metastatic lung cancer but not early-stage lung cancer patients.[24] In contrast, the ERβ-2 and -5 isoforms have been linked to better lung cancer outcomes.[25] ERβ survival studies are summarized in Table 1.

There is no consensus on effect on survival of expression of ERα protein, which as noted above is predominantly found as smaller variant proteins. It is variously reported that ERα has no effect on survival, or to correlate with poor prognosis.[15,16,22] Nuclear and cytoplasmic ERs may have distinct functions and each component should be assessed both separately and together in lung cancer patient tissue specimens. A growing literature also shows that ERs localize to mitochondria and that estrogen can induce expression of the mitochondrial genome, as well as increase vulnerability to oxidative stressors such as hydrogen peroxide. There are recent reports of mitochondrial action of ERβ in lung cancer cells where it appears to protect against apoptosis[26] and to show reduced activity during allergic airway inflammation in a mouse model of asthma.[27] Analysis of the different ERβ isoforms and their cellular localizations will be necessary to understand completely the role of ERβ in lung cancer. If standardized approaches can be developed, these hormone receptor markers may become useful biomarkers, potentially able to predict the aggressiveness of lung cancers and to identify patients who might respond to hormonal therapy.

Women with advanced NSCLC live longer than men,[28] although this observation is not specific to lung cancer, but is found in many tumor types. How much of this survival differences might be attributed to hormonal differences is not clear. A study of lung cancer presentation in pre- versus postmenopausal women showed more advanced disease including poorly differentiated tumors with less favorable histologies in premenopausal women.[29] Despite this, a significant survival difference between pre- and postmenopausal women was not seen. In a more recent study, women over the age of 60 years had a significant survival advantage over both men and younger women, a difference potentially attributable to hormonal status since men did not show survival differences by age.[30]

HORMONE REPLACEMENT AND LUNG CANCER SURVIVAL

Exposure to hormone replacement therapy (HRT) has negative effects on lung cancer survival. Ganti et al[31] reported that a significant association between both a lower median age at lung cancer diagnosis and a shorter median survival time in women who used HRT around the time of diagnosis versus those who did not. This effect was more apparent in women who smoked, suggesting an interaction between estrogens and tobacco carcinogens. The Women's Health Initiative, a randomized, placebo-controlled trial in which more than 16,000 postmenopausal women received placebo or daily HRT for 5 years, also reported a strong negative effect on survival after a

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