

# **Estradiol increases lung tumor development in female mice through stromal estrogen receptor**

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Introduction: Several epidemiological, clinical and preclinical studies have reported gender differences in lung cancer risk and development. These observations suggest that estrogens might be implicated in the etiology of lung cancer development in women. However, the role of estrogens and their receptors remains unclear and data available in the literature are conflicting. The aim of this study is to understand gender differences observed in lung cancer progression and to define the molecular implications of estrogens.

Methods: Lung cancer development was compared in male and female immunocompetent mice through an orthotopic instillation of lewis lung carcinoma cells (LLC) into the lung parenchyma.

Results: Lung cancer development was increased in female mice, compared to male. In addition, ovariectomized female mice displayed decreased lung cancer development and exogenous estradiol (E2) supplementation rescued lung cancer growth in ovariectomized mice. In order to further characterize the molecular mechanisms induced by E2 to increase lung cancer development, we treated mice with estrogen receptor (ER) antagonists targeting ER $\alpha$  or ER $\beta$ . In female mice treated with tamoxifen (ER antagonist used in clinic to treat breast cancer) or with MPP (ER $\alpha$  antagonist), lung tumor growth was significantly decreased. ER $\beta$  antagonist (PHTPP) did not display any significant effects. In male mice, the various ER antagonists tested did not modulate lung cancer development. These results suggest that ER $\alpha$  is the receptor mediating the pro-tumor effect of E2 observed in female mice. However, E2 did not increase LLC proliferation in vitro. This suggests that a modulation of the tumor microenvironment was responsible for the increased cancer development observed in vivo under estrogenic condition. Interestingly, we observed that E2 increased tumor angiogenesis and lymphangiogenesis in ovariectomized female mice, in an ER $\alpha$ -dependent manner.

Conclusion: Our results support that E2 favors the development of lung cancer in female. E2 promotes lung cancer growth through a modulation of tumor microenvironment, in an ER $\alpha$ -dependent manner. Especially, E2 increases tumor angiogenesis and lymphangiogenesis. These new insights may lead to an optimization of lung cancer therapy through the development of gender-based treatment.

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