

Title (200 characters max): Gender differences in lung tumor development: implication of estrogens

Authors and affiliations: Calibri 12

C. Dubois, N. Rocks, S. Blacher, D. Cataldo, C. Péqueux

Laboratoire de Biologie des Tumeurs et du Développement, GIGA-cancer, Université de Liège, CHU-B23, 13 av.d'Hippocrate, 4000 Liège, Belgique

Abstract (400 words max):

Several epidemiological, clinical and preclinical studies reported gender differences in lung cancer risk. 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 available data are conflicting.

Aim: Our aim is to understand gender differences observed in lung cancer progression. In this study, we compared lung cancer development in male and female immunocompetent mice in two different experimental models: 1) chemically-induced lung cancer, 2) orthotopic instillation of lewis lung carcinoma cells (LLC) into the lung parenchyma.

Results: We did not observe any differences between male and female regarding lung carcinogenesis (model 1). However, in the orthotopic instillation model (model 2), lung cancer development was increased in female mice. In addition, ovariectomized female mice displayed decreased lung cancer development and exogenous 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 α or ER β . In female mice treated with tamoxifen (ER antagonist used in clinic to treat breast cancer) or with MPP (ER α antagonist), lung tumor growth was significantly decreased. ER β 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 α is the receptor mediating the pro-tumor effect of E2 observed in female mice. Finally, we showed that E2 does not increase LLC proliferation suggesting that a modulation of the tumor microenvironment is responsible for the increased cancer development

Conclusion: E2 promotes lung cancer growth in female through a modulation of tumor microenvironment via the activation of ER α . These new insights may lead to an optimization of lung cancer therapy through the development of gender-based treatment.