学位の種類	博士（医学）
報告番号	甲第１５５８号
学位記番号	第１１１３号
氏名	鈴木　あゆみ
授与年月日	平成 29 年 3 月 24 日
学位論文の題名	Exon 7 splicing variant of estrogen receptor alpha is correlated with pathological invasiveness in smoking independent lung cancer（非喫煙者肺癌におけるエストロゲン受容体αのエクソン７欠損型と病理学的浸潤性の相関） Oncology Letters accepted Nov.23, 2016
論文審査担当者	主査：　中西 良一 副査：　新実 彰男，道川 誠

Abstract

Objective: Lung cancer has the highest mortality worldwide. Smoking has been known as the main reason for causing lung cancer, but as the smoking population has been decreasing, understanding carcinogenesis of smoking independent lung cancer will be crucial for treating lung cancer in the next generation. Smoking independent lung cancers are consisted mainly of female patients, but the molecular background of this epidemiological feature other than EGFR mutation is still vague. Several studies have reported the correlation between female hormone related factors and the prognosis of lung cancer, but the results are still inconsistent. We focused on the expression of ER alpha in order to elucidate this correlation in smoking independent lung cancer.

Material and Methods: Immunohistochemistry staining (IHC) of aromatase, ER alpha, and ER beta was performed against formalin treated tissues from 38 never-smoking patients who underwent complete surgical resection from 2012 to 2013. Among them, adequate RNA of the tumor and adjacent normal lung cancer was extracted from 31 matching deep frozen samples. Considering the IHC results, quantitative RT-PCR (RT-qPCR) was performed to measure the expression level of 2 different exons of ER alpha (exon6, and exon7) which composes the ligand binding motif using the Taqman® method.

Results and Conclusion: Extra nuclear expression of ER alpha with IHC showed significant correlation with pathological invasiveness, statistically. RT-qPCR results showed decreased expression of ER alpha exon7 in invasive tumor tissues, compared with their adjacent normal tissues. This is consistent with previous in vitro results

indicating that extra nuclear ER alpha were exon7 splicing variants. There was no difference of ER alpha exon7 expression between normal and tumor tissues in non-invasive lung cancer tissues. While ER alpha exon6 expression showed no correlation with extra nuclear expression of ER alpha by IHC, ER alpha exon7 expression levels were significantly lower in extra nuclear ER alpha positive tumors compared with extra nuclear ER alpha negative tumors. When considering EGFR mutation status, EGFR wild type lung cancers showed lower ER alpha exon7 expressions compared with EGFR mutated lung cancers. Extra nuclear expression of ER alpha, which may represent exon7 splicing variants of ER alpha, correlates with pathological invasiveness in smoking independent lung cancer. The post-translational splicing mechanism of ER alpha may be involved in acquired invasiveness of smoking independent lung cancer.