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Stratifin regulates stabilization of receptor tyrosine kinases via activation of ubiquitin-specific protease 8 in lung adenocarcinoma

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論文の内容の要旨
Abstract of thesis

The doctoral thesis of Ms. Kim YunJung elucidated the novel molecular mechanism of stratifin in early lung adenocarcinoma progression through stabilization of ubiquitin-specific protease 8 and following attenuation of receptor tyrosine kinase degradation. Abstract of the thesis is as follows.

【目的　Purpose】

Receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR) and hepatocyte growth factor receptor (MET) are the best-known targets of therapy for non-small cell lung cancer (NSCLC). Previous work in the applicant's research group revealed that stratifin (SFN, 14-3-3 sigma) acts as a novel oncogene, accelerating tumor initiation and progression of lung adenocarcinoma and interacts with ubiquitin-specific protease 8 (USP8). In this study, Ms. Kim investigated whether SFN enhances RTK stabilization through USP8 activation in lung adenocarcinoma.

【対象と方法　Materials and methods】

Expression of USP8 and SFN in human lung adenocarcinoma tissues (n=193) was examined by immunohistochemistry and statistically analyzed with clinicopathological features of patients. Functional analyses of USP8 and SFN such as cell proliferation assay, apoptosis assay, and wound healing assay were

examined after siRNA transfection against USP8 or SFN. Regulatory mechanism of RTKs stabilization by USP8 and SFN was demonstrated using co-immunoprecipitation, western blot analysis, and immunofluorescence observation.

【結果　Results】

USP8 specifically bound to SFN in lung adenocarcinoma cells. Both USP8 and SFN showed abundant expression in human lung adenocarcinoma tissue than in normal lung tissue, and USP8 expression was significantly correlated with SFN expression. Expression of SFN, but not that of USP8, was associated with histological subtype, pathological stage, and prognosis. *In vitro*, USP8 bound SFN at the early and late endosomes in immortalized adenocarcinoma *in situ* (AIS) cells. Moreover, USP8 or SFN knockdown led to down-regulation of tumor cell proliferation, abundance of RTK and phosphorylation of downstream factors including AKT and STAT3, as well as accumulation of ubiquitinated RTKs for degradation. Additionally, mutant USP8 and mutant SFN, which are unable to interact each other, reduced the amount of RTKs and phosphorylation levels of their downstream factors.

【考察　Discussion】

RTKs are regulated by ubiquitin-mediated degradation, and aberrant stabilization of RTKs contributes to the proliferative activity of many human cancers, including NSCLC. Based on the IHC results, the biological effect of increased USP8 might be involved in the oncogenic function of SFN. From the facts that phospho-USP8 binds to SFN and knockdown of SFN reduces the amount of USP8 protein, the enhanced expression of SFN in lung adenocarcinoma might promote the interaction with USP8 and induce a conformational change of USP8 that may result in an acceleration of its stability and enzymatic activity.

【結論　Conclusion】

In this study, Ms. Kim demonstrated that SFN induces aberrant activation of USP8 and subsequent protection of RTKs from degradation, resulting in hyperactivation of these signaling pathways. Therefore, SFN may be a promising therapeutic target to develop a useful therapeutic strategy for both early and advanced lung adenocarcinomas.

審査の結果の要旨
Abstract of assessment result

【批評　General Comments】

The doctoral thesis of Ms. Kim elucidated the molecular mechanism of stratifin in early lung adenocarcinoma progression through stabilization of ubiquitin-specific protease 8 and following attenuation of receptor tyrosine kinase degradation. Data are novel, solid and clear. The discovery can be applicable for future translation to the clinical development.

【最終試験の結果　Assessment】

The final examination committee conducted a meeting as a final examination on June 7, 2017. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

【結果　Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.