（様式4）（Form4）

学 位 論 文 の 内 容 の 要 旨

Dissertation Abstract

（氏　　名）Name　Bilguun Erkhem-Ochir　印

（学位論文のタイトル） Title

Distinctive roles of syntaxin binding protein 4 and its action target, TP63, in lung squamous cell carcinoma: a theranostic study for the precision medicine
（肺扁平上皮がんにおけるシンタキシン結合タンパク質4とその作用標的であるTP63の特徴的な役割：精密医療のための診断・治療研究）

（学位論文の要旨）2,000字程度、A4判　（approx. 800 Words in English /A4 size）

Background:

Despite recent advances in therapeutics, lung squamous cell carcinoma (LSCC) remains a challenging disease to treat. The advent of immune-checkpoint inhibitors along with several active target agents such as antiangiogenic agents has altered LSCC treatment to some extent, but treatment options remain limited. To date, very few druggable mutations and active predictive biomarkers have been identified; thus, no LSCC-specific target therapy has yet been established. The development of precision medicine with truly active target drugs is eagerly awaited.

We previously found that Syntaxin Binding Protein 4 (STXBP4) plays a crucial role in lesion growth and, therefore, clinical outcomes in LSCC patients through regulation of tumor protein p63 (TP63) ubiquitination. ΔNp63 is an isoform of TP63, a member of the TP53 family, and its expression is widely used as a highly specific diagnostic marker for LSCC. STXBP4 binds to ΔNp63 and suppresses the anaphase-promoting complex/cyclosome (APC/C) complex-mediated proteolysis of ΔNp63, and drives the oncogenic potential of ΔNp63α. STXBP4 may be a useful therapeutic target and/or marker for patients with LSCC.

Methods:

To clarify the impact of STXBP4 and TP63 for LSCC therapeutics, we assessed relevance of these proteins to outcome of 144 LSCC patients at Gunma University Hospital from April 2001 to December 2014.

In addition, we examined whether its action pathway is distinct from those of currently used drugs in in vitro experiments including RNA-seq analysis through comparison with the other putative exploratory targets and/or markers including VEGFR2 (vascular endothelial growth factor receptor 2), TUBB3 (tubulin beta 3), and PD-L1 (programmed cell death 1 ligand 1), along with p53 (tumor protein p53), ΔNp63 and STMN1 (stathmin 1).

Results:

Kaplan- Meier analysis revealed that, along with vascular endothelial growth factor recept or 2 (VEGFR2), STXBP4 expression signified a worse prognosis in LSCC patients, both in terms of overall survival (OS, p = 0.002) and disease-free survival (DFS, p = 0.041). These prognostic impacts of STXBP4 were confirmed in univariate Cox regression analysis, but not in the multivariate analysis. Whereas, TP63 (ΔNp63) closely related to OS (p = 0.013), and shown to be an independent prognostic factor for poor OS in the multivariate analysis (p = 0.0324). The action pathway of STXBP4 on suppression of TP63 (ΔNp63) was unique: Ingenuity pathway analysis using the knowledge database and our RNAseq analysis in human LSCC cell lines indicated that 35 pathways were activated or inactivated in association with STXBP4, but the action pathway of STXBP4 was distinct from those of other current drug targets: STXBP4, TP63 and KDR (VEGFR2 gene) formed a cluster independent from other target genes of tumor protein p53 (TP53), tubulin beta 3 (TUBB3), stathmin 1 (STMN1) and cluster of differentiation 274 (CD274: programmed cell death 1 ligand 1, PD-L1). STXBP4 itself appeared not to be a potent predictive marker of individual drug response, but we found that TP63, main action target of STXBP4, might be involved in drug resistance mechanisms of LSCC.

Conclusion:

STXBP4 and the action target, TP63, could afford a key to the development of precision med icine for LSCC patients.