Lysyl oxidase impacts disease outcomes and correlates with global DNA hypomethylation in esophageal cancer

（食道癌におけるLysyl oxidase発現と予後、ゲノム全体の低メチル化との関係）

Introduction and objectives: Abnormal function of human body enzymes and epigenetic alterations such as DNA methylation have been shown to lead to human carcinogenesis. Lysyl oxidase (LOX) enzyme has attracted attention due to its involvement in tumor progression in various cancers. The purpose of this study was to clarify clinical importance of LOX expression and its epigenetic regulation in pathogenesis of esophageal squamous cell carcinoma (ESCC).

Method: Using a database of 284 ESCCs, we examined LOX expression and its prognostic characteristics. The functional role of LOX was assessed by *in vitro* growth, migration and invasion assays. The relationship between LOX expression and global DNA hypomethylation (i.e., LINE-1 methylation) was evaluated by using mRNA expression arrays and pyrosequencing technology.

Results: High LOX expression cases had a significantly shorter overall survival and cancer-specific survival (log rank $P<0.001$). The prognostic effect of LOX expression was not significantly modified by other clinical variables (all P for interaction >0.05). LOX silencing and enzymatic inhibition suppressed growth and reduced invasion and migration ability of ESCC cell lines along with the downregulation of AKT and MMP2. An integrated gene analysis in tissues and cell lines revealed that *LOX* was the most highly upregulated gene in LINE-1 hypomethylated tumors. *In vitro*, LOX expression was upregulated upon DNA demethylation.

Conclusion: LOX expression was associated with poor prognosis in ESCC and was regulated epigenetically by genome-wide hypomethylation. LOX can serve as a prognostic biomarker in ESCC patients, and therapeutically targeting LOX may reverse the progression of esophageal cancer.