博士論文（要約）

非小細胞肺癌における
インテグリンα2およびインテグリンα5の機能と
術後再発に関する解析

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[Rationale] Integrins are transmembrane proteins that mediate cell adhesion to extracellular matrix. Whereas expression of ITGA2 and ITGA5 is associated with motility, invasiveness, and cellular differentiation in various tumors, the role of ITGA2 and ITGA5 in lung cancer has not been studied in detail. The aim of this study was to determine whether and how aberrant ITGA2/ITGA5 expression in non-small cell lung cancer (NSCLC) leads to different outcomes.

[Methods] We measured expression of ITGA2/ITGA5 by quantitative PCR in 100 samples collected from NSCLC patients who had undergone surgical resection. We assigned patients to high and low expression groups and analyzed survival. Cellular morphology, adhesion, proliferation, migration, and invasion were examined in human lung cancer cell lines.

[Results] Among 100 cases, 41 were female, with a median age of 71 years. High expression of ITGA2 and ITGA5 in NSCLC was associated with lower recurrence-free survival ($p = 0.004$ and 0.025, respectively). Overexpression of ITGA2 in human lung cancer cell lines had no effect on cell proliferation or invasion but resulted in increased cell size (1416 μm^2 versus 470 μm^2 in H522 cells, $p < 0.001$; 1822 μm^2 versus 1029 μm^2 in H661 cells, $p = 0.02$), adhesion ($p < 0.001$ in H522 and H661 cells) and migration (gap area filled was 71% versus 36% in H522 cells, $p < 0.001$; 57 % versus 26 % in H661 cells,

p = 0.001). These changes were suppressed by E7820, an inhibitor of ITGA2. Overexpression of ITGA5 in human lung cancer cell lines resulted in increased cell size (1067 μm^2 versus 815 μm^2 in H522 cells, $p < 0.001$; 412 μm^2 versus 246 μm^2 in LK2 cells, $p = 0.004$; 1238 μm^2 versus 758 μm^2 in H2170 cells, $p = 0.003$), adhesion ($p < 0.001$ in H522 cells, $p = 0.005$ in LK2 cells and $p = 0.003$ in H2170 cells) and migration (gap area filled was 65% versus 42% in H522 cells, $p = 0.037$; 41 % versus 29 % in LK2 cells, $p = 0.004$; 30 % versus 10 % in H2170 cells, $p = 0.032$).

[Conclusion] ITGA2 and ITGA5 may play a significant role in lung cancer adhesion and migration, and may lead to a higher risk of recurrence.