Interaction between non-small-cell lung cancer cells and fibroblasts via enhancement of TGF-β signaling by IL-6

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Osaka University
Interaction between non-small-cell lung cancer cells and fibroblasts via enhancement of TGF-β signaling by IL-6

**Synopsis of Thesis**

**Name**

**Title**

Fibroblasts are key components of the tumor microenvironment. We clarified the role of transforming growth factor (TGF)-β and interleukin (IL)-6 in the interaction between fibroblasts and non-small-cell lung cancer (NSCLC) cells.

**Methods/Results**

We used NSCLC cells (A549, NCI-H358) and normal human lung fibroblast (NHLF) cells to evaluate phenotypic changes in the presence of human IL-6, TGF-β1, and conditioned media (CM) from these cells. Possible pathways were evaluated with SB431542, a TGF-β receptor inhibitor, or an anti-human IL-6 receptor neutralizing antibody (IL-6R-Ab).

A549 and NCI-H358 cells incubated with IL-6 (50 ng/mL) and TGF-β1 (2 ng/mL) showed significantly increased epithelial-mesenchymal transition (EMT) signaling compared to those treated with TGF-β1 alone. Furthermore, NHLF cells were synergistically activated by IL-6 and TGF-β1. IL-6 increased the expression of TGF-β type I receptors on the surface of A549, NCI-H358 and NHLF cells and enhanced TGF-β signaling. TGF-β1 induced phenotypic changes were attenuated by IL-6R-Ab. NHLF cells were activated and A549 cells showed induction of EMT in response to CM from the other cell type. These activities were attenuated by SB431542 or IL-6R-Ab, suggesting that interplay between NSCLC cells and NHLF may lead to increased EMT signaling in NSCLC cells and activation of NHLF cells through TGF-β and IL-6 signaling. Subcutaneous co-injection of A549 and NHLF cells into mice resulted in a high rate of tumor formation compared with injection of A549 cells without NHLF cells. SB431542 or IL-6R-Ab also attenuated the tumor formation enhanced by co-injection of the two cell types.

**Conclusion**

IL-6 enhanced epithelial cell EMT and stimulated tumor progression by enhancing TGF-β signaling. IL-6 and TGF-β may play a contributing role in maintenance of the paracrine loop between these two cytokines in the communication between fibroblasts and NSCLC cells for tumor progression.
論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

上記学生は、当教室において「肺癌における炎症性サイトカインを介した線維芽細胞とのクロストークの解析」に関する研究について従事しました。本研究では癌細胞と線維芽細胞との間で、TGF-βとIL-6が相互的に癌細胞や癌周囲の線維芽細胞に働く、癌細胞でのEMTシグナルが増強、さらに癌周囲の線維芽細胞が活性化した。またTGF-β receptor阻害剤であるSB4391542やIL-6 receptor中和抗体を投与することにより癌細胞の増殖を抑制する結果に明らかにしました。本研究の結果は肺癌治療において、新たな治療手法としての可能性を示すものであり、肺癌臨床に携わる呼吸器外科の観点から興味深い研究成果であります。また、肺癌以外の他の腫瘍の悪性腫瘍の治療にも応用、発展が期待されました。以上より、学位授与に相当する価値ある研究と考えます。