Analysis of angiogenesis factors in cancer cells

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Recent advances in molecular biology have clarified the mechanisms of the vasculogenesis, and these have been helped by the isolation of endothelial cell-specific growth factors and their signaling receptors. Vascular endothelial growth factor (VEGF) is well known as an important stimulator of vascular endothelial cell proliferation, migration and permeability and is up-regulated in response to hypoxia. We studied the correlation between VEGF-C and vascular endothelial growth factor receptor-3 (VEGFR-3) expression of 85 primary gastric cancers by RT-PCR and immunohistochemistry, and the results were correlated with the number of lymphatic vessels, stained with anti-VEGFR-3 antibody. RT-PCR and immunohistology demonstrated that VEGF-C was mainly produced from cancer cells, but not from stromal elements. These results strongly indicate that VEGF-C may induce the proliferation of lymphatic vessels in the stroma of primary gastric cancer via activation of VEGFR-3, expressed on the endothelial cells of lymphatic vessels. In these circumstances, cancer cells can easily invade the lymphatic vessel, because of the increase of the contact points of cancer cells with the lymphatic vessels

Expression of VEGF-C and that of its receptors were assessed in non-small cell lung cancer. Immunohistochemistry revealed positive VEGF-C expression in 38.7%(24/62) of the patients studied. A significant positive correlation was found between VEGF-C in cancer cells and VEGFR-3 in vascular endothelial cells, but not between VEGF-C in cancer cells and VEGFR-2 in endothelial cells. We conclude that VEGF-C plays an important role in lymphatic invasion/metastasis and tumor progression in non-small cell lung cancer.

We assessed the association of VEGF on the formation of carcinomatosa pleuritis in orthotopic model systems. Immune-deficient rats were inoculated with PC-14 cells into i) a sub-pleural space of the parietal pleura after pneumonectomy or ii) into the thoracic cavity directly. In the first model, despite no significant difference in the mean volume of the subpleural tumors between the groups, the degree of dissemination was suppressed in the treatment group with less tumor vasculature and with reduced expression of autocrine motility factor receptor in tumor cells. In the second model, although the inhibitory effect on dissemination was not clear, the formation of pleural effusion was inhibited in the treatment group. In addition to the ability of vascular permeability, the results demonstrated here showed the possible association of VEGF with the development of pleural dissemination/metastasis in the context of blood/lymphatic routes and cancer cell motility affected by autocrine motility factor receptor.

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