

Anti-cancer Approach with NK4 and Anti-angiogenic Mechanism of NK4: Inhibition of Endothelial Fibronectin Assembly and Colon Cancer Metastasis

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We previously showed that NK4 inhibited angiogenic responses driven by VEGF and bFGF, as well as HGF. However, elucidation of the mechanism by which NK4 inhibits angiogenesis has remained. In vascular endothelial cells, NK4 allowed activation of VEGF receptor and Erk1/2, whereas NK4 inhibited cyclin D1 expression and Rb phosphorylation. NK4 inhibited cell surface assembly of fibronectin and integrin-dependent signaling pathway. Endothelial cell inhibition by NK4 occurred regardless of Met/HGF receptor expression. These results suggest that NK4 may bind to a cell surface molecule different from the Met and that the binding of NK4 to this molecule may inhibit cell surface assembly of fibronectin (Fig. 1).

When mouse colon cancer cells (MC-38) were inoculated into the spleen, the cancer cells metastasized to the liver and subsequently invaded into surrounding liver. In this model, hepatic gene expression of NK4 suppressed hepatic metastasis and intrahepatic growth of metastases. In situ Met tyrosine phosphorylation was inhibited by NK4 and this was associated with inhibition of invasion of metastases in the liver. NK4 inhibited tumor angiogenesis and this was associated with suppression of tumor growth in the liver (Fig. 2). The invasive and metastatic behavior of cancer leads to difficulty in attaining a long-term survival. We propose that simultaneous targeting of both the HGF-mediated invasion-metastasis and tumor angiogenesis may prove to be a new approach for treatment of malignant tumor.

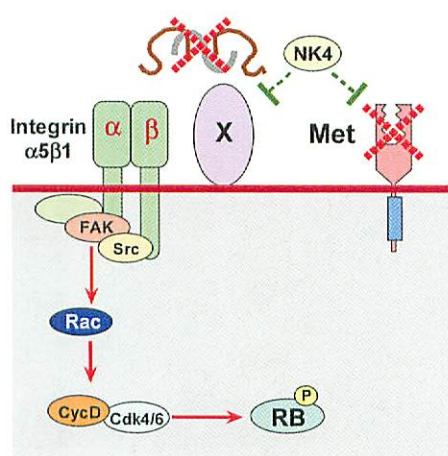


Fig. 1. Possible mechanism for angioinhibitory action of NK4.

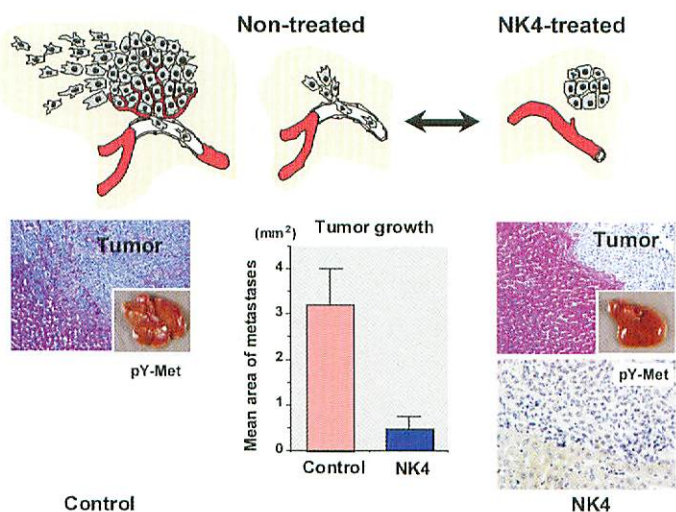


Fig. 2. Inhibition of metastasis and invasive growth of colon cancer by NK4 in mice. NK4 inhibited liver metastasis (inset) and growth of metastases (middle graph). NK4 inhibited Met phosphorylation in cancer cells (lower panels) and this was associated with inhibition of invasion of cancer cells.