

Anti-cancer Approach with NK4 and Anti-angiogenic Mechanism of NK4: NK4 Gene Therapy for Malignant Mesothelioma

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Malignant pleural mesothelioma is highly invasive, diffuse neoplasm arising from mesothelial-lined surfaces in the pleural cavity. The exposure to asbestos is causative for the development of malignant pleural mesothelioma and this disease is expected to increase dramatically over the next few decades. New approaches for the treatment of malignant pleural mesothelioma are clearly needed. We studied on HGF-Met in migration and invasion of malignant mesothelioma cells and therapeutic approach by NK4 gene therapy in mice.

In seven human malignant mesothelioma cell lines in culture, HGF stimulated Met tyrosine phosphorylation and migration of the cells. NK4 inhibited HGF-induced Met phosphorylation and migration. Among seven different human malignant mesothelioma lines, EHMES-10 cells formed growing tumor, when they were subcutaneously implanted into nude mice. Therapeutic effect of NK4 was examined in mice using recombinant adenovirus (Ad-NK4) for expression of NK4 gene. Ad-NK4 was intratumorally administered with an interval of 7 days. The growth of subcutaneous tumor was inhibited in Ad-NK4 treated mice as compared to control mice given Ad-LacZ (Fig. 1A). Analysis of blood vessels in tumor tissues indicated that NK4 inhibited the tumor angiogenesis, thereby suppressing angiogenesis-dependent tumor growth. In collagen gel culture of EHMES-10 cells, HGF enhanced invasion of the cells, whereas NK4 inhibited invasion and growth of the cells (Fig. 1B).

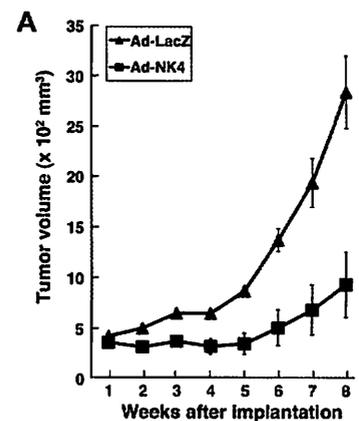


Fig. 1. Inhibition of subcutaneous mesothelioma growth by Ad-NK4 (A) and inhibition of invasion of malignant mesothelioma in collagen gel (B).

HGF-Met pathway plays a significant role in migration and invasion of malignant pleural mesothelioma cells. Together with angioinhibitory action of NK4, therapeutic value of NK4 and its combined therapy for treatment of malignant pleural mesothelioma is considerable. Further study on Ad-NK4 therapy in an orthotopic implantation model of malignant mesothelioma and its preclinical safety test are ongoing for clinical study of NK4 gene therapy.