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The Two Faces of IL-18 in Tumor Immunology

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IL-18 has been found to have multiple effects upon various cells involved in tumor immunology. Here, we discuss opposite effects of IL-18 in tumor immunology. IL-18 has been shown that it has significant anti-tumor effects, which are mediated by T cells and NK cells, in a manner similar to IL-12. First, we investigated the evaluation of the effects of the systemic administration of IL-18 in combination with B7-1 (CD80) against murine B16 melanoma *in vivo*. After the subcutaneous inoculation of B16 melanoma, B16 tumors grew progressively in immunocompetent syngeneic C57BL/6 mice. Mice treated with either IL-18 or immunized with B7-1-transduced B16 did not demonstrate significant anti-tumor effect. The combination of the two treatments, however, resulted in dramatic suppression of melanoma formation, metastasis and a significant improvement in survival. Collectively, combination with IL-18 and B7-1 expression has synergistic anti-tumor effects against B16 murine melanoma.

It has been known that melanoma cells can suppress the immune system by the Fas ligand. Next, we investigated whether IL-18, which can enhance Fas ligand expression, is produced by B16 melanoma cells and is involved in immune escape of tumor cells. Immunohistology, RT-PCR, intracellular FACS analysis, and immunoblotting demonstrated that melanoma cells express IL-18. In addition to IL-18, the IL-18 receptor was also detected in B16 melanoma cells, suggesting a role of this cytokine in regulating the functions of B16 melanoma cells. Transfection of IL-18 antisense cDNA into melanoma cells increased the susceptibility of tumor cells to NK cells *in vitro*. When IL-18 antisense transfectants were implanted into syngeneic mice, severe reduction of tumor cell growth was observed with concomitant infiltrated NK cells in the tumor area. Collectively, endogenous IL-18 modulates immune escape of murine melanoma cells. Also, we investigated the pattern of IL-18 expression in the human skin tumors. Enhanced IL-18 expression was positively correlated with malignant

skin tumors such as SCC and melanoma, suggesting the importance role of IL-18 in malignancy of skin tumors. Thus, evaluating two independent experiment systems, IL-18 plays a dual role in tumor immunology.