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Enhancement of Anti-tumor Immunity by B16 Melanoma Cells Transfected with a Membrane-bound Form of IL-2 and the Stromal Cell-derived Factor-1a

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The eventual goal of tumor immunotherapy is to develop a vaccine inducing a specific anti-tumor immunity. Cytokine gene therapy is an effective way at least in animal models, but limited efficacy and various side effects obstruct clinical applications. In previous studies, we produced tumor vaccines expressing membrane-bound form of cytokines; IL-2, or IL-4. The membrane-bound form of cytokine was expected to functions as a costimulatory signal (signal 1) for tumor-associated antigen (signal 2)-specific CTL activation. The tumor vaccines induced systemic anti-tumor immunity, but the therapeutic effect of the tumor vaccines against to pre-formed tumors was limited. In this study we developed another tumor vaccine expressing a membrane-bound form of IL-2 (mbIL-2) and SDF-1 in B16F10 melanoma and MethA fibrosarcoma cells. The additional expression of SDF-1 over mbIL-2 in tumor cells may be helpful in recruiting tumor-specific CTL into tumor growth sites. As expected, the tumor vaccine reduced tumorigenicity and metastatic ability of tumors cells. The mice once rejected the live mbIL-2/SDF-1 clone acquired systemic immunity against parental B16F10 cells. The mbIL-2/SDF-1 clone was superior in stimulation of the CD8+ T cell population in vitro. These results suggest that the mbIL-2/SDF-1 clone is effective in calling CXCR4 positive T cells into tumor growing sites and stimulates tumor specific CD8+ T cells by direct priming. In NK-depleted mice, tumor growth of the mbIL-2 tumor clone was increased, but no change was recognized in the group injected with mbIL-2/SDF-1, suggesting that the enhanced immunogenicity of mbIL-2 clone may require the NK cells partially, but the anti-tumor immunity by mbIL-2/SDF-1 clone is independent on NK cells. These results indicated that the expression of mbIL-2 and SDF-1 in tumor cells causes the enhancement of immunogenicity of tumor cells and induction of systemic anti-tumor immunity.