Development of chemokine gene therapy against tumors

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Immunocompetent BALB/c mice rejected mouse adenocarcinoma cell line, colon 26, genetically engineered to express constitutively IL-4 gene (colon 26/IL-4) but not parental cells or cells transduced with a control gene (colon 26/control). On rechallenge, parental cells and colon 26/control cells were rejected by normal BALB/c mice that had previously rejected colon 26/IL-4. Moreover, several lines of evidence indicate that challenging mice with colon 26/IL-4 tumor cells resulted in the generation of memory cytotoxic T lymphocytes in the draining lymph nodes in an IFN-γ-dependent manner. Furthermore, we provide definitive evidence that the gene expression of a chemokine, monocyte chemoattractant protein (MCP)-1, was enhanced in the draining lymph nodes of the mice injected with colon26/IL-4. Finally, we proved that MCP-1 has essential roles in regulation of dendritic cell trafficking from the tumor sites to the draining lymph nodes and eventually generation of memory T lymphocytes. These observations suggest the potential usefulness of MCP-1 for gene therapy against tumors.

The therapeutic efficacy of herpes simplex virus thymidine kinase/ganciclovir (HSV-tk/GCV) system in many types of tumors is unsatisfactory due to the insufficient spread of gene transfer and insufficient cell killing. Hence, we investigated whether adenovirally delivered MCP-1 potentiates the antitumor effects of the HSV-tk/GCV system in hepatocellular carcinoma (HCC) cells. Subcutaneous tumor foci of the human HCC cell line, HuH7, established in athymic mice were directly transduced with a recombinant adenovirus (rAd) harboring an HSV-tk gene driven by a human α-fetoprotein promoter, followed by GCV administration. Subsequently, another rAd expressing MCP-1 under the universal CAG promoter was injected. The growth of tumors was markedly suppressed by codelivering HSV-tk and MCP-1 genes compared to that by either HSV-tk/GCV or MCP-1 delivery. In the tumor tissues, monocyte/macrophage infiltration was detected immunohistochemically. The antitumor effects of the rAd expressing MCP-1 were markedly reduced by the administration of carrageenan, a compound known to inactivate macrophage. These results indicate that adenovirally delivered MCP-1 enhanced the antitumor effects of the HSV-tk/GCV system synergistically by recruitment/activation of macrophages in tumor tissues, suggesting an effective immunotherapy for HCC and other lineages of tumors when used adjuvantly with a suicide gene.

References

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