Prolonged, NK cell-mediated antitumor effects of suicide gene therapy combined with monocyte chemoattractant protein-1 against hepatocellular carcinoma.

T. Tsuchiyama, Y. Nakamoto, Y. Sakai, N. Mukaida, N Sawabu and S. Kaneko

Tumor recurrence rates remain high after curative treatments for hepatocellular carcinoma (HCC). Immunomodulatory agents, including chemokines, are believed to enhance the antitumor effects of tumor cell apoptosis induced by suicide gene therapy. Recently, the antitumor effects of the herpes simplex virus thymidine kinase / ganciclovir (HSV-tk / GCV) system were observed to be enhanced by codelivery of monocyte chemoattractant protein-1 (MCP-1). The current study was designed to evaluate the immunomodulatory effects of a bicistronic adenovirus vector expressing both HSV-tk and MCP-1 on HCC cells.

Using an athymic nude mouse model (BALB/c-nu/nu), subcutaneous tumors were completely eradicated by rAd followed by treatment with ganciclovir, subsequently these mice were re-challenged with HCC cells and tumor development was monitored. In addition, after the administration of re-challenged tumors, the serum levels of interleukin (IL)-12 and IL-18 were measured, and the recruitment or activation of natural killer (NK) cells was analyzed immunohistochemically or by measuring interferon (IFN)-γ mRNA expression. Finally, we evaluated the antitumor response in immunocompetent wild type mice (BALB/c-jcl) using the same experimental protocol.

Tumor growth was markedly suppressed compared with mice treated with rAd expressing HSV-tk gene alone ($P<0.001$). Suppression of tumor growth was associated with elevation of serum IL-12 and IL-18. During suppression, NK cells were recruited exclusively, and T helper 1 cytokine gene expression was enhanced in tumor tissues. The antitumor activity, however, was abolished when the NK cells were inactivated with anti-asialo GM1 antibody. Moreover, the effects of the anti-tumor response in wild type mice were comparable to them in nude mice.

In conclusion, these results indicate that suicide gene therapy, together with delivery of MCP-1, eradicates HCC cells and exerts prolonged NK cell-mediated antitumor effects in a model of HCC, suggesting a plausible strategy to prevent tumor recurrence.