Summary

Genes for cytokines and chemokine and angiostatic gene have been used in this work *in vitro* cultivated tumour cells as their recipients. Main characteristics of transduced cells were tested *in vitro* and *in vivo* with respect to parental tumor cells.

In the first part I used a thymidine-kinase deficient (cTK$^-$) cell line designated 123IA, which had been derived from HPV16 transformed mouse (C57BL/6) cells MK16. To obtain genetically modified cells, 123IA cells were transfected with bicistronic plasmids carrying the herpes simplex type 1 thymidine kinase (*HSV-TK*) gene and either the gene for the mouse *B7-1 (CD80)* co-stimulatory molecule or the gene for the monocyte-chemoattractant protein 1 (*MCP-1*). For control purposes, a plasmid vector carrying only the HSV-TK gene was used. For comparative purposes we also used B9 cells, which express the mouse granulocyte-macrophage colony stimulation factor (GM-CSF) and HSV-TK gene. All of the cell lines isolated were found to be sensitive to minute amounts of ganciclovir, revealing the production of HSV-TK, and to express the respective transgenes. When inoculated into syngeneic mice, cells expressing either GM-CSF or B7-1 were non-oncogenic. Nearly all mice inoculated with MCP-1-producing cells developed tumours. Animals injected with GM-CSF or B7-1-producing cells were protected against challenge with the parental MK16 cells. When another mouse (C57BL/6) HPV16-transformed oncogenic cell line, TC-1, which differs from the MK16 cells in a number of properties such as MHC-I and B7-1 expression, was used for the challenge, the protective effect was much less pronounced.

In the second part, MK16 cells and TC-1 cells, which had been also derived from HPV16 transformed mouse (C57BL/6) cells, were transduced with the gene for angiostatic mouse endostatin. Two clones constitutively expressing endostatin were isolated from each of them. They were denoted ME3 and ME9 (derived from MK16 cells), and TE2 and TE5 (derived form TC-1 cells), respectively. When inoculated into mice, ME3 cells were non-oncogenic. Nearly all mice inoculated with ME9 cells developed tumors, but metastasis formation was strongly reduced in these animals. TE2 and TE5 cells displayed oncogenic potential similar to that of the parental TC-1 cells. Animals immunized with ME3 cells were protected against challenge with the parental MK16 cells. Cell lysates of all six lines studied were tested for the content of 25 factors known to be involved in angiogenesis. The MK16 cells differed from the TC-1 cells and also from all endostatin producing sublines by a markedly higher production of interleukin-1α (IL-1α·) Additional experiments indicated that the suppression of the production of IL-1α by the parental MK16 caused by endostatin was due to an autocrine mechanism.