SUMMARY

Recombinant vaccinia virus has been used for elicitation of the immune response against expressed heterologous proteins which has led to protection of the host organisms against the agents producing that antigen (viruses, cancer cells). In our laboratory, we designed and evaluated several vaccines against cancer caused by human papillomavirus type 16 (HPV16). Vaccinia viruses derived from replication competent strain P13 or attenuated MVA were used for construction of recombinant viruses expressing HPV16-E7 in highly immunogenic fusion construct SigE7LAMP. Recombinant viruses were used both in prophylactic and therapeutic settings in mouse tumor models using TC-1 or TC-1/A9 cells. The genes encoding stimulatory cytokines GM-CSF or Flt3 ligand were inserted into the above viruses to support the immune system and to potentiate the anticancer response. Tumor microenvironment was modified using the recombinant viruses expressing both the E7 gene and soluble receptor for TGF-β which should decrease the inhibition of immune system caused by tumor TGF-β cytokine and elicit the response against tumor cells. Intratumoral or intraperitoneal administration of viruses enhanced anticancer response in mice, the viruses expressing Flt3 ligand induced the proliferation of E7-specific cytotoxic T lymphocytes. The expression of GM-CSF and Flt3 ligand prevented the formation of suppressor cells MDSC; however, the expression of receptor for TGF-β did not influence the numbers of suppressor regulatory T lymphocytes.

We further determined that the strong Flt3 ligand expression by single recombinant virus led to several changes in protein composition of virions *in vitro*. The low-glycosylated molecule of the ligand was incorporated into virion core, proteolytical cleavage of viral proteins was incorrect and there were also changes in composition of major viral membrane proteins. The virus multiplication was affected in cell cultures derived from hematopoietic cells as well as in mouse ovaries. The attenuation of virus *in vivo* has led also to decreased Flt3 ligand level in serum of infected mice in comparison with other recombinant viruses expressing the cytokine.