Gene Therapy for Cancer and Rheumatoid Arthritis (RA) Using Replication-Defective Viral Vectors

We explored the potential use of prothymosin (ProT), a putative thymic hormone, in gene therapy for bladder cancer. Our results showed that expression of ProT in cancer cells is associated with decreased tumor growth in vivo, suggesting that ProT exerts antitumor effects through its immunomodulatory activities. However, cell growth in monolayer culture and colony formation in soft agar were enhanced in ProT gene transfected cells. Furthermore, ProT could not be detected in the majority of loci. To investigate the promiscuous expression of prothymosin in the tumors, we used a transgenic mouse model. ProT expression was detected in a variety of tissues, including the liver, lung, and brain. ProT expression was also observed in the tumors after systemic administration. Our study provides strong evidence demonstrating that the growth of orthotopic ML-1 tumors could be delayed by ProT treatment. Such combination treatment promoted the accumulation of S. choleraesuis within tumors, increased the amounts of infiltrating neutrophils and CD8+ T cells, and increased the number of cells undergoing apoptosis in the tumors. We also demonstrated its tumor-targeting potential in various syngeneic murine tumor models. Systemically administered S. choleraesuis carrying the PrV gD gene conferred protective immunity in mice against a lethal dose of cisplatin for cancer therapy. Our results indicated that the PrV vector-based system is useful for generating AAV vectors carrying various transgenes.

Development of DNA Vaccines for Infectious Agents and Cancer

Attenuated viral vectors, such as Salmonella, have been exploited as a tumoricidal agent and a vector to deliver antiangiogenic genes for tumor-targeted gene therapy. We have demonstrated its tumor-targeting potential in various syngeneic murine tumor models. Systemically administered S. choleraesuis carrying the PrV gD gene conferred protective immunity in mice against a lethal dose of cisplatin for cancer therapy. Our results indicated that the PrV vector-based system is useful for generating AAV vectors carrying various transgenes.

Therapy Laboratory

We have previously constructed E1B-55 kD-deleted adenovirus driven by its endogenous promoter, designated Ad5WS1, and demonstrated its efficacy in various syngeneic murine tumor models. Ad5WS1 induced cytokines in cancer cells lacking functional p53 but spared normal cells. Disruption of the p53 function sensitized cells to Ad5WS1-induced cytokides. Introduction of dominant negative p53 into cancer cells harboring wild-type p53 rendered them susceptible to Ad5WS1-induced cytokides. In combination therapy, Ad5WS1 and cisplatin have an additive or synergistic effect on an syngeneic H1299-expressing mouse L1 metastatic lung cancer.

Oct-3/4 transcription factor is specifically expressed in embryonic stem cells and tumor cells. We have developed an oncolytic adenovirus Ad9OC-940 driving the HA-tagged VEGF promoter, and found that HA-tagged VEGF is overexpressing metastatic bladder cancer. Our results demonstrated that Ad9OC may have therapeutic potential for treating Oct-3/4-expressing tumors.

We have previously generated a novel conditionally replicating pseudorabies virus (PrV) mutant carrying glycoprotein D and herpes simplex virus type 1 thymidine kinase genes linked together with the internal ribosomal entry site (IRES) under the control of the HER-2/neu promoter. The recombinant PrV, designated YF2, selectively replicated in and had potent HER-2/neu-overexpressing human and murine bladder cancer cells and inhibited the growth of human bladder tumors. Our results revealed that YF2 may have therapeutic potential for the treatment of invasive bladder cancer. Furthermore, because HER-2/neu is overexpressed in a broad spectrum of cancers, this replication-selective PrV may be broadly applicable.


We also reported that oral DNA vaccination with attenuated Salmonella choleraesuis carrying the PrV gD gene confers protective immunity in mice against a lethal dose of cisplatin for cancer therapy. Our results indicated that the PrV vector-based system is useful for generating AAV vectors carrying various transgenes.

We investigated the modulation of immunoregulatory genes by murine Fms-like tyrosine kinase 3 ligand (Flt3L) and granulocyte–macrophage-colony stimulating factor (GM-CSF) in cancer cells and tumor vascular endothelial cells. The PrV DNA vaccine carrying the gD gene conferred protective immunity in mice against a lethal dose of cisplatin for cancer therapy. Our results indicated that the PrV vector-based system is useful for generating AAV vectors carrying various transgenes.

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