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The Application of Dual Suicide Gene in Targeted Gene Therapy

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Apotosis is an active, engry-dependent process of cellular self-destruction that involves cell shrinkage, membrane blebbing, chromatin condensation, and eventual internucleosomal DNA cleavage, or formation of a 180 bp DNA ladder. Since several studies demonstrate that chemotherapeutic agents such as 5-fluorouracil cause apoptotic cell death, a role gor apoptosis in cancer therapy has been highlighted. In particular targeted gene therapy can enhance the effectiveness of treatment bu localizing apoptotic cell death in tumor cells without damaging normal cells.

Current advances in targeted gene therapy open up new frontiers for molecular therapies of cancer. However, inefficient gene delivery transfection, lack of tumor specific promoters as well we inadequate bystander killing, represent three major hurdles in the development of a toxin-mediated gene therapy for cancer. Thus, we are attempting to develop a new strategy for targeted gene therapy. Using viral recombinant constructs with stress-inducible promoters that drive local expression of two toxin genes, E.coli cytosine deaminase (CD) and herpes simplex virus-thymidine kinase (HSV-TK) may offer a novel approach to improving tumoricidal efficacy of targeted gene therapy for cancer. This idea is based on observations and hypotheses that (1) mammalian cells do not contain the E. coli CD or HSV-TK gene, (2) expression of genetically engineered E. coli CD/HSV-TK fusion gene is capable of activating relatively nontoxic prodrugs, 5-fluorocytosine (5-FC) and unphosphorylated ganciclovir (GCV), to a toxic form, 5-fluorouracil (5-FU) and phosphorylated GCV, respectively. These two toxic drugs will cause localized tumor cytotoxicity synergistically without increasing normal tissus toxicity. Bystander toxicity will also effectively will kill neighboring tumor cells that do not express these genes; (3)stress-inducible promoters will allow high level expression of the fusion gene within a target tissue. Recent studies also demonstrate that administration of prodrugs to E. coli/HSV-TK fusion gene expressed tumor cells enhances radiosensitivity. We believe that targeted gene therapy with promoters reponsive to stresses that exist within a macroscopic solid tumor, can enhance treatment effectiveness by inducing dual suicide genes.