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Gene Therapy for Malignant Pleural Mesothelioma

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The molecular revolution in biology in general, and in oncology in particular, has facilitated the development of genetic manipulation (gene therapy) as a new therapeutic modality. Investigations into the role of gene therapy in cancer have involved the insertion of therapeutic genes via various delivery systems (vectors) into tumor cells for the purpose of inducing apoptosis, necrosis, and anti-tumoral immune responses.

Malignant pleural mesothelioma (MPM) has several characteristics that make it an attractive target for gene therapy: (1) paucity of effective therapies, (2) accessibility of the pleural space for biopsy and localized delivery of experimental agents, and (3) morbidity and mortality primarily related to regional disease extension. Unlike other malignancies that metastasize earlier in their course, mesothelioma exerts its morbidity and mortality through local spread to adjacent vital intrathoracic structures. New treatment modalities that decrease local tumor burden can translate into significant palliative benefits (and potentially prolonged survival). Gene therapy clinical trials for MPM also could serve as a paradigm for treatment of other malignancies localized to body cavities, such as ovarian or bladder carcinoma.

GENE THERAPY: PRINCIPLES AND VECTORS

Gene therapy was originally conceived as a putative treatment for inherited recessive disorders in which transfer of a normal copy of a defective gene could forestall disease onset or reverse phenotypic expression [1]. It soon became clear, however, that cancer would be one of the most important targets for gene

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therapy. Cancer gene therapy is defined as the transfer of genetic material, including full-length genes, complementary DNA, RNA, or oligonucleotides into cancer or host cells, for the ultimate purpose of killing autologous tumor.

Vectors Used in Gene Therapy: Adenovirus

The transport mechanism for delivery and expression of this genetic material is termed the "vector." Various viral and nonviral gene transfer vectors are currently available, ranging from replicating and nonreplicating viruses to bacteria and liposomes. Each of these vectors has certain advantages with regard to DNA carrying capacity, types of targeted cells, in vivo gene transfer efficiency, duration of expression, and degree of induced inflammation (Table 1). It has become clear that no single gene delivery system is suitable for all candidate disorders.

Recombinant adenoviruses (rAd) have been the most widely used vector system for in vivo cancer gene therapy. Most rAd vectors used for in vivo gene therapy study were derived by genomic deletion of early replicatory viral genes (ie, the E1A/B regions) and provision of these functions in trans via a packaging cell line [2–6]. Genomic deletion of the early Ad viral genes renders these vectors replication incompetent. The deleted gene regions can be replaced with expression cassettes that contain the desired gene under the control of general or tumor-specific promoters. rAd vector systems offer numerous advantages compared with other vector systems (see Table 1): efficient transduction of a wide range of target cells, transduction of dividing and nondividing cells, and resultant high target tissue expression of the therapeutic transgene [7,8]. Importantly, these vectors are stable in vivo, which permits direct gene delivery to many tissue sites, including the mesothelium of the pleural space. Recombinant adenoviral vectors carry distinct disadvantages associated with vector toxicity and delivery limitation: transient gene expression and virion-induced local and systemic inflammatory responses. The latter includes an early innate immune response that culminates in proinflammatory cytokine release and a late acquired immune response that results in the generation of neutralizing antiadenoviral antibodies and cytotoxic T lymphocytes [9–14].

Adenoviral-mediated Gene Therapy Strategies in Mesothelioma

Several different cancer gene therapy approaches have been studied in MPM, including use of so-called "suicide genes," delivery of tumor suppressor genes, and transfer of immunomodulatory genes. Several of these approaches have been applied in phase I clinical trials of MPM using various vector systems, including rAd, recombinant vaccinia virus (VV), and modified ovarian carcinoma cells [7,15,16]. Others remain in the preclinical stage but with plans for future clinical trials (see Table 1).

Suicide gene therapy

Suicide gene therapy was an early approach in mesothelioma gene therapy experimentation. This method involves the transduction of tumor cells with complementary DNA encoding for an enzyme that converts a benign prodrug to