Gene Therapy for Prostate Cancer

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Introduction

Advances in radical prostatectomy surgical technique and in radiation therapy delivery have currently resulted in effective treatment options for localized prostate cancer with generally acceptable mortality and morbidity. However, because of the remaining risk for clinical failure after definitive treatment, the persistent potential for morbidity resulting from prostatectomy or radiation therapy, and the lack of an effective, durable treatment modality for locally advanced or hormone-refractory disease, novel treatment strategies for prostate cancer are still needed. Our understanding of prostate cancer initiation and promotion continues to rapidly increase at the molecular level. The hope of identifying genes whose expression level can be modulated to affect the development and progression of prostate cancer has led to efforts to develop “gene therapy” as a viable new treatment strategy to treat or potentially even to prevent prostate cancer. In this article, after a brief introduction of gene therapy, current strategies for prostate cancer gene therapy and initial results of preliminary clinical trials are reviewed.

Gene Therapy

It has been estimated that the human genome contains approximately 60,000 to 100,000 genes. Because each cell in the body contains a complete set of all genes, which genes are transcribed and translated into protein at a particular time within a particular cell must be highly regulated by a combination of factors. The first “rough draft” determining the sequence of all 23 pairs of human chromosomes, known as the Human Genome Project, is now nearing completion. Once finalized, this resource will allow researchers to better decipher how these genes are individually regulated and how they collectively work together to create and maintain the human body.

It is anticipated that a better understanding of gene expression during development, aging, and pathologic processes will identify opportunities for preventive and therapeutic molecular interventions. Gene therapy involves the transfer of DNA into cells to replace or to affect the expression of the cell’s native (endogenous) genes. This transfer may occur while the cell is outside the body (ex vivo) and then returned to the body, or the gene may be introduced into the cell while it remains in the body (in vivo) in its natural microenvironment (Fig. 1). To transfer DNA into a cell with sufficient efficiency, a DNA transporter or “vector” is generally required. Methods used to transfer genes into cells are broadly categorized as either nonviral or viral based and have recently been nicely summarized [1••,2•,3••].

In general, viral gene therapy techniques have tended to be more popular due to higher rates of gene transfer efficiency. Viral-based vector systems take advantage of the inherent ability of viruses to shuttle foreign DNA into cells and in some cases to even facilitate incorporation of the inserted DNA into the host cell DNA. The most commonly used viral vectors have been adenoviruses. They have the advantage of transferring genes into both dividing and nondividing cells. To limit potential pathogenicity due to the virus, early viral vectors were designed so that reproduction was prohibited through deletion of critical viral sequences. The resulting “replication-deficient” recombinant virus binds to a cell surface receptor and is taken into the cell where its genes are then expressed. However, due to immune system surveillance, therapeutic gene expression has generally been only transient, thereby providing a built-in safety feature. Therefore, unless immune system surveillance can be abrogated, adenoviral vectors may not be ideal if the intention is to have the therapeutic gene permanently expressed.
More recently, as will be discussed further, replication competent viral vector strategies have been designed. Unfortunately, adenoviruses, which had generally been accepted as quite safe for gene therapy applications, have recently shown potentially lethal consequences after vascular administration and will require continued evaluation [4]. Fortunately, regarding other biosafety issues, recent reports continue to confirm that concerns regarding germ line incorporation and transmission of adenoviral gene therapy vectors appear to be unwarranted [5,6]. Other examples of viral vectors include retroviruses and adeno-associated viruses, which are capable of integration into the DNA of dividing cells. Therefore, they may be expressed indefinitely in the originally infected target cell and any subsequent cells after mitosis. However, a limitation of retroviruses is that genes may be introduced only into dividing cells, which may be problematic because prostate cancer tends to have a low proliferative index, meaning they do not generally grow and divide very rapidly.

In summary, no perfect vector system and method of delivery have been identified yet. This has been in part due to differing goals for gene therapy under variable circumstances. Numerous viral and nonviral-based gene therapy strategies are currently under investigation and preclinical development. In addition, the ability to limit transfer of genes to specific cell types is currently being addressed by a number of strategies, including the incorporation of tissue-specific expression elements and through tumor cell targeting using surface protein antigens or antibodies that localize the vector to more specific cell types. Recent reports further characterizing androgen-independent prostate-specific antigen expression promise to improve the likelihood of effective tissue-specific gene therapy targeting to prostate cancer independent of the patient’s hormonal milieu [7].

Numerous other questions regarding optimal gene delivery such as the optimal delivery vehicle, volume, and injection methodology remain unanswered. Further studies, such as one by Siemens et al. [8] who recently reported a technique incorporating a gelatin sponge solid-state vehicle to improve the efficiency of gene delivery and to optimize gene expression levels, are needed. The ultimate goal of gene therapy is to develop the ability to administer vectors systematically, with highly efficient, regulatable, tissue-specific expression to limit potential toxicity. Considering the rapid evolution of vector technology, the vectors of the future are expected to be very different from the ones employed today.

Prostate Cancer and Gene Therapy
Prostate cancer is particularly suited for gene therapy for a number of reasons: 1) prostate cancer is quite common and for the patients diagnosed with locally advanced disease there is no cure currently available; 2) the prostate gland does not serve any life-sustaining function and therefore complete ablation of benign, pre-malignant, and cancerous prostate tissue could be desirable; 3) the prostate is accessible by transurethral, transperineal, and transrectal approaches for administration of gene therapy; 4) the prostate may be monitored by digital rectal examination, transrectal ultrasound, endorectal coil magnetic resonance imaging, and/or by serum prostate-specific antigen (PSA); and 5) the prostate gland produces high levels of several characterized proteins including PSA, whose promoters and other enhancers may be incorporated into vectors to direct prostate-specific expression of therapeutic genes.

However, prostate cancer also poses some unique challenges for gene therapy. Because less than 5% of cells are actively dividing at any one time within a tumor, the mean