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Gene Therapy for Erectile Dysfunction

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SUMMARY

Our current understanding of the underlying mechanisms of erectile dysfunction suggests that gene therapy will become a therapeutic treatment in the near future. Over the past decade, erectile dysfunction has been ameliorated in animal models using viral- and plasmid-based vectors. Genes that stimulate smooth muscle cell relaxation, such as neuronal, inducible, and endothelial nitric oxide synthase, or that inhibit smooth muscle cell constriction can restore erectile function in aging, diabetic, and other model systems. The future of erectile dysfunction gene therapy may lie in the use of tissue-specific and regulated gene expression, advanced viral vectors, or the combination of multiple genes to fine tune smooth muscle relaxation.

Key Words: Erectile dysfunction; gene therapy; nitric oxide synthase; nitric oxide; cGMP; phosphodiesterase.

INTRODUCTION

Despite the safety issues with human gene therapy clinical trials (1), this approach to the treatment of specific disease states continues to hold enormous promise. The remarkable scientific achievement of decoding the human genome (2) combined with the impact of the rapidly evolving micro-array and proteomic technologies is allowing researchers to reveal the “epigenome,” the sum total of how the genome executes all information (3–6). Understanding the epigenome allows precise identification of key targets for gene therapy. Considerable published evidence shows that the transfer of genes to humans is feasible, with expression varying from a few days to several months and years (7,8). Cystic fibrosis (9), adenosine deaminase deficiency (10), and Canavan disease (11) are some diseases in which a partial correction of the abnormality via gene therapy has already been obtained. Although the ultimate goal of a stable, tissue-specific, and efficient production of the recombinant protein is currently difficult to achieve, prospects are promising.

Comparatively, gene therapy of the diseases of the urogenital system has not obtained the same attention that has been directed toward other nonurogenital conditions. However, in the case of prostate cancer, several clinical trials are underway, including suicide genes,
immunomodulatory genes, autologous vaccines, tumor suppressor genes, antisense strategies, and anti-oncogenes \( (12,13) \). The same strategies are being tested with bladder cancer \( (14) \); in the case of bladder reconstructive surgery and incontinence, the possibility of combining tissue engineering based on autologous cells with ex vivo gene transfer opens other avenues where gene therapy may be applicable \( (15) \). Similar approaches are being applied to renal transplantation, certain kidney diseases, and renal hypertension \( (16,17) \).

Within this background of considerable clinical and scientific interest for the treatment of life-threatening diseases, male erectile dysfunction (ED) initially appears to be an unlikely candidate for gene therapy. The main reason is that although impotence is a serious condition that hampers the quality of life, it does not involve physical pain or endanger life, and, therefore, the perceived risks of gene therapy may not yet justify this approach. This article provides evidence showing that gene therapy for the treatment of ED is a logical and well-established concept where specific molecular targets and pathways for safe biological modulation are available and where the easy accessibility of the penis to external manipulation provides a good approach for complementary DNA (cDNA) delivery. Additionally, stem cell therapies can be combined with gene therapy for possible tailoring of treatment to each patient.

**GENERAL STRATEGIES OF GENE THERAPY**

Most gene therapy trials focus on the treatment of inborn errors of metabolism and cancer \( (7–11,18) \), with several hundred ongoing clinical studies and a larger number of preclinical trials in animal models. The main objective is to restore or modulate a biochemical pathway that is crucial for the desired physiological or pharmacological response by adding a recombinant cDNA to the affected tissue. The recombinant cDNA must be transfected with a DNA complex or infected with a viral DNA vector into the selected tissue, organ, or the body in general. The goal is to express the recombinant messenger RNA (mRNA) and, in turn, the enzymatic protein preferentially in the target tissue or organ at a therapeutic intracellular concentration for as long as necessary.

In some cases, the desired effect is to correct an inactivating mutation, in which case the cDNA must replace the silent gene by homologous recombination. In other cases, the protein is active but is expressed at low levels or its biological activity is downregulated so that the recombinant cDNA aims to hyperexpress the normal protein. Finally, in some conditions, it is fundamental to block the expression of a noxious protein. This can be done using an antisense cDNA that blocks its mRNA translation or a ribozyme (a small catalytic RNA) that cleaves specifically the target mRNA. Alternatively, antisense oligonucleotides representing a fraction of the coding sequence, rather than whole cDNAs, can be used to block mRNA transcription, or a small interfering RNA (siRNA) that activates a degradation pathway specific to the target mRNA may be used to achieve the same inhibition.

The success of gene therapy essentially depends on six main factors: (a) efficient delivery of the cDNA construct or siRNA; (b) preferential tissue or organ targeting; (c) selective tissue or organ expression; (d) persistent hyperexpression or inhibition of the desired active protein; (e) absence of immune responses against the proteins encoded by the recombinant vector or cDNA; (f) if possible, conditional activation of protein expression to permit selective time frames for biological effects. The overall objective is to satisfy as many of these requirements as possible so that an efficient, sustained expression of the desired gene product eventually occurs exclusively in the selected tissue and organ within a certain period.