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Choosing Targets for Gene Therapy

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1. Introduction

Gene therapy is often attempted in fatal diseases with no known cure, or after standard therapies have failed. Targeting gene defects includes addressing a single mutation, multiple mutations in several genes, or even addressing missing or extra copies in a particular disease. A defect in one specific gene may impair normal function of the corresponding expressed protein. For example, in X-linked severe combined immunodeficiency (X-SCID), there is a mutation in the IL2 receptor $y$ gene. Another classic example occurs in thalassemia propagated by a defect in the $\beta$-globulin gene. Some diseases are caused by multiple mutations in several genes. For example, some cardiovascular diseases may manifest due to mutations in different chromosomes which are a result of inherited or environmental factors. Before approaching a disease using gene therapy, the key protein(s) and pathways involved in the disease should first be identified. However, in some cases an abnormal gene is formed that results in disease; such is the case for the Bcr-Abl gene. The oncogenic Bcr-Abl protein is the causative agent of chronic myelogenous leukemia (CML) which could be blocked for CML treatment. Genomic sequencing information, microarrays, and biochemical assays can be used to determine up- or down-regulated proteins involved in disease, and will help determine the function of these proteins. In the case of some cancers, the signal transduction pathways for oncogenesis have been mapped out, allowing hub proteins to be identified. Hub proteins are essential proteins that interact with multiple other proteins in signaling cascades. If selected properly, adding back a tumor-suppressing hub protein (such as p53), or blocking an oncogenic hub protein (such as survivin) could halt cancer or alter disease progression. Gene mutations can result in mislocalization of these key proteins which can cause cancer; this mislocalization can be exploited with gene therapy approaches. Further, new types of gene therapy are being developed in our lab to direct proteins to other cellular compartments where their function is altered. This chapter will summarize these and other known targets and also focus on choosing newer targets for gene therapy.

2. Known targets for gene therapy

The general aim of gene therapy is to introduce a well-defined DNA sequence into specific cells. Almost any disease can be targeted with gene therapy by replacing defective genes or imparting a new function. In fact, 85% of clinical trials in gene therapy have been conducted for cancer, cardiovascular diseases and for inherited monogenic diseases. In addition, 6.5%
of clinical trials have been conducted for infectious diseases (mainly HIV). Cancer, cardiovascular diseases and HIV are ideal gene therapy targets because of their enormous prevalence and the associated fatal consequences of these diseases, whereas monogenic disorders reflect the original idea of gene therapy which is replacement of a defective gene. Gene therapy offers a unique opportunity to cure patients with monogenic disorders. One third of clinical trials for monogenic disorders are for cystic fibrosis while about 20% are for SCID (Edelstein et al. 2004). This section highlights the advantages of gene therapy for multifactorial diseases such as cancer, vascular diseases, and HIV and describes the utility of gene therapy for monogenic diseases such as cystic fibrosis, SCID and β-thalassemia.

2.1 Cancer
Cancer was responsible for 7.6 million deaths in 2008 (WHO 2011) and is the largest target for gene therapy clinical trials. The complexity of cancer may make it difficult to bring a product to the market due to the number of genes involved compared to monogenetic disorders. However, gene therapeutics are not designed to correct these mutations by adding an enormous amount of DNA to the cells. Instead, they target critical proteins involved in signaling cascades such as the tumor suppressor p53. For example, the first gene therapy product was Gendicine™, an adenovirus containing the tumor suppressor p53. The tumor suppressor p53 is mutated in 40% of many types of cancers, and malfunction of p53 is the major contributor for chemotherapy resistance (Goh et al. 2011). Apoptosis can be triggered by transcriptionally active p53 in the nucleus (Taha et al. 2004) as well as by p53-mediated transcriptionally independent mechanisms in the mitochondria (Vaseva et al. 2009). Various animal studies have shown that p53 induces apoptosis even in advanced tumors such as lymphoma and hepatocellular carcinoma (Ventura et al. 2007; Palacios & Moll 2006; Xue et al. 2007).

The first p53 based gene therapy in humans was conducted in 1996. This trial used a retroviral vector containing wild type p53 with an actin promoter for the treatment of non-small cell lung carcinoma. In this study three patients showed tumor regression and three other patients showed tumor growth stabilization (Roth et al. 1996). China was the first country which approved a p53 adenovirus for gene therapy, Gendicine™ SiBiono, in combination with radiotherapy for head and neck squamous cell cancer in 2004 (Shi & Zheng 2009). Gendicine™ is a recombinant serotype 5 adenovirus with the E1 region replaced by the p53 expressing cassette (with a Rous sarcoma virus promoter). The adenovirus particles infect tumor target cells carrying therapeutic p53 (Peng 2005). Clinical trials for Gendicine™ showed that in combination with radiation therapy it caused partial or complete tumor regression (Peng 2005; Xin 2006). There were also some clinical trials for Gendicine™ in advanced liver cancer, lung cancer and other advanced solid tumors (Peng 2005). It should be kept in mind that China’s State Food and Drug Administration (SFDA) has different standards for the approval of a cancer drug compared to the U.S. FDA and the European Medicine Agency (EMA). Gendicine™ was approved in China on the basis of tumor shrinkage. The U.S. FDA and the EMA require novel cancer drugs to extend the lifetime of the treated patients (Guo & Xin 2006).

Another p53 product is Oncorine™ from Shanghai SunwayBiotech, an oncolytic virus. Oncorine™ was approved for the treatment of head and neck cancer in China in 2006 (Yu & Fang 2007). It is a replicative adenovirus 2/adenovirus 5 hybrid with deletion in E1B55K and E3B (Raty et al. 2008). This oncolytic virus was expected to infect and lyse cancer cells only and not affect normal cells (Guo et al. 2008). Even though clinical studies showed that it
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This book aims at providing an up-to-date report to cover key aspects of existing problems in the emerging field of targets in gene therapy. With the contributions in various disciplines of gene therapy, the book brings together major approaches: Target Strategy in Gene Therapy, Gene Therapy of Cancer and Gene Therapy of Other Diseases. This source enables clinicians and researchers to select and effectively utilize new translational approaches in gene therapy and analyze the developments in target strategy in gene therapy.

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