Obstacles and Opportunities for Regenerative Gene Therapies for Emphysema

By Frank Schneider

Abstract

The prospect for successful gene therapies in the treatment of human disease were significantly advanced when the completion of the human genome project was announced last year. A detailed map of DNA enables researchers to better understand the role of specific genes and gene products in a given disease, and should lead to better pre-clinical studies and, ultimately, clinically proven therapies. In the area of lung disease, gene therapy is thought to be particularly promising for the treatment or prevention of cystic fibrosis and emphysema.

However, much work remains to be done. The lung, itself, is an extraordinarily complex organ comprised of multiple cell types and genes which have yet to be explored and understood. In addition, understanding the structure of DNA is not the only obstacle as there are technical issues concerning the insertion and transference of new genetic material that have yet to be overcome. While there are many research projects underway, to date the promise of gene therapy has not been realized and there are no clinical applications for therapies that have been approved by the Food and Drug Administration.

Gene Therapy Basics

Gene therapy is broadly defined as the treatment of disease by the transfer of "healthy" genetic material into specific cells in order to replace non-functional, disease-causing material. The first problem to be solved is to understand the genes of interest, how they are expressed (or unexpressed), how they interact with other genes, and ultimately how they cause the disease in question.

Once this is known, a strategy for transferring the "normal" genetic material to the target cell can be developed. This can be performed in vivo (directly transmitted to the patient's tissues) or ex vivo (in an artificial environment for reintroduction to the patient).

The actual gene transfer is performed by a carrier molecule, known as a vector. The technology of vectors is a subject of considerable research as they have proven difficult tools to master.

A good deal of vector research is focused on viruses, which are seen as particularly good carriers because of their ability to penetrate and attack target cells. Some viruses have a strong ability to transfer genetic material but are unstable; others are quite stable but are less adept at transfering genetic material. Still others pose safety issues. The vector problem is a major impediment to progress in gene therapy.

Current Thinking about Emphysema

COPD (Emphysema and Chronic Bronchitis) affects approximately 14 million people in the U.S. and costs the American economy $15 billion annually. It is the fourth leading cause of death and is expected to become the third leading cause of death by the year 2020. Emphysema, which accounts for about 15% of COPD cases, is characterized by weakening, overinflation and enlargement of the alveoli. The alveoli lose elasticity and coalesce or consolidate. The result is a decreased surface area for gas exchange and oxygen diffusion into the blood.

Smoking is the primary cause of COPD; in emphysema it causes approximately 85% of all cases. The remainder is caused by an inheirited deficiency of the protease alpha-1 antitrypsin (AAT). The discovery of AAT deficiency has led researchers to speculate that emphysema may involve the production of proteases and antiproteases. The exact mechanism by which smoking causes alveolar damage is not completely understood, but it is thought that a protease-antiprotease imbalance causes the alveoli to activate macrophages and to release elastase, which destroys lung tissue.

An alternative hypothesis explored in a recent study is that cigarette smoking causes a blockade of Vasular Endothelial Growth Factor (VEGF), which plays a role in the production and survival of vascular endothelial cells in lung tissue. Loss of VEGF leads to cell apoptosis (programmed cell death) and the loss of vascularized tissue. Other

targets of study are genes that affect the metabolism and detoxification of cigarette smoke, genes that influence tissue inflammation and genes that affect mucociliary clearance.

Current and Evolving Treatment Options

Damage to the alveoli is degenerative and irreversible. Current treatment is aimed at behavior modification (smoking cessation and exercise) and relief of symptoms (bronchodilators, oxygen therapy and other medications). Exacerbations are treated with corticosteroids and antibiotics.

Lung transplantation surgery is an effective but expensive treatment; however, many emphysema patients are unable to withstand the trauma of surgery. Lung Volume Reduction Surgery is another procedure, whereby the most heavily damaged areas of the lung are removed, allowing the remaining parts of the lung to work more efficiently. The benefits of lung reduction surgery have been mixed and are typically of short duration.

Many new therapies and drug compounds are in development and offer great hope for relieving symptoms or for slowing disease progression. These include new bronchodilators, corticosteroids, anticholinergics, phosphodiesterase inhibitors, and tachykinin receptor antagonists. There is promising research with retinoic acid, which has been associated with alveolar growth in rats.

Protease inhibitors, neutrophil elastase inhibitors, new corticosteroids, interleukin 10, and adenosine receptor agonists represent some of the research in development. Retinoic acid has been shown to increase alveolar growth in rats; however, a short-term clinical trial in humans humans with emphysema did not show any improvement and it is not known whether this approach will be successful.

Gene Therapy and Alveolar Regeneration

While many new drugs are under development, the goal of gene therapy is to actually reverse alveolar damage caused by emphysema. It has been shown that stem cells derived from bone marrow can promote the growth of cardiac, liver and vascular tissue. Researchers have hypothesized that stem cells could similarly promote the growth of alveolar tissue ("alveolorization") in lungs. Theoretically lung tissue that has been damaged from diseases such as emphysema could be regenerated if the right gene or genes could be expressed ("switched on").

As an example, Transforming Growth Factor (TGF) has been associated with the growth and differentiation of embryonic and fetal organs. A gene therapy approach would be to identify the specific gene or genes of interest and to transfer them to existing tissue in order to stimulate total or partial alveolar regeneration.

Challenges and Obstacles

The lung is made up of many different cell types, each expressing many genes. Their identities and roles are not completely understood but it is known that emphysema is mediated by a multiplicity of genetic interactions. This complexity presents significant challenges when compared to, for example, cystic fibrosis, which is thought to originate as a defect in one specific gene. There is currently no technology that can influence the expression of different genes at the level of complexity represented by the human lung.

Donnelly and Rogers have suggested a that future pulmonary research will require solving for the following variables: (1) understanding the expression of genes in the lung, starting with specific cell types and then in a more integrated fashion; (2) identifying the genes associated with specific lung disorders; (3) understanding how environmental factors affect gene expression; (4) understanding the interactions of genetic variations and how they relate to susceptibility to diseases. With these conditions met, researchers can begin capitalizing on genetic medicine and gene therapy.

It is likely that a complete understanding of how genes in the lung interact to cause or prevent disease will be achieved in the near future. A number of therapies that exploit these new insights, such as chemical mediators of AAT, are in development and testing. These therapies will offer greater sympomatic relief than the current mainline medications, and to a lesser extent will slow or prevent (again, AAT deficiency) lung disease.

However, there is no technology available now that can influence these genes for lung regeneration purposes. A more complete understanding of the complex genetic and environmental interactions is required. In addition, gene transfer technologies such as vectors must be developed before practical application of this understanding can be achieved. However, researchers are optimistic in the long run that these obstacles can be overcome and that true lung regeneration can be achieved.

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