PERSPECTIVE

Therapy for acute lung injury via gene transfer through non-viral vector

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ABSTRACT

Acute lung damage is one of the most common types of serious sickness, and despite its high death rate and rapid progression, there is presently no clinically effective treatment for it. The significance of gene therapy in acute lung injury has grown over time as our understanding of the disease's pathological mechanism has deepened. Gene therapy for acute lung injury now focuses mostly on improving alveolar fluid clearance, reducing pro-inflammatory response, and mending lung barrier. Viral and non-viral vectors are currently used as gene delivery vehicles. Though less efficient than viral vectors, non-viral delivery technologies have the advantages of being less immunogenic, more affordable, and easier to mass-produce.

Key Words: *Gene therapy; Pleural disease; Interventional pulmonology; Lung injury*

INTRODUCTION

Damage to the alveolar epithelial and pulmonary vascular endothelial cells known as Acute Lung Injury (ALI) is brought on by infection, trauma, shock, and exposure to toxic gases. Inflammatory cell infiltration, pro-inflammatory factor release, increased pulmonary microvascular permeability, ventilation/blood flow imbalance, and impaired lung compliance are some of the pathological characteristics of ALI. Clinical signs of ALI may include respiratory distress, refractory hypoxemia, and edoema in the lung parenchyma and alveoli. If this illness is not properly treated, it can lead to the development of Multiple Organ Dysfunction Syndromes (MODS) and Acute Respiratory Distress Syndrome (ARDS), which pose a serious threat to human health and have a fatality rate of 30–50%. Even if a patient survives ALI, lung function damage will lower their quality of life, increase the financial and emotional strain on their loved ones, and increase the overall cost of healthcare. There are three stages to the ALI pathogenic process: pulmonary edoema is brought on by a significant infiltration of inflammatory cells into the lung tissue caused by damaged endothelium of the pulmonary vasculature and the alveolar epithelium; Type II alveolar epithelial cells proliferate and differentiate, leading to pulmonary interstitial fibroblast proliferation and pulmonary tissue repair and remodeling. Some individuals get pulmonary fibrosis as a result of excessive repair and remodelling. Vasodilators, corticosteroids, and mechanical ventilation are the current treatments for ALI. Because they focus more on preventing more harm than on treating the underlying issue, these therapeutic tactics' effectiveness is extremely constrained. Extracorporeal Membrane Oxygenation (ECMO), which employs an external machine to deliver full blood oxygenation and CO2 removal along with milder breathing, has considerably improved patients with ARDS. It "bypasses" the heart and lungs, allowing them time to rest and heal. However, it raised the dangers of significant bleeding and infection incidents. While this treatment helps ease symptoms, it is crucial to expand the ALI treatment plan and decrease mortality by addressing the underlying molecular pathways. Exogenous or endogenous functional genes are transfected into target cells or tissues during gene therapy in order to express the appropriate proteins and carry out their tasks. Due of the following benefits, gene therapy has gradually gained prominence in ALI. It is possible to target different stages of ALI with gene therapy. Gene therapy can focus on a specific aspect of ALI, such as endothelial function, oxidative stress, inflammatory response, and pulmonary fibrosis. ALI is a syndrome with an acute attack and a relatively short course of the disease, necessitating a short-term gene therapy and avoiding adverse events caused by repeated administration. Gene therapy has so made significant advancements in the treatment of ALI. However, bare genes have weak cell transduction and low immunity as well as an inflammatory response. The success of gene therapies is highly

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correlated with the delivery method. Therefore, the ideal gene carrier should be capable of effectively delivering target genes into cells and reliably inducing the expression of particular products to carry out biological functions. Viral, non-viral, and cellular vectors are some of the current gene delivery vehicles. The most frequent viral vectors are adenovirus, adeno-associated viruses, and retroviruses. The highly immunogenic nature of viral vectors, however, can readily cause an inflammatory reaction in the host and decrease the effectiveness of gene transfection, limiting their therapeutic use. Studies on non-viral gene vectors, like cationic liposomes and cationic nanoparticles, have recently gained attention. By adjusting the chemical structure, particle size, and surface modification with biological function molecules on non-viral gene carriers, researchers can increase the efficacy of gene transfection and decrease toxicity. Additionally, a variety of modifications can be used to improve the delivery system's targeting ability and plasma stability as well as to achieve the intelligent medication release of genes. The review provides a brief summary of the development of non-viral vector-based gene therapy for ALI treatment. In recent years, gene therapy has become a very popular approach for treating ALI. Huge strides have been made in the previous few years with gene-based therapeutics. Appropriate ALI gene targets are crucial for achieving the intended therapeutic effect. To find therapy targets for enhancing lung pathology and lowering ALI mortality, many investigations have been carried out. Alveolar fluid clearance (AFC) is severely harmed in the case of ALI. Higher mortality has reportedly been linked to lower AFC. A primary treatment objective of ALI/ARD gene therapy is thought to be improving AFC. When ALI is in its early stages, the creation of cytokines and chemokines sets off a pro-inflammatory response that worsens lung injury. As a result, numerous in vitro and in vivo studies using ALI animal models have demonstrated the effectiveness of gene therapy designed to reduce pro-inflammatory effects or increase anti-inflammatory effects. Additionally, when the alveolar-capillary barrier is broken, protein-rich fluid can flow into the alveoli and build up, causing pulmonary edema. When cell connections between epithelial and/or endothelial cells are damaged, cells die, or both, the alveolar-capillary barrier is breached. Studies have also examined the possibility of employing gene therapy to reestablish lung barrier function in recent years. The research that is now being conducted is exciting even if none of these potential targets are being explored as therapies in clinical trials. identifies some of the ALI-related gene therapy targets with the highest promise. In-depth research has been done on a variety of nonviral gene delivery techniques. Lipids, dendrimers, polymers, graphene, and inorganic nanoparticles are a few of these. Dendrimers are potential polymers for gene delivery among nanomaterials because they may assemble nonviral into compact structures with DNA, oligonucleotides, genes, aptamers, siRNA, and other compounds. In order to achieve combined chemotherapy and gene therapy of ALI, Changsheng Li et al. proposed a nano drug delivery system using generation (G5) poly (amidoamine) dendrimer encapsulated Gold Nanoparticles (Au DENPs) for co-delivery of dexamethasone (Dex) and a microRNA-155 inhibitor (miR-155i). As a result, the injured lung was successfully restored, suggesting that using dendrimers to enable concurrent chemotherapy and gene therapy may be a promising approach for ALI therapy. The protein *Heme Oxygenase-1* (*HO-1*) has been thought of as a helpful therapeutic agent in the treatment of inflammatory diseases like ALI due to its anti-inflammatory and antiapoptotic effects. PamHRchol/GA micelles were formed and the *HO-1 gene* was delivered using Myoungjee Choi's amphiphilic Glycyrrhizic Acid (GA) modified cholesterol-conjugated histidine- and arginine-grafted polyamidoamine (PamHRchol) nanomaterial. In their investigation, amphiphilic GA was combined with prepared PamHRchol to produce PamHRchol/GA mixed micelles. In additionally to its anti-inflammatory actions, GA also served as a factor that facilitated the transfer of genes within cells. Nanosized lipid particles, such as solid lipid nanoparticles and nanostructured lipid carriers, can be used to transport DNA across membranes, protect it from nuclease cleavage, and eject it from endosomes. The ability of lipid nanoparticles to overcome numerous biological barriers for gene transfection has led to their reputation as a promising candidate for gene delivery among non-viral vectors.

Angiopoietin-1, also known as Ang-1, is a ligand for the endothelial Tie2 receptor and is essential for maintaining vascular integrity and promoting the growth of new blood vessels. ICAM-1 (intercellular adhesion molecule-1) expression is markedly elevated on the pulmonary endothelium during inflammatory circumstances, as has been previously demonstrated. High electrical concentration polycations may associate with negatively charged genes to form electrostatic complexes. The hydrophilic head group with a positive charge interacting with DNA with a negative charge is a key domain responsible for plasmid condensation, enhanced cellular absorption, and endosome escape. Excellent intracellular gene delivery has been demonstrated via Polyethylene (PEI). The complexes made of PEI enlarge in the endosome environment due to their high buffering capacity, which leads to endosomal rupture. In comparison to the binary complex pHO-1/PEI-DA, the generated ternary complex pDNA/PEI-DA/LBP showed higher transfection efficiency. In Raw264 macrophage cells exposed to LPS, the ternary complex markedly reduced TNF secretion. Recently, peptides of various sizes and structural properties, including those that are synthetic, hybrid, and naturally generated, have been used to transport genes. Peptides are considered to be efficient biomaterials for gene delivery and transfer due to their exceptional physicochemical characteristics and biocompatibility. The expression of RAGE, a receptor involved in the response to inflammation, has been found to be noticeably upregulated in lung epithelial cells. RAGE may bind to a RAGE-Antagonist Peptide (RAP), which was from high-mobility group box-1 and abundant in positive amino acids, lessening the inflammatory response. Chunxian Piao et al. created a RAP-based gene delivery system with Plasmid DNA (pDNA) encapsulated using the charge interaction. RAP was shown to be less effective when transfection efficiency in L2 lung epithelial cells was assessed. Cell therapy for ALI has advanced quickly with the advent of biotechnology, and Mesenchymal Stem Cells (MSCs) and Endothelial Progenitor Cells (EPCs) have received the most attention. The vector used for gene delivery has also made significant progress. Effectively preventing or reducing the body's immunological reaction is possible with MSCs and EPCs. MSCs can move to the damaged area following transplantation in ALI mice, develop into endothelial cells, epithelial cells, etc., and take part in the healing and regeneration of damaged lung tissue. MSCs, on the other hand, have the power to control immunological activity, reduce the expression of inflammatory mediators, neutralize free radicals, and boost antioxidant activity.

MSCs may also help with pulmonary fibrosis. In the LPS- or linoleic acid-induced ALI animal model, it has been demonstrated that EPCs can differentiate into endothelial cells and restore the damaged alveolar-capillary barrier after transplantation, leading to a reduction in the lung injury score. As a result, MSCs and EPCs have a positive therapeutic effect on ALI. Through the synergistic effect of cell therapy and gene therapy, gene therapy using MSCs and EPCs as delivery vehicles may boost the therapeutic effect. According to the research, MSCs-HO-1 are significantly more efficient than MSCs at decreasing the inflammatory response and oxidative stress injury caused by LPS on pulmonary microvascular endothelial cells. Recent studies on genetically modified MSCs and EPCs in ALI (the sole literature examining the therapeutic effectiveness of the created gene delivery system) Exosomes form by the process of budding at the plasma membrane and endosomal membrane. They are abundant in proteins, lipids, nucleic acids, and glycoconjugates, circulate in the extracellular environment, and have the same topology as cells. Exosomes are therefore thought of as the natural equivalent of cell messengers. Exosome-based medication delivery methods have recently attracted a lot of attention. Exosomes have the following benefits over alternative gene delivery mechanisms: The versatility of exosomes makes them optional for encapsulating a variety of biological payloads, including miRNAs and siRNAs; the ability of exosomes to naturally cross a variety of biological barriers; and the potential for exosomes to reach areas of the body with insufficient blood flow. The current research shows promising results, and the developed gene delivery method can reduce lung fibrosis, improve endothelial cell function, repair the damaged barrier, and regulate the inflammatory response, among other symptoms of ALI. Gene-based therapy still confronts several difficulties even though it is becoming increasingly important in the treatment of ALI. First off, gene transfection's effectiveness is still far from ideal. The microenvironment and inflammatory response brought on by ALI may further lessen the efficacy of gene transfection. Second, the respiratory tract and alveolar surface have defense mechanisms including mucus that operate as a physiological barrier to gene delivery and gene transfection. Thirdly, the process of gene expression in vivo may be unpredictable and the delivery and transfection of genes lack selectivity.