Extracellular Vesicles in Lung Disease

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The use of MSC-derived EVs as a potential therapy for lung disease is a fairly young but rapidly growing field, with current research covering a wide variety of lung diseases. The majority of the current research evaluating the therapeutic potential of EVs has been performed in in vitro or pre-clinical animal model systems. This review will describe current published research using EVs as a potential therapy for acute lung injury/acute respiratory distress syndrome (ALI/ARDS), bronchopulmonary dysplasia (BPD), idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH), asthma, and silicosis.

Keywords: extracellular vesicles ; lung disease ; mesenchymal stem cells ; pulmonary disease

1. Introduction

Stem cell research has garnered significant attention over the last few decades, especially regarding potential applications for the regeneration of damaged or diseased tissue [1]. Stem cells are self-renewing and undifferentiated cell types that are classified by their potential to differentiate into functional cells and further described as totipotent, pluripotent, multipotent, and unipotent [1][2][3]. Multipotent stem cells are able to differentiate into cell types of a particular cellular lineage. Mesenchymal stem cells (MSCs) are multipotent cells found in multiple anatomic compartments (e.g., bone marrow, adipose tissue, umbilical cord, and lungs) which, in addition to serving as progenitors for connective tissue cells, are able to stimulate the growth, repair, and survival of other cells and tissues [4]. MSCs have been shown to have a beneficial immunomodulatory and regenerative capacity. There is a significant body of research published describing MSCs as a potential therapy for several acute and chronic lung diseases [3][5][6]. While many experimental and clinical studies have established the use of MSCs in lung disease, there have been some safety concerns raised related to MSC-based therapy, which include the undesirable differentiation of transplanted MSCs resulting in possible malignant transformation, as well as vascular occlusion caused by injected MSCs [7]. More recent studies have discovered that the MSC secretome contains soluble factors and extracellular vesicles (EVs), which can mimic many of the desired clinical effects of MSCs [8]. EVs are hypothesized to be a safer alternative to MSCs since they are cell free and appear to have a better immunogenicity, tumorigenicity, and embolism formation side effect profile than MSCs [9][10]. This has led to increased efforts to develop MSC-derived extracellular vesicles (MSC-derived EVs) as a potential therapeutic agent.

2. Therapeutic Use

The use of MSC-derived EVs as a potential therapy for lung disease is a fairly young but rapidly growing field. The majority of the current research evaluating the therapeutic potential of EVs in lung disease has been performed in in vitro or pre-clinical animal model systems. Pre-clinical animal models have demonstrated that MSC-derived EV-based therapy may be a viable therapeutic option for the reversal or prevention of various lung diseases. This beneficial effect appears to be the result of the activation of the signaling pathways via the transfer of EV contents containing miRNA, RNA, and proteins; however, the molecular mechanisms of the different EV components is poorly understood. The current literature using MSC-derived EVs as a treatment for lung diseases in pre-clinical animal models use different methods of quantifying the dose of EVs, making direct comparison between the studies impossible. In addition, a consensus on the best method to define the optimal EV dose needs to be determined so the therapeutic effectiveness of EVs can be compared across studies. Furthermore, there remains the challenge of scaling-up the production of EVs to a level that could be produced with clinical-grade quality and quantity. Thus, there are many questions and technical issues that need to be addressed before MSC-derived EVs can make the transition from animal models to humans. If these different challenges can be overcome, then MSC-derived EVs hold great promise as a potential therapeutic for numerous lung diseases, such as, acute lung injury/acute respiratory distress syndrome (ALI/ARDS), bronchopulmonary dysplasia (BPD), idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH), asthma, and silicosis.

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