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Stem Cells in Cystic Fibrosis: Hope or Hype

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Abstract

Stem cell therapy for lung disorders has turned a new leaf, several recent reports have highlighted the promising role of stem cells as a potential therapeutic for CF, however there a several challenges ahead which need to been resolved for its effective translation into the clinic. The present review focusses on understanding the progress made in this cutting edge field so far and the potential challenges which lie ahead.

Keywords: Stem cell; Cystic fibrosis

Introduction

Cystic fibrosis (CF) is a multisystem genetic disorder which results from the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1,2]. CF lung disease is characterized by a viscous cycle of persistent infection and excessive airway inflammation, which inflicts tremendous lung tissue damage, resulting in high morbidity and mortality rates [3,4]. Therapy for CF relies on several strategies including gene therapy that aims to correct the basic defect [5,6] and the use of therapeutics for combating the persistent, uncontrolled lung infection and inflammation [7,8]. However the limited success of gene therapy as a viable therapeutic for CF, has resulted in exploring alternative cellular strategies including the use of stem cells to correct the basic defect [9,10]. The present review focuses on understanding the current status of stem cell therapy as a potential therapeutic for CF lung disease.

Mesenchymal Stem Cells: A Preferred Choice for Cellular Therapeutics

Mesenchymal stem cells (MSCs) are multipotent cells which have the ability to differentiate into diverse cell-types including bone, adipose, cartilage and non stromal cells including lung epithelial cells [11,12]. MSC are known to be a preferred cellular choice in regenerative medicine due to their ease of isolation and expansion in culture, their ability to secrete several potent biofactors which aid tissue repair and regeneration [13,14]. MSCs can be readily transduced by viral and non-viral vectors for gene correction [15]. Mesenchymal stem cells are immunomodulatory in nature since they are able to regulate immune responses through the secretion of growth factors and anti-inflammatory cytokines, these cells are immune privileged due to low expression of MHC I and lack of constitutive expression of MHC II and Co stimulatory molecules including CD80 and CD86 [14].

Stem Cells as a Viable Therapeutic for CF: The Progress so Far

For stem cell therapy to serve as a viable therapeutic for CF the use of heterologous or gene corrected autologous stem cells which are capable of infusing back into the CF airways and perform the desired role of Chloride secretion would be required. A recent study in experimental animal model for CF has reported the usefulness of MSC as an attractive therapeutic in murine model of CF lung infection and inflammation [15,16]. In this model, MSCs were shown to improve gross lung pathology and decreased the cellular recruitment into the lung, furthermore MSCs shifted the pulmonary cell predominance from neutrophils to an evenly distributed predominance of macrophages and neutrophils, thus promoting the resolution of infection in CF lung[16], since a predominately neutrophilic inflammation observed in CF airways is responsible for inflicting a tremendous tissue damage and an even distribution of macrophages would insure a better response to the infection through cell mediated immunity.

Previous reports have demonstrated that bone marrow derived stem cells differentiate into epithelial lineages and preferentially home to the damaged respiratory epithelium [17,18]. A recent study has shown the promising role of endogenous progenitor cells as a promising candidate for cell based therapeutics in CF [19]. Several research reports in experimental models of CF have demonstrated the attractive role of bone marrow derived MSCs as a viable therapeutic option in CF to restore the altered expression of CFTR which is underlying defect in patients with CF. Autologous transduced bone marrow derived MSCs were mixed with primary airway epithelial cells obtained from patients with CF, which resulted in restoring the altered expression of CFTR. Furthermore, it was shown that wild type bone marrow cells were able to engraft the lungs of CFTR knock out mice and expressed epithelial phenotypes including the expression of CFTR mRNA [20,21].

Challenges Ahead

There are several challenges which need to be overcome for the effective translation of stem cells as a viable therapeutic for CF. Firstly, understanding the mechanisms by which stem cells get recruited to the airway epithelium and are induced to undergo phenotypic conversion to functional epithelial cells could pave the way for a sustained engraftment of these stem cells expressing CFTR into airway epithelium of patients with CF. Another major challenge will be to characterize the cell populations that are involved in airway remodeling after lung injury.

Conclusion

The extensive research over the past decade both in vitro and in experimental models for CF has put the bone marrow derived adult

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progenitor cells at the forefront as potential candidates for CF based cellular therapeutics, however future insights into the molecular mechanisms governing the recruitment and phenotypic conversion of bone marrow derived of stem cells in the lung will be required for its effective translation from bench to bedside.

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