A PRECLINICAL STUDY OF CELL BASED GENE THERAPY FOR THE TREATMENT OF CHRONIC LUNG DISEASE: AN AEROSOL BASED CELL DELIVERY

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ABSTRACT

Cell-based therapy has great potential as an alternative modern treatment for patients with lung diseases. Cellular engraftment hinders the therapeutic benefit of stem cell-based therapies in which infusion of stem cells in the lung has been found not to necessarily being attributed to tissue regeneration. Safety of the stem cell therapies increasingly become a major concern such as factors that regulating maintenance and differentiation of the stem cells are also involved in tumour progression. Route of stem cell delivery are debating amongst the translational and clinical scientists where the intravenous (IV) injection have shown a significant improvement of lung function over intraperitoneal (IP), however it’s contributed to 6∼17% treatment-related mortality due to pulmonary emboli or infarctions. Therefore, the effective and safe stem cell delivery methods are the main interest and focus of our group with the higher engraftment rate is expected to contribute to lung tissue regeneration and repair. A novel method of aerosol-based delivery of cells was developed as to investigate the possibility of delivering aerosolized airway epithelial cells and mesenchymal stem cells (MSCs) into the lungs. The ability of the aerosolised cells to survive and engraft in vitro and in vivo was studied on the airway of the rabbit in both acute and chronic lung injury models. The tracheal-derived airway epithelial and human adipose-derived MSCs (hAD-MSCs) were labelled with BrdU, and later aerosol delivery was performed following 24-hr induced injury. Our study demonstrated that cells can be aerosolized without the risk of low cell survivability and stress. The hAD-MSCs and tracheal-derived airway epithelial cells were found to be engrafted and localized at the top of the damaged epithelium layer. Engraftment of cells was also found in the lung areas, precisely at the epithelium layer of the bronchiole. The high survival rate of cells following aerosolization illustrates the potential for delivering of such cells in future aerosol-based cell and gene therapy to treat lung diseases. The disruption of epithelial barriers and lung parenchyma by tracheal brushing and ovalbumin inhalation imitates of both acute and chronic lung injury. The possible therapeutic application of gene delivery using the aerosol-based delivery was also assessed in which the adipose-derived mesenchymal stem cell was served as a vehicle to deliver a therapeutic gene for cell-based gene therapy to treat these lung diseases, whereas direct administration of airway epithelial cells is sought as a more feasible and less-time consuming technique of delivering cells.

KEYWORDS
Aerosol delivery
Airway epithelial cell
Mesenchymal stem cell
Angiopoietin
Chronic lung disease
Given the expression of angiopoietin-1 ANGPT-1 convey the anti-inflammatory, antipermeability, and endothelial-protective characteristics in the cells, MSCs transfected with this gene can effectively promote lung repair and also protect the lung from chronic or acute lung injury. However, genetic manipulation of MSCs is challenging due to its resistance to commonly used methods to introduce exogenous DNA or RNA. The microporation technology was used to introduce the plasmid encoding for ANGPT-1 and enhanced green fluorescent protein (eGFP) into hAD-MSCs with only up to 50% of the viable hAD-MSCs being transfected without affecting their proliferation and differentiation capabilities. Furthermore, our data also demonstrated that chronic lung injury treatment with MSCs alone was significantly reduced ovalbumin-induced chronic lung injury in rabbit, as reflected by cell counts in bronchoalveolar lavage (BAL) fluid and pro-inflammatory cytokine levels in lung parenchymal homogenates by qPCR analysis. In addition, inflammatory cells percentage (neutrophils and lymphocytes) were showed decrement, which indicated the possibility of paracrine stimulation of the delivered allogeneic airway epithelial cells. Furthermore, administration of MSCs transfected with human ANGPT1 plasmid (MSCs-pANGPT1) resulted in further improvement of the injured lung in chronic lung injury model. Our data demonstrate the feasibility and effectiveness of aerosol-based cell and gene therapy for experimental chronic and acute lung injury, and provide the basis for the development of an innovative approach for the treatment of clinical lung diseases.