Effects of lung resident mesenchymal stromal cells administration in an animal model of elastase-induced emphysema

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the world. COPD economic and social burden are expected to dramatically grow due to population aging and accumulating exposure to COPD risk factors. COPD is characterized by chronic airway inflammation, mucus hypersecretion, airway remodeling and emphysema, leading to reduced lung function, breathlessness and disability (Ghorani et al., 2017). Development of COPD is slow and progressive. The pathophysiology of COPD is poorly understood and effective treatments are still missing.

Cell therapy represents a promising tool in degenerative lung diseases (Kotton et al., 2014). Since mesenchymal stromal cells (MSCs) can be easily harvested from adult mesenchymal tissues and possess low immunogenicity, they have been widely investigated. In papain-, elastase-, or cigarette smoke–induced emphysema models, MSCs successfully regenerated damaged lungs (Oh et al., 2017). Emerging evidences suggest that MSCs act through paracrine and immune-modulatory mechanisms. MSCs release a variety of growth factors and immune-modulatory cytokines (Kumar et al., 2014) and mediators (HGF, FGF, EGF, VEGF and TGF β) that are up-regulated during reparative/regenerative processes (McQualter, Bertoncello, 2012). Lung hosts several types of resident stem cells with self-renewal and differentiation capabilities that may represent the target of MSCs paracrine effect (Kotton et al., 2014).

The aims of this study were to investigate the pathophysiology of emphysema and to test the ability of resident mouse MSCs in modulating lung repair processes in an elastase-induced experimental model of emphysema.

Emphysema was induced in C57BL/6J mice through intratracheal administration of porcine pancreatic elastase (80 U/kg) at day 0. Lung MSCs were isolated from 2-3-month-old C57BL/6J mice. After removal of non-adherent cells, the adherent layer was cultured in fresh medium and used from passage 1 to 3. Lung mesenchymal phenotype was confirmed by FACS analysis (CD44+, CD90+, CD105+, CD14-, CD34-, CD44-). Cells were intratracheally administered on day 21. 10 days after cell delivery, pulmonary function was assessed with the static pulmonary compliance (CL) technique and lung samples were collected for morphological and molecular analysis.

Static LC analysis confirmed that elastase increased lung stiffness. MSC administration restored lung elasticity. Consistently, histological data showed that MSC treatment partially recovered alveolar architecture after elastase-induced damage. The severity of emphysema, measured by the mean linear intercept and the tissue area vs alveoli ratio, was reduced in MSC-treated animals, as compared to the elastase group. The airway remodeling induced by elastase was also confirmed by a reduced protein expression level of the tissue inhibitor of matrix metalloproteinase 1,

detected by western blotting. The reduction in surfactant protein C expression observed in the elastase group supported a reduction in lung elasticity that was restored by MSCs administration.

In the search for molecular mechanisms and effective therapies for COPD, our study shed light on regenerative and supportive properties of lung resident MSCs. The identification of molecular mechanisms responsible for this effect may be useful to better understand and potentially boost local tissue repair.

References

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