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Specific subsets of mesenchymal stroma cells to treat lung disorders – Finding the Holy Grail

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ABSTRACT

Accumulating studies, both in animals and human clinical trials with mesenchymal stroma cells (MSC) support the hypothesis of therapeutic effects of these cells in various disorders. However, despite success in immune-mediated disorders such as Crohns' disease, lung disorders such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary disease (IPF) treated with MSC have so far not yielded a revolutionary effect on clinical symptoms. Promising data on immunomodulatory effects in COPD have kept nourishing the research into finding specific traits of MSC beneficial in disease. A heterogeneous population of injected cells might drown a potential therapeutic role of a specific group of MSC. Thus careful analysis of MSC regarding their molecular capabilities such as delivering specific therapeutic vesicles to the environment, or plain cytokine/chemokine fingerprinting might prove useful in augmenting therapies against lung diseases.

1. Background

Over the last decades, promising results have been generated for cell-based therapies with somatic stem cells in models of serious lung disorders such as acute respiratory distress syndrome [1]. Accumulating data from several clinical trials indicates that transplantation of bone marrow or adipose derived mesenchymal stroma cells (MSC) to patients is safe and non-toxic [2]. Moreover, MSC have been demonstrated to exert a beneficial effect in both phase 1 and 2 clinical trials in immune-mediated diseases such as graft-versus-host disease (GVHD) [3] and Crohn's disease [4]. However, data are not consistent and other studies have even showed opposing effects of MSC in GVHD [5].

2. MSC-based therapies – importance of clinical trial set-up

Despite promising results from the clinical applications in immunological diseases, less success has been achieved in other disorders. Clinical trials with autologous MSC in heart diseases like myocardial infarction and heart failure have so far not succeeded [6,7]. In line, a clinical randomized placebo-controlled trial of MSC in chronic obstructive pulmonary disease (COPD) showed no significant amelioration in pulmonary function or frequency of exacerbations. However an early decrease in C-reactive protein (CRP) still gives promise for future investigations [8]. Weiss et al. used allogeneic bone marrow derived MSC from healthy donors and patients were either treated with intravenous infusion of MSC or vehicle (placebo). Importantly, their study demonstrates that intravenous infusion of bone marrow derived MSC is safe in patients suffering from COPD [8].

Additionally, a prospective, non-randomized, non-placebo-controlled phase Ib trial was performed on patients with idiopathic pulmonary fibrosis (IPF). Here, autologous MSC derived from lipo-aspirations were used. The MSC were diluted in saline and given by endobronchial infusions. This administration route is different from the intravenous application applied in most studies so far; nevertheless the results showed that endobronchial administration of adipose-derived stem cells is safe in IPF patients [9].

3. MSC treatment in lung disorders

Chronic lung diseases, like COPD and asthma, represent a world-wide high socio-economic burden and COPD is today the fourth

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leading cause of death in the world and is expected to rise to third place by 2020 [10]. Therapies manage to control, in most cases, the inflammation, but no cure exists and the remodeling of lung tissue leads to chronicity and the deleterious decline in lung function. The only treatment that is available for patients with end-stage lung diseases is lung-transplantation but unfortunately, 50–60% of the lung-transplanted patients develop chronic rejection [11,12]. In light of the success of cell therapy in blood disorders, lots of attention and efforts are being put into developing successful cell therapies and particularly MSC therapies also for chronic lung disorders. There is hope that MSC might be able to affect the course of the disease – potentially preventing development of bronchiolitis obliterans syndrome (BOS).

Besides adipose and bone marrow derived MSC, there is an increasing interest also in lung-resident MSC. Evolving evidence points toward lung resident MSC that have been isolated from bronchoalveolar lavage fluid from lung-transplanted patients [13] and also from lung tissue [14]. We have recently demonstrated that MSC can be isolated from lung tissue of lung-transplanted patients both from central and peripheral locations within the lung. Furthermore, we have isolated primary MSC based on the expression of CD90/CD105 and we showed that they are located perivascularly [15]. We and others have further described that MSC are tissue specific and differ from bone marrow derived MSC phenotypically as well as functionally [15,16].

4. Therapeutic effects of MSC

It has been reported that the majority of MSC are trapped within the lung after intravenous administration in different animal models, however, pulmonary engraftment has been demonstrated to be very low, after both, transtracheal – [17] and systemic administration [18]. Therefore, the effect of MSC treatment has been suggested to result from paracrine mechanisms rather than through engraftment or differentiation. Following systemic administration, MSC initially localize in lung and the existence of lung injury may attract the MSC and prolong their retention in the lung. Locally, the MSC have been described to secrete a variety of cytokines and growth factors including TNF-stimulated gene-6 (TSG-6), which is an anti-inflammatory protein that interestingly also is involved in hyaluronan deposition [19,20]. There are studies suggesting that conditioned medium from MSC is sufficient for improving acute lung injury and that the MSC themselves are redundant [21]. Interestingly, MSC have been shown to secrete microvesicles that might have a larger impact than what has previously been appreciated [22]. Microvesicles can transfer for example mRNA, miRNA, signal molecules, and surface receptors. A proteomic analysis on microvesicles isolated from bone marrow derived MSC revealed that they contain at least 730 proteins, whereof a few of them were suggested to be associated with the therapeutic effect [23]. These promising data thus open new avenues for treatment of various lung diseases.

5. Conclusions

Despite promising results both in animal models of lung disorders and clinical studies, there is – as unfortunately also observed in other (stem) cell therapy areas – an unjustified hope and hype that cell-based treatments will help to cure all lung diseases within a short time. Before succeeding with MSC treatment of lung diseases, however, open questions regarding the basic biology of MSC and especially lung-derived MSC need to be thoroughly investigated. Important questions regarding lung MSC relate to their physiological role in the normal lung and their possible involvement in pathological processes. Recent research indicates that a more precise sub-division of specific diseases and importantly, the specific sub-grouping of MSC will be a future challenge. In fact, a growing body of evidence indicates that the therapeutic effect of MSC in various conditions is mediated by different MSC subtypes, which are part of a heterogeneous pool of different MSC. These MSC subtypes might show a different homing capacity to the lung, thereby exerting their cell-specific effect [24].

Thorough care needs to be taken to characterize specific pathological conditions. Future research on MSC therapy in lung disorders may shed light on specific functions of different homogeneous subsets of MSC and hopefully allow designing a tailor-made treatment according to patient-specific conditions.

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References

[1] Lalu MM, Moher D, Marshall J, Fergusson D, Mei SH, Macleod M, et al. Efficacy and safety of mesenchymal stromal cells in preclinical models of acute lung injury: a systematic review protocol. Syst Rev 2014;3(1):48 [Epub 2014/06/03].
[2] Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. PloS One 2012;7(10):e47559 [Epub 2012/11/08].
[3] Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008;371(9624):1579–86 [Epub 2008/05/13].
[4] Duijvestein M, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW, et al. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. Gut 2010;59(12):1662–9 [Epub 2010/10/06].
[5] Calkoen FG, Vervat C, van Halteren AG, Welters MJ, Veltrop-Duits LA, Lankester AC, et al. Mesenchymal stromal cell therapy is associated with increased adenovirus-associated but not cytomegalovirus-associated mortality in children with severe acute graft-versus-host disease. Stem cells Transl Med 2014 Aug;3(8):899–910. http://dx.doi.org/10.5966/sctm.2013-0191.
[6] Williams AR, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. Circ Res 2011;109(8):923–40 [Epub 2011/10/01].
[7] Perico N, Casiraghi F, Introna M, Gotti E, Todeschini M, Cavinato RA, et al. Autologous mesenchymal stromal cells and kidney transplantation: a pilot study of safety and clinical feasibility. Clin J Am Soc Nephrol 2011;6(2):412–22 [Epub 2010/10/12].
[8] Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. Chest 2013;143(6):1590–8 [Epub 2012/11/23].
[9] Tzouvelekis A, Paspaliaris V, Koliakos G, Ntolios P, Bouros E, Oikonomou A, et al. A prospective, non-randomized, no placebo-controlled, phase Ib clinical trial to study the safety of the adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis. J Transl Med 2013;11:171 [Epub 2013/07/17].
[10] Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349(9064):1498–504 [Epub 1997/05/24].
[11] Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transpl 2002;21(3):297–310 [Epub 2002/03/19].
[12] Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. Am J Respir Crit Care Med 2002;166(4):440–4 [Epub 2002/08/21].
[13] Lama VN, Smith L, Badri L, Flint A, Andrei AC, Murray S, et al. Evidence for tissue-resident mesenchymal stem cells in human adult lung from studies of transplanted allografts. J Clin Invest 2007;117(4):989–96 [Epub 2007/03/10].
[14] Sabatini F, Petecchia L, Tavian M, Jodon de Villeroche V, Rossi GA, Brouty-Boye D. Human bronchial fibroblasts exhibit a mesenchymal stem cell phenotype and multilineage differentiating potentialities. Lab Invest 2005;85(8):962–71 [Epub 2005/06/01].
[15] Rolandsson Sara, Andersson-Sjöland Annika, Brune Jan Claas, Li Hongzhe, Kassem Moustapha, Mertens Fredrik, et al. Primary mesenchymal stem cells

in human transplanted lungs are CD90/CD105 perivascularly located tissue-resident cells. BMJ Open Respir Res 2014;1:e000027. http://dx.doi.org/10.1136/bmjresp-2014-000027.

[16] Hoffman AM, Paxson JA, Mazan MR, Davis AM, Tyagi S, Murthy S, et al. Lung-derived mesenchymal stromal cell post-transplantation survival, persistence, paracrine expression, and repair of elastase-injured lung. Stem Cells Dev 2011;20(10):1779–92 [Epub 2011/05/19].

[17] Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, et al. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. Proc Natl Acad Sci U S A 2003;100(14):8407–11 [Epub 2003/06/20].

[18] Xu J, Woods CR, Mora AL, Joodi R, Brigham KL, Iyer S, et al. Prevention of endotoxin-induced systemic response by bone marrow-derived mesenchymal stem cells in mice. Am J Physiol Lung Cell Mol Physiol 2007;293(1):L131–41 [Epub 2007/04/10].

[19] Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell 2009;5(1):54–63 [Epub 2009/07/03].

[20] Swaidani S, Cheng G, Lauer ME, Sharma M, Mikecz K, Hascall VC, et al. TSG-6 protein is crucial for the development of pulmonary hyaluronan deposition, eosinophilia, and airway hyperresponsiveness in a murine model of asthma. J Biol Chem 2013;288(1):412–22 [Epub 2012/11/03].

[21] Ionescu L, Byrne RN, van Haaften T, Vadivel A, Alphonse RS, Rey-Parra GJ, et al. Stem cell conditioned medium improves acute lung injury in mice: in vivo evidence for stem cell paracrine action. Am J Physiol Lung Cell Mol Physiol 2012;303(11):L967–77 [Epub 2012/10/02].

[22] Baglio SR, Pegtel DM, Baldini N. Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. Front Physiol 2012;3:359 [Epub 2012/09/14].

[23] Kim HS, Choi DY, Yun SJ, Choi SM, Kang JW, Jung JW, et al. Proteomic analysis of microvesicles derived from human mesenchymal stem cells. J Proteome Res 2012;11(2):839–49 [Epub 2011/12/14].

[24] Wong AP, Keating A, Lu WY, Duchesneau P, Wang X, Sacher A, et al. Identification of a bone marrow-derived epithelial-like population capable of repopulating injured mouse airway epithelium. J Clin Invest 2009;119(2):336–48 [Epub 2009/01/24].