Symposium 2: State of art: New treatment for moderate to severe atopic dermatitis

Successful Treatment of Atopic Dermatitis with Subcutaneously Administered Human Umbilical Cord Blood-Derived Mesenchymal Stem Cell

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Mesenchymal stem cells (MSCs) and their potential therapeutic uses in human have generated considerable interest due to their unique regenerative and anti-inflammatory capabilities.[1,2] Here, we sought to evaluate the efficacy and safety of subcutaneously administered human umbilical cord blood-derived MSCs in the treatment of atopic dermatitis (AD). Thirty four adult patients with moderate-to-severe AD were randomly allocated to receive low dose (2.5×10^7) or high dose (5.0×10^7) of MSCs subcutaneously. Eczema Area and Severity Index (EASI) score, Investigator's Global Assessment (IGA) score, Severity Scoring for Atopic Dermatitis (SCORAD) score, adverse effect assessments, and serum biomarker levels were evaluated as end points. Single subcutaneous injection of MSCs dose-dependently improves the disease symptoms based on the evaluation of various parameters such as EASI, IGA, and SCORAD score. Administration of MSCs showed improved AD symptoms involving skin lesions on the neck, trunk, and leg of the participants compared to the baseline. Moreover, MSCs significantly downregulated the levels of serum total IgE and blood eosinophil count. Our data provide convincing evidence for safety and therapeutic properties of MSCs in human patients with no adverse effects.

Preclinical studies have shown that MSCs can significantly inhibit proliferation and maturation of T cells and B cells, and alleviate AD through reducing mast cell degranulation in prostaglandin E2 and transforming growth factor β1-dependent manner.[3] Recently, cutaneous mesenchymal stem cells isolated from psoriatic patients were shown to have impaired antioxidant capacity with excessive reactive oxygen species (ROS) level, and increased angiogenic factors like vascular endothelial growth factor, suggesting the pivotal role of oxidative stress in disease pathogenesis and indispensable role of antioxidant therapy.[4,5] Considering the importance of antioxidant therapy, reduced antioxidant capacity of skin resident MSCs from psoriatic patient, and control of superoxide dismutase 3 (SOD3) over innate and adoptive immune responses[4-6], Sah et. al. tested the therapeutic efficacy and revealed the pathways of immunomodulation of SOD3 overexpressed in

MSCs using the mouse model of imiquimod-induced psoriasis-like skin inflammation.[7] It is shown that subcutaneous administration of SOD3-transduced MSCs significantly prevented the development and severity of psoriasis with reduced epidermal hyperplasia, ROS levels and infiltration of T cells, dendritic cells, and neutrophils in skin of mice. Interestingly, they also observed the systemic effect of subcutaneous administration of SOD3-tranduced MSCs with reduced splenomegaly and swollen lymph nodes, and further decrease in accumulation of effector immune cells. Overexpression of SOD3 in MSCs strongly affected their immunosuppressive properties and exerted more potent effect on reducing the expression of inflammatory molecules such as interleukin (IL)-1β, IL-6, IL-17, and IL-23 in psoriatic skin of mice.[7]

Therefore, to demystify the role of MSCs in alleviating AD which shares several pathogenic features with psoriasis, and also exploring the possibilities of antioxidant therapy in combination with MSCs for broad spectrum effect, we aimed to use MSCs transduced with extracellular superoxide dismutase (SOD3-MSC) in ovalbumin (OVA)-induced AD-like skin inflammation in mice, and also evaluated the their role in regulating keratinocyte and mast cell function during AD pathogenesis in *in-vitro*. Our *in-vitro* and *in-vivo* results from co-culturing of SOD3-MSCs or MSCs with human mast cells, human epidermal keratinocytes, mouse CD4+ T cells and OVA-induced mouse model of AD, respectively, showed that SOD3-transduced MSCs can have stronger immunosuppressive and immunomodulatory effect likely through the suppression of proliferation and infiltration of various effector cells into the skin with a concomitantly modulated inflammatory mediators expression, and inhibition of underlying signaling pathways. These results further support the development of SOD3-MSCs or MSCs for the treatment of AD and several other inflammatory diseases including psoriasis, asthma, and allergic rhinitis.

References

1. Salem HK, Thiemermann C. Mesenchymal stromal cells: current understanding and clinical status. Stem Cells 2010; 28(3): 585-596.
2. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, Zhao RC, Shi Y. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell 2008; 2(2):141-150.
3. Kim HS, Yun JW, Shin TH, Lee SH, Lee BC, Yu KR, Seo Y, Lee S, Kang TW, Choi SW, Seo KW and Kang KS. Human umbilical cord blood mesenchymal stem cell-derived PGE2 and TGF-β1 alleviate atopic dermatitis by reducing mast cell degranulation. Stem Cells 2015; 33: 1254-1266.
4. Orciani, M, Campanati A, Salvolini E, Lucarini G, DiBenedetto G, Offidani A, Di Primio R. The mesenchymal stem cell profile in psoriasis. Br J Dermatol 2011; 165: 585-592.
5. Campanati A, Orciani M, Gorbi S, Regoli F, Di Primio R, Offidani A. Effect of biologic therapies targeting tumour necrosis factor-α on cutaneous mesenchymal stem cells in psoriasis. Br J Dermatol 2012; 167(1): 68-76.
6. Kwon MJ, Jeon YJ, Lee KY, Kim TY. Superoxide dismutase 3 controls adaptive immune responses and contributes to the inhibition of ovalbumin-induced allergic airway inflammation in mice. Antioxid Redox Signal 2012; 17(10): 1376-1392.
7. Sah SK, Park KH, Yun CO, Kang KS, Kim TY. Effects of human mesenchymal stem cells transduced with superoxide dismutase on imiquimod-induced psoriasis-like skin inflammation in mice. Antioxid Redox Signal 2016; 24(5): 233-248.