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Tissue-Specific Differences in Mesenchymal Stromal Cells Influence Homing and Function

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Abstract

Mesenchymal Stromal Cell(MSC) therapies to modulate inflammation and promote tissue regeneration in Recessive Dystrophic Epidermolysis Bullosa(RDEB) are under active investigation in clinical trials. However, optimal tissue source and fundamental mechanisms of clinical benefit of MSCs require additional investigation. Riedl et al. recently published "ABCB5+ dermal mesenchymal stromal cells with favorable skin homing and local immunomodulation for Recessive Dystrophic Epidermolysis Bullosa treatment," in Stem Cells [1] highlighting differences in homing of MSCs, impact on local macrophages, and distinct transcriptional profiles related to tissue of origin (skin dermis versus bone marrow). Elucidation of these critical features and underlying mechanisms will aid in translation of MSC cellular therapies to promote wound healing in RDEB.

Keywords: Mesenchymal Stromal Cell; Recessive Dystrophic Epidermolysis Bullosa; Mesenchymal Stromal Cells; Bone Marrow

Commentary

Recessive Dystrophic Epidermolysis Bullosa(RDEB) is a genodermatosis characterized by exquisite mucocutaneous fragility. Affected individuals have biallelic mutations in COL7A1 resulting in absent or abnormal type VII collagen (C7). C7 is most abundantly produced by epithelial cells but can additionally be secreted by fibroblasts and mesenchymal stromal cells. C7 is critical to the mechanical integrity of the mucocutaneous barrier. In RDEB, minor trauma results in separation, or blistering, of skin at the dermal-epidermal junction. Infants are born with blisters and erosions. Over a lifetime, individuals with RDEB experience repeated cycles of wounding and healing, inducing dermal fibrosis, contractures, and pseudosyndactyly of digits, esophageal strictures [2], and increased risk of lethal squamous cell carcinoma as early as the second decade of life [3]. Chronic pain and itch, high metabolic demand and malnutrition, micronutrient deficiencies, corneal abrasions, and anemia of chronic disease are common features in severe, generalized RDEB. RDEB is a disease of systemic inflammation without a cure. RDEB care consists exclusively of symptomatic management including avoidance of trauma; wound care; protective bandages; treatment of infections, pain and itch; and nutritional, micronutrient, and iron supplementation [4-7]. Translational research efforts in RDEB aim to provide more targeted therapies.

Regenerative medicine approaches to RDEB have focused on two main endpoints (1) increased functional C7 and (2) immunomodulation. For the former, active clinical trials include use of gene-corrected *ex vivo* skin grafts, topical and systemic agents for premature termination codon read through, and delivery of C7 topically. Intradermal injection of gene-corrected autologous fibroblasts to provide C7 demonstrated wound healing benefits and persistence of skin C7 for up to 12 months [8]. Mesenchymal stromal cells, initially pursued for C7 production capabilities, but have more recently gained interest for their immunomodulatory effects.

Mesenchymal stromal cells (MSCs) were first described as fibroblastic cells from the bone marrow capable of clonal production of bone [9]. With subsequent characterization, MSCs are now defined as cells of stromal origin, capable of self-renewal and trilineage chondrogenic, osteogenic and adipogenic differentiation [10]. Following successful restoration of C7 with allogeneic Bone Marrow Transplant(BMT) in a murine model of RDEB[11], BMT was instituted as a systemic therapy for human patients [12]. While patients demonstrated improvement in their blistering phenotype, C7 was not similarly increased as in the mice. Researchers hypothesized a portion of the clinical benefit could be attributable to Bone Marrow(BM)-derived MSCs in the donor inoculum during BMT. Indeed non-hematopoietic donor cells could be identified in the dermis following BMT [13]. To leverage this benefit, subsequent clinical protocols incorporated BM-MSCs, initially 3rd party and more recently donor-derived to avoid immune rejection of the cells [14]. At the same time, both intradermal injection[15,16] and intravenous [17,18] administration of allogeneic BM- MSCs for RDEB as monotherapy have demonstrated benefit with regard to improved wound healing, presumably by dampening local inflammation. Yet, are BM-MSCs the ideal MSC population for a disease process anchored in the skin?

With identification of MSCs in tissues beyond the BM, nomenclature evolved to reflect the unique characteristics of MSCs from difference niches [19]. At the same time, researchers began studying a unique subpopulation of MSCs resident in the skin dermis-ABCB5+DSCs (dermal MSCs). ABCB5, or ATP-binding cassette

subfamily member 5, is a surface glycoprotein that identifies (and allows for purification of) a population of DSCs with immunosuppressive qualities, including expression of Programmed cell Death(PD)-1 to inhibit T-cell activation, evasion of immune rejection, and induction of tolerogenic regulatory T cells[20]. ABCB5+DSCs were shown upon neonatal systemic administration in a murine model of RDEB to prolong life and decrease infiltration of macrophages in the skin[21]. Further investigation in another murine model of nonhealing wounds (iron-overload) demonstrated ABCB5+ DSCs to influence immunosuppressive M2 over proinflammatory M1 skewing of macrophage differentiation through interleukin-1 receptor antagonist (IL-1RA) secretion [22]. These cells were subsequently characterized and manufactured for clinical trial use [23] in a variety of inflammatory conditions, including RDEB (Phase I/II trial results pending).

To better understand niche differences in MSC populations relevant to clinical use in RDEB, Riedl et al. [1] directly compared ABCB5+DSC and BM-MSC influence on macrophage cytokine production in co-cultures, skin homing in mice, and transcriptional profiles of the two MSC populations. Increased macrophage anti-inflammatory IL-RA secretion had previously been demonstrated in co-culture with ABCB5+DSCs [22], but we showed greater IL-1RA secretion following direct co-culture compared to a Tran's well system, suggesting a direct interaction between cell types as opposed to a paracrine effect. As anticipated, we found superior homing of ABCB5+DSCs to skin and wound engraftment 14 days after injection compared to BM-MSCs (2.7 increase, $p<0.001$). Transcriptional analysis revealed ABCB5+DSCs to have increased expression of 17 homeobox(Hox) genes, as well as Vascular Cell Adhesion Molecule(VCAM-1) and major Histocompatibility Complex(MHC) Class II protein, HLA-DPB1, compared to BM-MSCs.

Conclusion

Conclusion: The significance of differences between ABCB5+ DSCs and BM-MSCs reported by Riedl et al.[1] requires further investigation but are intriguing considering the importance of Hox genes (particularly HOXA3) in coordination of wound healing, VCAM-1 in homing to the perivascular skin niche, and MHC Class II in immune evasion. In aggregate, our investigations confirm superior cutaneous anti-inflammatory benefits of ABCB5+DSCs compared to BM-MSCs in vitro and in pre-clinical murine studies, suggest mechanism for such benefits, and support further investigations of ABCB5+DSCs in skin diseases including RDEB.

Conflict of Interest

The authors have no potential conflicts of interest to disclose.

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