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Modulation of MMP-2 function in bone marrow mesenchymal stromal cells requires sphingosine 1-phopsphate receptor 1 mediated signaling: implications for cytoskeletal assembly and proliferation

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Bone-marrow-derived mesenchymal stromal cells (BM-MSCs)–based therapy represents a promising option in the field of regenerative medicine. Their therapeutic potential is mainly dependent on paracrine secretion, proliferation and ECM remodeling abilities whose modulation involves Matrix Metalloproteinase (MMP)-2 functionality. Thus, the identification of paracrine/autocrine factors regulating MMP-2 expression/activity may be of great biological relevance for potentiating BM-MSC therapeutic efficacy.

Our research group has demonstrated that BM-MSCs release the bioactive lipid sphingosine-1-phosphate (S1P). Here we demonstrated : i) the requirement for BM-MSC of S1P production to synthesize functional gelatinases; ii) an impairment of gelatinolytic activity and MMP-2 expression/release when the S1P receptor subtype 1 (S1PR1) is blocked. Notably, in these experimental conditions BM-MSCs did not exhibit the formation of plasmamembrane-associated F-actin structures (lamellipodia, filopodia, microspikes) and, in turn, showed a reduction of the proliferation rate. Moreover, S1P1-mediated signaling is required for HIF-1alpha expression and MMP-2 expression/activity, reduction of vinculin expression and stress fiber formation and proliferation in hypoxia, an experimental condition mimicking the injured/regenerating tissue microenvironment.

In conclusion, our findings, demonstrating the trophic role exerted by the autocrine S1P/S1PR1 signaling in maintaining BM-MSC ability to modulate MMP-2 function, required for ECM remodeling, cytoskeleton assembly and cell proliferation may provide perspectives for considering S1P/S1PR1 as a pharmacological target to preserve BM-MSCs properties and improve their efficacy in tissue repair.

Keywords

Bone marrow-derived mesenchymal stromal cells (BM-MSCs), sphingosine 1-phosphate (S1P) receptor 1, metalloproteinases, cell proliferation, cytoskeleton remodeling, regenerative medicine