

Regulation of MMP2 and MT1-MMP/MMP14 expression in mesenchymal stromal cells: a role for the bioactive lipid sphingosine 1-phosphate

Chiara Sassoli¹, Alessia Tani¹, Flaminia Chellini¹, Federica Pierucci², Elena Bruzzone², Larissa Vallone¹, Daniele Nosi¹, Francesca Matteini², Elisabetta Meacci², Sandra Zecchi Orlandini¹

¹ Dipartimento di Medicina Sperimentale e Clinica-Sezione Anatomia, Università degli Studi di Firenze, Firenze, Italy - ² Dipartimento di Scienze Biomediche, Sperimentali e Cliniche "Mario Serio"-Unità di Scienze Biochimiche e Biologia Molecolare, Università degli Studi di Firenze, Firenze, Italy

Bone-marrow-derived mesenchymal stromal cells (MSCs) are currently considered among the best candidates for cell-based therapy in regenerative medicine due to their ability to secrete paracrine factors with multiple effects on the injured tissue, including modulation of inflammation and immune reaction, ECM remodeling, angiogenesis and protection from apoptosis [1]. Moreover, MSCs have been proved, in some tissues, to affect the fate of resident progenitor cells by positively influencing the endogenous mechanisms of tissue repair/regeneration [2,3]. We have recently demonstrated that MSCs are able to produce and secrete sphingosine 1-phosphate (S1P), a bioactive lipid exerting a broad range of biological responses in many cell types [4]. On these bases, the aim of this study was to evaluate whether S1P could exert an autocrine effect on MSCs, influencing expression and release of enzymes involved in the ECM remodeling, namely matrix metalloproteinases (MMPs), such as MMP2 and its activator MT1-MMP/MMP14. By multiple approaches (confocal immunofluorescence, western blotting, zymography and gelatinase assays) we first found that MSCs express and release active MMP2 and MT1-MMP/MMP14. These cellular events appear to be mediated by S1P1, a specific G-coupled receptor subtype of the bioactive lipid, abundantly expressed in MSCs. In fact, when MSCs were cultured in the presence of a specific S1P1 antagonist (W146) they exhibited a down-regulation of MMP2 and MT1-MMP/MMP14; of note the addition of a receptor agonist (SEW 2871) was not able to up-regulate MMPs thus suggesting that S1P1 signalling plays a trophic role in MSCs. In parallel experiments, the expression of MMP2 and MT1-MMP/MMP14 was evaluated in MSCs cultured in low oxygen conditions (2%) in order to mimic the hypoxic microenvironment occurring in a damaged/regenerating tissue. These preliminary data contribute to add new insights into the functional mechanisms by which MSCs exert beneficial effects on tissue repair/regeneration.

This work was supported by Grants from CARIPT e CARIFI.

References

- [1] Sassoli C et al. 2012 *Cells*. 1:832-850. doi: 10.3390/cells1040832
- [2] Formigli L et al. 2015 *Wound Repair Regen*. 23:115-123. doi: 10.1111/wrr.12251.
- [3] Sassoli C et al. 2012 *PLoS One*. 7:e37512. doi: 10.1371/journal.pone.0037512.
- [4] Sassoli C et al. 2014 *PLoS One*. 9:e108662. doi: 10.1371/journal.pone.0108662.

Keywords

Matrix metalloproteinases; mesenchymal stromal cells; sphingosine 1-phosphate; S1P1.