

Mesenchymal stromal cells and their paracrine factors regulate MMP-2 and MMP-9/TIMP-2 balance in skeletal myoblasts and fibroblasts: new insights into the potential role of MSC-cell therapy in muscle regenerative medicine

Chiara Sassoli¹, Daniele Nosi¹, Alessia Tani¹, Flaminia Chellini¹, Benedetta Mazzanti², Franco Quercioli³ and Lucia Formigli¹

¹ Dept. of Experimental and Clinical Medicine - Section of Anatomy and Histology, University of Florence, Florence, Italy

² Dept. of Experimental and Clinical Medicine- Section of Haematology, University of Florence, Florence, Italy

³ CNR-National Institute of Optics (INO), Arcetri-Florence, Italy

Recent studies showed that mesenchymal stromal cell (MSCs) transplantation improves healing of injured and diseased skeletal muscle, although the mechanisms of benefit are still poorly understood. In the present study, we investigated whether MSCs and/or their trophic factors were able to regulate matrix metalloproteinase (MMPs) expression and activity in different cells of the muscle tissue. It was found that MSCs in co-culture with C2C12 cells up-regulated MMP-2 and MMP-9 expression and function in the myoblastic cells; these effects were concomitant with the down-regulation of the tissue inhibitor of metalloproteinases (TIMP)-2. Similar results were obtained upon incubation of conditioned medium from MSCs (MSC-CM) or in experiments where MSCs were separated from myoblasts by polycarbonate membranes, enabling diffusion of soluble factors while preventing the physical contact between the two cell types, suggesting that MSCs regulated MMP/TIMP balance in skeletal myoblasts by paracrine factors. In the single muscle fibre experiments, MSC-CM administration increased MMP-2 and MMP-9 expression in Pax-7⁺ satellite cells and stimulated their mobilization, differentiation and fusion into multinucleated myotubes. The anti-fibrotic properties of MSC-CM involved also the regulation of MMPs by skeletal fibroblasts and the inhibition of their differentiation into myofibroblasts, as detected by reduced expression of α -smooth actin and type-I collagen in the fibroblasts incubated with MSC-CM. These findings add novel information on the effects of MSCs on the skeletal muscle healing, suggesting that growth factors and cytokines released by these cells may modulate the fibrotic response and improve the endogenous mechanisms of muscle repair/regeneration.

Key words

Matrix metalloproteinases (MMPs), mesenchymal stromal cells (MSCs), myoblast differentiation, satellite cells, skeletal fibroblasts.