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Systemic Sclerosis Mesenchymal Stromal Cells Exhibit Senescence and Profibrotic Features with Preserved Immunomodulatory and Anti-fibrotic Function.

Human Mesenchymal stromal cells (MSC) are non-hematopoietic cells localized in the perivascular niche. They interact with endothelial cells and the extracellular matrix. MSC have proangiogenic, immunomodulatory and antifibrotic properties mainly mediated by secreted factors (i.e. MSC secretome). The composition of the secretome changes depending on the MSC microenvironment. Systemic sclerosis (SSc) is a prototypic profibrotic disease characterized by microvascular dysfunction, chronic inflammation and fibrosis. Data on MSC from SSc patients is limited and contradictory. In vitro studies of SSc MSC, showed reduced proangiogenic capacity, proliferation, and differentiation. We aimed to compare the transcriptomic signatures of adipose-derived MSC from SSc patients and controls and perform an in vitro evaluation of the MSC immunomodulatory capacity and the antifibrotic effects of their secretome.

MSC were isolated from the adipose tissue contained in two 4mm punch forearm skin biopsies performed on 15 SSc donors and 15 age- and sex-match controls. We characterized MSCs according to the minimal definition criteria proposed by the International Society for Cellular Therapy (ISCT): plastic adherence, surface markers, and tri-lineage differentiation. Bulk RNA sequencing was done on 8 Ctrl-MSC and 8 SSc-MSC. We evaluated in vitro MSC proliferation (Doubling time), stemness (CFU-F assay,) and immunopotency (flow cytometry). The cytokine profile of MSC-CM was determined in multiplex assays (Luminex xMAP). The anti-fibrotic effects of MSC conditioned medium (MSC-CM) were tested in in vitro assays (i.e. prevention of TGF- β induced fibroblasts activation and myofibroblast deactivation assays) which had α -SMA and procollagen I as readouts (Western blot).

SSc-MSC have an increase in IGFBP4, IL1A, IL15 and IL1B among other transcripts supporting the concept of a senescent phenotype. In vitro, SSc-MSC had reduced proliferation and clonogenicity capacity compared to controls but preserved immunopotency. A subgroup of SSc-MSC, characterized by higher α -SMA and increased CCL2, had a prominent myofibroblast-like phenotype. We found no association between the profibrotic MSC phenotype and SSc clinical manifestations or treatment. CCL2 levels, a profibrotic cytokine, were also elevated in SSc MSC-CM. MSC-CM from SSc and controls to the same extent inhibited TGF- β induced fibroblast activation and deactivated myofibroblasts.

SSc-MSC have features of senescence and in a subset of SSc patients they have a profibrotic phenotype. The reduced MSC proliferation and clonogenic capacity functionally support the senescent signature. The profibrotic MSC do not have reduced anti-fibrotic effects in vitro.