Adipose stromal vascular fraction and regenerative therapy in SSc: response to the article by Magalon *et al*

We read with interest the report by Magalon *et al*,¹ supporting the use of stromal vascular fraction (SVF) derived from adipose tissue, as an innovative autologous biotherapy for patients affected by systemic sclerosis (SSc). This disease is a complex multisystem disorder, characterised by microvascular damage, dysregulation of innate and adaptive immunity and generalised fibrosis in the skin and multiple organs, lacking a specific therapy. SSc is classified into two subsets: limited cutaneous (lcSSc), in which the skin fibrosis is limited to the extremities (hands, arms and face), and diffuse cutaneous (dcSSc), in which the skin fibrosis progresses more rapidly, affecting the trunk and extremities, frequently involving the internal organs.² Due to this heterogeneity, in terms of extent, severity and rate of progression, it is still a matter of debate if both the subsets share a common pathogenic mechanism. At present, a growing body of evidence has been published concerning mesenchymal stem cells (MSCs) therapy for patients with SSc—the cell population larger represented in the SVF, in the last few years. In this work, the authors¹ showed that the transcriptome profile of SVF, derived from patients with SSc, exhibited a profibrotic signature, without compromising the vascular repair capacity of SVF. In this context, we previously published data, confirmed also by other groups, showing a strong profibrotic signature in the MSCs, derived from patients with dcSSc,^{2–6} and thus suggesting their involvement in the rapid evolution of fibrosis. Furthermore, the authors enrolled nine patients with dcSSc and 15 patients with lcSSc. Of note, the authors¹ did not stratify the results between the two subsets and analysing the graphs of the paper, we may observe a large distribution of the data which partially impairs the results. Furthermore, the majority of the experiments were performed in very small number of patients (from 4 to 8) and without any explanation about how they were selected. Given the different profibrotic fate of patients with dcSSc and the significant profibrotic signature of MSCs derived from these patients, it should be important to compare the presence of possible different SVF effects, deriving from the two different subsets of the disease. Paradoxically, due to the MSCs profibrotic signature in SSc, it could be possible that the pathogenic milieu may force autologous cells to transdifferentiate to myofibroblasts, thus increasing the fibrotic burden.^{2–6} In fact, the transcriptomic analysis, in the study of Magalon *et al*¹ confirmed the GDF15 gene over-expression which is strongly related to the fibrotic pathway. Further refinements in the understanding of SSc-SVF profile, together with targeted approaches to both SSc endothelial cells and pathological microenvironment, are needed to improve the regenerative approach of SSc.

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