M-CSF and GM-CSF monocyte-derived macrophages in systemic sclerosis: the two sides of the same coin?

We read with interest the article by Moreno-Moral *et al*[1] exploring the contribution of monocyte-derived macrophages (MDMs) in mediating genetic susceptibility to systemic sclerosis (SSc). By conducting RNA sequencing and genome-wide genotyping in a model of MDMs differentiated by macrophage colony-stimulating factor (M-CSF), this article provides new insights in the activation/polarisation states of blood MDMs in SSc.

In this work, the blood MDMs from 57 patients with SSc present a mixed activation signature state (figure 1 in ref.[1]): on the one hand, the down-regulation of interferon gamma response is in favour of an alternative (M2) activation, but on the other hand, the downregulation of the interleukin (IL)-6/JAK/STAT3 signalling pathway may limit this alternative polarisation as IL-6 promotes IL-4Rα expression in macrophages in an IL-10-independent manner.[2] Therefore, blood MDMs' polarisation states contrast with the macrophage signature from other tissues in SSc,[3] such as lung, in which a STAT3-dependent enhanced expression of CD163 has been associated with an immune-driven pulmonary fibrosis. The results of Moreno-Moral *et al* on MDMs are consistent with the results of previous studies on undifferentiated peripheral blood monocytes in SSc[4] in which the inflammatory component of the immune-fibrotic processes is only found in peripheral blood, illustrating this mixed (M1/M2) polarisation signature of blood monocytes and MDMs.[1 3] Altogether, these results reinforce the vision of a wide and heterogeneous functional range of activated macrophages, not only depending on the disease at stake and its stage of evolution, but also on the organ of interest, highlighting the need for a more refined phenotypic characterisation of these so-called 'M1 and M2' macrophages in inflammatory and fibrotic disorders.

However, the relevance of these results at a protein level is still to be evaluated in this in vitro model of MDMs. Moreover, we and others have demonstrated that the CSF used for differentiating MDMs, that is, M-CSF or GM-CSF, has a major impact at a functional and phenotypic level.[5] Therefore, the results of this RNA sequencing and genome-wide genotyping in the M-CSF-driven MDM model may vary in GM-CSF MDMs. This GM-/M-CSF duality may also influence and partly explain the variations of phenotypes and polarisation states among tissues in SSc, as GM-CSF classically characterises lung macrophages and M-CSF is involved in the physiology of macrophages from tissues like digestive tracts. The issue of macrophage ontogeny in human fibrotic diseases is still unsolved,[6] and the question of the most relevant CSF for obtaining MDMs in vitro is still to be determined. The comparison of M-CSF and GM-CSF MDMs using the same methodology as Moreno-Moral *et al* may highlight key pathogenic processes both in SSc and in the understanding of macrophage physiology in general.

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