Response to: 'M-CSF and GM-CSF monocyte-derived macrophages in systemic sclerosis: the two sides of the same coin?' by Lescoat *et al*

In the quest for identification of genes for complex disorders, the functional annotation of disease-risk variants in the relevant cell type remains a challenge. Lescoat and colleagues[1] pose the question '*what is a scleroderma macrophage?*' and in view of current literature (including the study by Moreno-Moral *et al*[2]), argued how the heterogeneous range of activated macrophages can vary between target organs of interest and possibly across different fibrotic diseases.

While we share Lescoat's point of view on the underlying complexity of functional cells in disease, it remains open to debate whether GM-CSF or M-CSF-mediated differentiation conditions of peripheral blood monocytes are sufficient to fully capture the characteristics of these cells in their disease context. As stated by Lescoat *et al*,[1] whether and to which extent the in vitro defined M1/M2 macrophage subtypes reflect the context-specific activation of macrophages observed in different organs (eg, skin, lung) in scleroderma remains to be demonstrated. In this respect, the proposed spectrum model of human macrophage activation[3] argues in favour of a scleroderma-specific macrophage activation profile which does not fall into the binary M1/M2 categorisation.[1]

The experimental challenges encountered in finding the 'best' cell culture conditions for modelling disease could be eased by investigating the genetic control of gene expression (ie, expression QTL or eQTL). Theoretically, these studies can test, regardless of culturing conditions, whether certain DNA variants affect the expression levels of core susceptibility genes expressed by myeloid cells, in general. Recent eQTL studies in humans showed context-specific variants (ie, on stimulation) in monocytes and macrophages but there is also evidence of some transcripts which are regulated by DNA sequence variation (eg, SNPs) independently of the stimulus[4] or the differentiation state of the cell (monocyte vs macrophage). For instance, Fairfax et *al* identified *GSDMA* as an eQTL in activated monocytes[4] and Moreno-Moral *et al*. (figure 2 in reference 2) showed the same gene being under local genetic control in M-CSF-derived macrophages isolated from patients with scleroderma. Notably, *GSDMA* associates with asthma susceptibility[5] and scleroderma.[6] This suggests genotype-dependent *GSDMA* expression in a wider monocyte/macrophage compartment, which is likely to be a risk component in these diseases. It is therefore plausible that the genetic control of *GSDMA* mRNA levels will be conserved in both M-CSF and GM-CSF-derived scleroderma macrophages but further experiments will be required to reach a definite conclusion.

Interestingly, human monocytes share eQTLs with CD4+ T cells[7] and neutrophils,[8] indicating that common DNA variants regulate mRNA levels of target genes in multiple immune cell types, suggesting the possibility of disease risk variants impacting on the wider immune response. As highlighted by Lescoat *et al*,[1] whether the effect of particular disease susceptibility variants on a gene's mRNA level is also conserved at the protein level remains to be examined, and we reckon that additional layers of regulation (eg, post-transcriptional, translational) are likely to be at work. Still, there are examples of robust conservation between expression and protein QTLs associated with disease.[9] Ultimately, the eQTL approach, while informative in linking *bona fide* disease risk variants with target cells (as shown by Moreno-Moral *et al*[2]), should be considered in the broader target tissue context rather than in specific cell culture conditions,[10] and recent advances in ATAC-seq, single cell RNA-seq will allow the refinement of causal variants for systemic sclerosis in a setting closer to their in vivo context.

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