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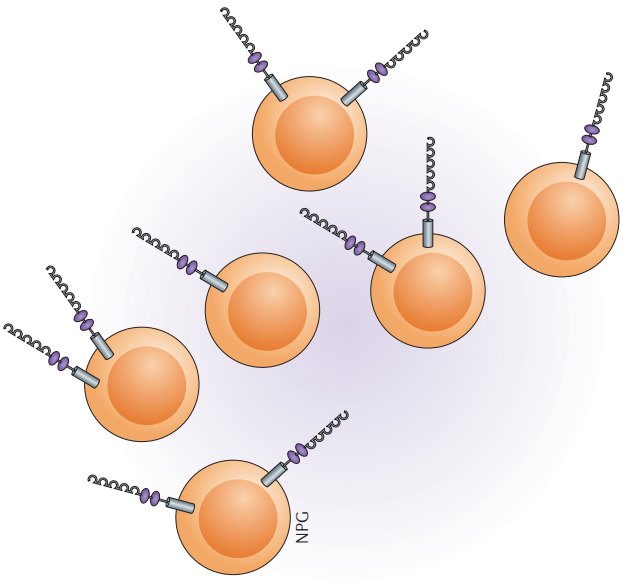
SYSTEMIC SCLEROSIS

The future is CD56-bright

Persistent hyperactivation of natural killer (NK) cells and natural killer T (NKT)-like cells might contribute to the aberrant innate immune system responses seen in individuals with systemic sclerosis (SSc), new data suggest. "These changes in the immune system are present in individuals years before the actual onset of disease, and could represent a window of opportunity to stop the fibrotic process before it occurs," highlights Marta Cossu, the study's corresponding author.

In previous work, the researchers identified a deregulated response to Toll-like receptors (TLRs) in dendritic cells and a prominent type I interferon signature in whole blood from patients with SSc, especially those in the earliest stages of this disease. "That focus led us to expand our interest to the CD56$^+$ NK and NKT-like cell populations, and to explore the degree of their activation, not only in the earliest phases of disease (before fibrosis actually occurs) but also in preclinical SSc," comments Cossu.

> "Activation of [NK and NKT]-like cells might contribute to the aberrant innate immune system responses seen in … SSc"



In the present study, Cossu's group found a linear increase in markers of activation of CD56-bright NK and NKT-like cells after TLR stimulation, from healthy controls (lowest) through individuals with Raynaud phenomenon only, patients with early SSc (defined as having Raynaud phenomenon plus SSc-specific autoantibodies or vascular changes on nailfold video-capillaroscopy), and patients with definite SSc but still lacking any sign of skin or organ fibrosis (highest). In particular, the researchers found that NK and NKT-like cell production of IL-6, TNF and CCL3 was augmented after TLR1 or TLR2 stimulation, as well as (albeit to a lesser extent) after TLR7 or TLR8 stimulation, suggesting the relevance of these pathways to the pathogenesis of SSc. "Our work contributes to understanding of the role of NK and NKT-like cells in the pathogenesis of SSc — which has been limited until the present moment — and indicates these cell populations as possible players in the developmental stages of disease," Cossu goes on to explain.

The team's next step will be to investigate the phenotype of NK and NKT-like cells in preclinical, early and late (that is, fibrotic) stages of SSc. "We aim to provide a broad characterization of the subsets of NK and NKT-like cells most likely to be responsible for the hyperactivated stage," Cossu confirms.

Cossu's group is now focusing on a systems medicine approach involving bioinformatic data integration and transcriptomic, methylomic and metabolomic deep profiling of immune cells. "This technique is currently being applied extensively within our group to understand the molecular hits that precede the onset of SSc, with the ultimate goal of highly personalized disease interception," she elaborates.

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ORIGINAL ARTICLE Cossu, M. *et al.* The magnitude of cytokine production by stimulated CD56$^+$ cells is associated with early stages of systemic sclerosis. *Clin. Immunol.* http://dx.doi.org/10.1016/j.clim.2016.09.004 (2016)

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