Clinical & Experimental Immunology
The Journal of Translational Immunology

doi: 10.1111/cei.13452
Clinical and Experimental Immunology
EDITORIAL
REVIEW SERIES: INNATE IMMUNITY IN SYSTEMIC SCLEROSIS
Series Editors: Stephen O'Reilly

Innate immunity in systemic sclerosis

OTHER ARTICLES PUBLISHED IN THIS REVIEW SERIES
Toll-like receptors in mediating pathogenesis in systemic sclerosis. Clinical and Experimental Immunology 2020, 201: 14-24.
Novel insights into dendritic cells in the pathogenesis of systemic sclerosis. Clinical and Experimental Immunology 2020, 201: 25-33.
The role of innate immune cells in systemic sclerosis in the context of autologous hematopoietic stem cell transplantation. Clinical and Experimental Immunology 2020, 201: 34-39.

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Summary

Systemic sclerosis (SSc) is an autoimmune idiopathic connective tissue disease that results in skin and lung fibrosis. In line with all autoimmune diseases, women are disproportionally affected. The end target cell that results in the tissue fibrosis is the fibroblast that differentiates into a myofibroblast, which produces copious amounts of extracellular matrix and alpha-smooth muscle actin that endows the cell with a contractile phenotype. However, in recent times it has become clear that, along with the adaptive immune system, the innate immune system is critically involved [1,2]. A renaissance in innate immunity research has recently taken place, and this has led to new understanding of disease processes. This collection is a series of reviews on the role of innate immunity in SSc.

Toll-like receptors (TLRs) are a family of germline-encoded innate pattern recognition receptors that are both membrane-bound and intracellular. Activation of these TLRs results in downstream signalling through a variety of transcription factors that drive inflammation [1]. In recent years, identification of dysregulated TLRs in SSc has led to a resurgence of research in this area and the identification of endogenous ligands that mediate activation. Recent endogenous ligands that elicit a TLR response in SSc include DNA and single-stranded RNA [3]. These may be released from damaged cells in the endothelium instigating the activation of the TLRs. In this special collection, Frasca and Lande examine the role of TLRs in SSc with a focus on endogenous damage-associated molecular patterns (DAMPs) [4] that can mediate the activation of both immune cells and stromal cells [5].

Carvalheiro *et al.* review the roles of dendritic cells in the pathogenesis of SSc [6]. Dendritic cells are the sentinels of the immune system, sensing their environment for antigen, and are the most potent antigen-presenting cells promoting T cell activation, thus directing adaptive immunity. Therefore, their role in SSc can be profound. Dendritic cells in the form of Langerhans cells are found within the skin, and plasmacytoid dendritic cells are also found in the blood. It has recently emerged that plasmacytoid dendritic cells are particularly prominent in systemic sclerosis pathogenesis, with alterations in epigenetic marks associated with enhanced maturation of these cells. Carvalheiro *et al.* examine, in particular, the role of plasmacytoid dendritic cells in disease pathogenesis and how their development can be regulated epigenetically. Plasmacytoid dendritic cells are particularly efficient at producing and releasing larger amounts of type I interferons, as well as cytokines such as B cell-activating factor (BAFF) that can direct antibody production; thus, they can be important for many facets of the disease.

Servaas *et al.* describe the role of the innate immune system in the context of autologous haematopoietic stem cell transplantation [7]. It has been demonstrated that autologous stem cell transplant can reverse fibrosis in carefully selected diffuse systemic sclerosis patients, although the treatment is not without risk [8]. The mechanism of immune system 'resetting' is unclear; however, Servaas *et al.* suggest that alterations in the innate immune system could underpin the therapeutic effect of this transplant. They examine this in more detail expanding on possible mechanisms that lead to 'tolerance'.

Recent advances in understanding the role of the innate immune system and the intricate network of cytokines in SSc pathogenesis may yield opportunities for therapeutic intervention, particularly in the earliest stages of disease, where inflammation is predominant [9]. Advances in genetic sequencing and the omics revolution have allowed us to gain insights into the pathogenesis of the disease at unprecedented resolution, and I am convinced that this will allow us to tailor our treatments.

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