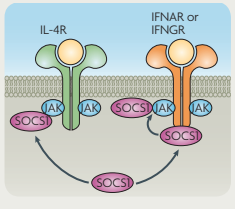


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Cytokines and interventional immunology

Alterations in cytokine expression associated with inflammation have long been observed in individuals with immune-mediated disease. Clinical trials carried out almost a decade ago were the first to show that therapeutic manipulation of cytokines with monoclonal antibodies targeting tumour-necrosis factor could change the course of an autoimmune disease. With this finding, the modern era of interventional immunology emerged.

This Focus issue of *Nature Reviews Immunology*, produced in collaboration with the Federation of Clinical Immunology Societies (FOCIS) and with support from Beckman Coulter, highlights recent advances in cytokine research, encompassing experimental studies in animal models, *ex vivo* studies with human cells and human clinical trials. This research strategy, similar to that used by scientists and clinicians in studies that resulted in the approval of therapy targeting tumour-necrosis factor (TNF) for rheumatoid arthritis, has led to several new and targeted approaches for the treatment of human inflammatory diseases. As the field of clinical immunology has developed, it has evolved from an observation-based science to an interventional discipline and the development of new therapies for inflammatory diseases has greatly accelerated.

Besides TNF, numerous other cytokines are intricately involved in the pathogenesis of rheumatoid arthritis, many of which have potential as therapeutic targets, as is discussed in a Review by Iain McInnes and Georg Schett in this issue. In particular, these authors describe the imbalance between pro- and anti-inflammatory cytokine activities in rheumatoid joints and how this imbalance favours the induction of autoimmunity, chronic inflammation and joint damage. They highlight that whereas the understanding of the hierarchical regulatory cytokine network is clearly of central importance, the clinical application of these findings to determine which cytokines might be the best targets for clinical intervention remains a major challenge for interventional immunologists.

Suppressor of cytokine signalling (SOCS) proteins are important in this hierarchical regulatory cytokine network. Recent studies have shown that SOCS proteins are key physiological regulators of both innate and adaptive immune responses. These molecules positively and negatively regulate macrophage and dendritic-cell activation and are essential for T-cell development and differentiation. Evidence is also emerging for an involvement of SOCS proteins in inflammatory diseases,

possibly through their influence on the differentiation of T cells into inflammatory interleukin-17-producing T helper cells. Akihiko Yoshimura and his colleagues review our current knowledge on the functions of SOCS proteins and their role in the immune system and propose a cohesive model of how cytokine signalling regulates immune-cell function.

Besides functioning as direct mediators of inflammation, cytokines have therapeutic potential in the regulation of immune responses. This is perhaps best exemplified by recent studies showing that signalling in T cells induced by the cytokine transforming growth factor- β (TGF β) plays a crucial role in preventing autoimmune disease. Yuri Rubtsov and Alexander Rudensky review recent advances in our understanding of a role for TGF β -mediated signalling in the regulation of T-cell differentiation in the thymus and in the periphery, with a particular emphasis on TGF β -mediated control of self-reactive T cells.

Inflammation underlies so many of the diseases that we study as physicians and scientists, afflicting virtually all of the organ systems. The discipline of immunology is the basis of our understanding of underlying disease pathophysiology of the inflammatory diseases, whether they be multiple sclerosis, type 1 diabetes, rheumatoid arthritis, asthma and allergy, or transplant-related disorders. However, the barriers associated with clinical specialization have created 'islands' of knowledge with little communication between specialists focusing on different organ-specific diseases. FOCIS was created to weave the fabric of basic science with clinical specialties to create a cross-disciplinary matrix of science and medicine. Founded in 1997, FOCIS celebrates a decade of dramatic advancement for interventional immunology as a cross-disciplinary field of medicine. The topic of this issue of *Nature Reviews Immunology*, cytokines and cytokine therapy, is illustrative of the mission of FOCIS, which seeks to foster interdisciplinary approaches to both understand and treat immune-based diseases.