Symposium A

Inflammation

SA-1

IL-21 IS A KEY CYTOKINE IN TH2 BUT NOT TH1 INFLAMMATORY RESPONSES

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Interleukin-2 (IL-2), IL-4, IL-7, IL-9, and IL-15 belong to the type I cytokine family, their receptors share the common γ_c chain and signal via the Jak/STAT pathway. These cytokines play crucial roles in T cell responses including cell proliferation, differentiation, and maintaining memory populations. IL-21 is the most recently described member of this cytokine family, and a series of studies have shown that it has pleiotropic effects upon the development of immune responses. However, the data to date concerning the role of IL-21 in Th1 and Th2 responses remains controversial. We have generated IL-21R-deficient mice and have investigated the role of IL-21R signaling using a series of *in vivo* experimentally induced disease models. In an attempt to clarify the role of IL-21 in both Th1 and Th2 immune responses, we have generated mice deficient in the IL-21 receptor, and extensively assessed their ability to mount Th1 and Th2 responses *in vivo*. We have found that IL-21R was central to the development of Th2-driven allergic airway inflammation as shown by impaired Th2 cytokine production, infiltration of eosinophils and airways hyperresponsiveness. Moreover, Th2 responses to gastrointestinal nematodes including type 2 granuloma formation, intestinal basophilia, and lung eosinophilia were severely impaired. In contrast, IL-21R-deficient mice mounted normal IFN-γ responses and containment of *Leishmania major* infection indicative of competent Th1 responses. Furthermore, development of Th17 driven experimental autoimmune myocarditis was normal in IL-21R-deficient mice.Together, these data show that IL-21 is a key cytokine in Th2 but not Th1 and Th17 effector responses.

SA-2

TOWARDS REMISSION IN INFLAMMATORY ARTHRITIS: CAN CYTOKINES OFFER THIS POTENTIAL?

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Despite the successful development of a variety of novel therapeutic agents, unmet clinical needs exist in rheumatoid and psoriatic arthritis. Therapeutic intervention should address inflammation, articular damage, co-morbidity and functional decline, all attendant to uncontrolled inflammatory arthritis. Several data now suggest that the kinetics of intervention are important – in principal earlier intervention leads to improved outcome regardless of the therapeutic agent employed. This is evident in comparing primary with subsequent DMARD interventions and in particular in comparing the clinical responses to TNF blockade in early versus later disease cohorts. Pathologic studies of synovial biology have not revealed particularly striking phenotypic differences in appearances over time – there are however limitations in the extent and rigour of sequential analyses in individual patients' biopsies and in the functional nature of such studies by necessity. This raises important issues in the design of optimal management strategies in inflammatory arthritis. (i) Upon clinical presentation, the inflammatory response should be limited rapidly to minimise the onset of damage to tissues that could provide an environment conducive to chronicity. There may be cytokines (in addition to TNF) that are effective as targets in this respect by virtue of their broad roles at early stages of inflammatory responses. (ii) Cytokines (e.g. IL-12, IL-23, IL-15) that regulate critical T cell, dendritic cell and B cell interactions remain relatively poorly understood in the context of inflammatory synovitis but may facilitate interventions that can promote tolerance induction. (iii) A variety of models now exist that facilitate analysis of such possibilities in particular in vivo. These will in turn instruct appropriate target selection – we should not at this stage assume that the same targets will be valid across the kinetics of an immune response and therefore a disease state.

SA-3

ROLE OF IL-22 IN INFLAMMATORY PROCESSES

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Originally identified as a gene specifically induced by IL-9 in a mouse T cell lymphoma, IL-22 is mainly produced by activated TH1 cells or upon inflammatory stimuli in vivo. Despite its structural relationship with IL-10, IL-22 exerts completely different activities, acting mainly on non hematopoietic cells, such as epithelial cells from lung and colon, hepatocytes and keratinocytes. In vivo administration of IL-22 upregulates the acute phase response and protects against ConA-induced hepatitis. Further studies using IL-22-deficient mice suggest that this cytokine plays a role in inflammatory processes including LPS-induced shock. IL-22 exerts its activity via a complex formed by IL-10Rb and IL-22R, associated with Tyk2 and Jak1, respectively. This receptor triggers different signalling cascades but turned out to be particularly potent in activating STAT3 through a unique SH2-independent recruitment of STAT3 to the cytoplamic domain of IL-22R. Beside its transmembrane receptor, IL-22 also binds to a soluble receptor, called IL-22BP. This soluble receptor turns out to be a natural antagonist of IL-22 biological activities at least *in vitro*.