EDITORIAL

Dual and Opposite Actions of Cytokines in Autoimmune Inflammatory Demyelination

The biological actions of cytokines in the immune system and specifically in autommunity have been carefully studied in the last few decades [1], in particular after Mosmann and Coffman observed that certain T helper cell populations could be categorised based on the cytokines they produce [2]. It was perhaps inevitable that progress in our knowledge of cytokine biology would generate simplified paradigms that have been challenged and refined over time. In the early stages of the definition of Th1 and Th2 cells, it was readily acknowledged by Mosmann and Coffman that "Further divisions of helper T cells may have to be recognized before a complete picture of helper T-cell function can be obtained" [3] and this is indeed what happened when Th3 [4] and more recently Th17 [5-7], Th9 [8, 9], and Th22 [10] subsets were recognised. While Th1, Th2 and regulatory T cells display a high degree of stability and can even enter the pool of memory cells, Th17 and other newly described populations appear to not truly represent a stable committed lineage. It now appears most likely that significant plasticity in T cell function enables them to produce even more varied combinations of cytokines that are "customised" to the systemic and local requirement of the immune system [11, 12].

One of the points we have learned is that even if sets of cytokines are produced together by individual cell types, each cytokine can have distinct effects on the outcome of the immune response depending on variables such as the cell source, the timing of cytokine production, the cell target and its functional state, the number and type of receptors for each cytokine, and its local or systemic action.

In autoimmunity and many other fields of immunology and biology, the contribution of gene-targeted mice to our understanding of pathophysiology has been striking. It was clear, however, that some misconceptions in the interpretation of data obtained in cytokine gene-knockout mice had to be prevented by careful consideration of biological redundancy, the existence of heterodimeric cytokines [13-15], limitations in gene-targeting technology, and the sheer complexity of living organisms [16]. In animal models of MS in particular, paradoxical findings on the role of cytokines such as TNF-α [17], IFN-γ [18] and IL-12 [13-15], have driven important advances in our knowledge of disease mechanism and T-cell biology, including the discovery of IL-17 secreting T cells coined "Th17". Review of these developments is beyond the scope of this editorial and for this purpose we refer the reader to excellent recent articles [12, 19, 20].

It was initially thought that resistance to autoimmune inflammatory demyelination in a cytokine-knockout mouse (e.g., IL-6) would necessarily imply a pro-inflammatory function of that cytokine in the disease process [21]. However, it is not unusual that the same cytokine, when administered systemically as a pharmacological agent, can have protective rather than inflammatory effects [22].

In this first special issue of the Open Autoimmunity Journal, we focus on 6 cytokines that have shown paradoxical and in some cases opposite effects on the susceptibility to autoimmune inflammatory demyelination. One original research article and five reviews are included.

In the first contribution, an original research article, we report the unexpected finding that IL-23, a heterodimeric cytokine known for its critical, non-redundant role in the development of experimental autoimmune encephalomyelitis (EAE) [15, 23] and other cell-mediated, organ-specific autoimmune diseases [24], suppresses autoimmune inflammatory demyelination when administered systemically. In both relapsing and chronic EAE models, we found that intraperitoneal administration of IL-23 caused clinical and pathological suppression of disease associated with reduced expansion of myelin-reactive T cells, loss of T-bet expression, loss of lymphoid structures, and increased production of IL-6 and IL-4. These findings demonstrate an unexpected function of IL-23 in limiting the scope and extent of organ-specific autoimmunity. Interestingly, they are reminiscent of another most recent report in a different experimental paradigm, in which IL-23 signaling was found to enhance Th2 polarization thereby regulating allergic airway inflammation [25]. We consider our report a good example of the unexpected, paradoxical role of a cytokine known to be strictly required for EAE susceptibility, but nevertheless found to suppress disease when administered as exogenous biological.

Sanvito *et al*. discuss research devoted to the study of IFN-γ, initially considered the hallmark of Th1 differentiation and pro-inflammatory responses, but in fact playing a much more complex role in autoimmunity. The article focuses on the apparent dichotomy between pro-inflammatory and protective effects of IFN-γ in CNS autoimmune demyelination and its implications for experimental therapies of MS.

Lim and Constantinescu review the role of TNF-α and its receptors at different stages of pathology in MS, including oligodendrocyte death, demyelination, immune cell trafficking, cellular proliferation and major histocompatibility (MHC) antigen expression. They also discuss the mixed results of anti-TNF-α therapy in EAE and the disappointment of clinical trials in MS, for which it was deleterious. The opposite, beneficial aspects of TNF-α are then addressed, including the promotion of neuroprotection and regeneration as reported in other types of pathology, including stroke and traumatic brain injury.

Ciric and Rostami describe how EAE was instrumental in the discovery of the IL-23/Th17 axis and how in spite of rapid progress in our understanding of T helper 17 cell function, the role of IL-17 in EAE and MS remains controversial. In spite of initial data suggesting a central role of IL-17 in EAE, significant questions have been raised by the recent reports that overex-

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pression and genetic deficiency or neutralization of IL-17A had only a minor effect in EAE, and by the negative results of a clinical trial utilising anti-IL-12/23p40 in patients with MS.

In their review of opposite functions of IL-22, Kreymborg and Becher argue that the tissue and the inflammatory context are key to the *in vivo* properties of this cytokine in autoimmunity and also host defense against extracellular pathogens.

Fonseca-Kelly *et al.* consider the studies that have elucidated the diverse and apparently paradoxical roles of IL-27, which was originally thought to play a pro-inflammatory role in immunity, but has in fact potent anti-inflammatory effects as well. Specifically, they look at the role of IL-27 in promoting early stages of Th1 development and suppressing later phases of Th1 responses, but also at its different effects on the development of Th2 and Th17 cell differentiation at different stages of the immune response and its implications in immunotherapy for autoimmune disease as well as cancer.

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