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Editorial

Special issue on Interleukin-6 (IL-6)

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Cytokines are essential modulators of the immune response. In the last decade there has been a number of cytokines considered targets for the development of biological therapies with the goal of blocking their activities and modulate the course of the immune response, primarily in the context of inflammatory diseases. IL-6 was first identified in the mid-1980s [1], but for almost two decades the enthusiasm for this cytokine as a potential active molecule and target for diverse diseases was not excessively high. However, it is now becoming clear that IL-6 plays an active role in modulating the immune response, and it has emerged as another successful target for a number of diseases such as inflammatory diseases [2]. Moreover, evidence is growing that IL-6 can also contribute to less expected diseases such as different types of cancer, neurological diseases or metabolic syndromes. Whether this effect of IL-6 is dependent or independent of its effect on the immune response remains to be addressed. In this special issue we provide six reviews that summarize what is known about the regulation, the role and mechanisms of IL-6 in a number of these diseases such as autoimmune diseases, colon cancer, neurodegenerative diseases and asthma.

The first review of the issue is by T. Kishimoto, who identified and cloned IL-6, IL-6R and gp130. Considering the clinical data showing persistent elevated levels of IL-6 in various autoimmune and inflammatory diseases and the data from mouse models suggesting an active role of IL-6 in the pathogenesis of these diseases, Kishimoto decided to go from bench to bed, and develop a blocking humanized anti-IL6R antibody (tocilizumab) that could be used as therapy for those inflammatory diseases. The success of such a therapy is evident with its approval worldwide for the treatment of rheumatoid arthritis and other autoimmune diseases. Kishimoto and co-worker summarize the active role that this cytokine has in a number of inflammatory diseases, and the results from the clinical trials and studies where IL-6R is the therapeutic target [3].

In addition to the signaling through the membrane-bound IL-6R, IL-6 can provide signaling to cells lacking IL-6R through its binding to the soluble IL-6R (sIL-6R) and association with gp130, pathway known as *trans*-signaling of IL-6. S. Rose-John, a pioneer in this alternative IL-6 signaling pathway, describes here the evidences to support different functions for the *trans*-signaling pathway (pro-inflammatory) and the conventional pathway (anti-inflammatory) of IL-6 [4]. Moreover, the review also provides an update of novel therapies for IL-6 based on the trans-signaling pathways.

Although for long it has been known that the levels of IL-6 in serum were elevated in a number of cancers and that IL-6 was expressed in tumor cells, it has not been until the last five years when a role of IL-6 in cancer development or progression was considered. Indeed, in the early-mid 1990's, instead of IL-6 being considered as a target in cancer treatment, there were several clinical trials administrating recombinant IL-6 in patients with breast, ovarian, prostate cancers among others. However, the association of IL-6 with poor prognosis it is now becoming evident in some types of cancer, and the concept of IL-6 being a potential target in cancer treatment instead of a therapy is emerging. The review by Neurath and

coworkers describes the results from clinical studies and experimental mouse models that support the contribution of IL-6 to the pathogenesis of sporadic colorectal cancer (CRC) [5]. The authors also describe recent evidences pointing to the inflammatory response as a major source of the IL-6 that contributes to CRC. While no clinical trials have yet been testing the role of IL-6 in CRC, the review also describes the potential therapeutic approaches to target both the conventional IL-6 signaling pathway or the *trans*-signaling pathway of this cytokines.

For a number of years, the role of IL-6 in the Central Nervous System (CNS) and neurological diseases has also been studied. IL-6 can be produced by astrocytes and microglia primarily, and to a lesser extent by neurons, in response to specific stimuli. Elevated levels of IL-6 in CNS have been reported in a number of neurological diseases associated with brain injury or inflammation in the brain. However, the role of this cytokine in the initiation and/or progression of the neurological disease remains uncertain. The review by Hidalgo et al. provides an extensive description of the studies that have approached the role of IL-6 in these diseases [6]. Although high levels of IL-6 can be found in a number of neurological disorders, this phenomenon does not necessarily indicate that IL-6 is pathogenic. Instead, Hidalgo et al. describe the studies supporting a protective role of IL-6 by providing survival to neurons, astrocytes and oligodendrocytes in models of brain injury, Parkinson disease, Huntington's disease, and Alzheimer disease. This review also describes how IL-6 can be pathogenic in other neuroinflammatory diseases such as multiple sclerosis (MS).

To further address the role of IL-6 in neuroimmune response, an independent review by Hirano and coworker [7] provides an alternative view of the relationship between IL-6 and CNS. They summarize the studies that have led to the concept of "IL-6 amplifier" and the involvement of this pathway in pathogenesis of neuroinflammatory disease such as MS. More importantly, this review describes the evidences indicating that regional neuronal activation regulates the "IL-6 amplifier" pathway where a NF-kB-mediated positive loop from IL-17 feeds into IL-6 production and provides an amplification of the pathogenic immune response.

While asthma and other lung diseases are not normally considered in the group of inflammatory diseases such as rheumatoid arthritis, colitis, MS etc, it is clear that the inflammatory response in the lung is essential for the pathogenesis (may add a reference here). The last review of this issue by Rincon and Irvin outlines the evidences in support of an active role of IL-6 in some aspects of the complex pathogenesis present in asthma and COPD [8]. In addition, the review describes recent genetic studies that further support the emerging concept of IL-6 being another novel potential target for inflammatory lung diseases.

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