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Editorial

Interleukin-6, A Grown-Up Cytokine in EAE

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Editorial

Three decades after its discovery by Kishimoto, et al [1], and this cytokine has been mentioned in more than 100.000 articles, 10.000 only in the last year, proving that it hasn't lost any piece of interest. Interleukin 6 (IL-6) is a cytokine so pleiotropic that it has caused confusion to researchers since the very beginning. Tadamitsu Kishimoto originally characterized it in 1985 as B-cell differentiation Factor (BSF-2) [1] after speculating that T cells must produce certain factors that induce growth and differentiation of B cells into antibody-producing cells [2]. Other labs were studying what was presumed unrelated growth factors at the time. These factors had several names and functions, interferon *b*2 [3,4], hybridoma growth factor [5], hepatocyte-stimulatory factor [6], cytotoxic T-cell differentiation factor [7], *b*2-fibrinogen [8], amyloid protein, haptoglobin and hemopexin, to name a few [9]. When IL-6 was cloned, it was clear that these seemingly different factors were the same molecule, highlighting many different IL-6 activities, not limited to B cell immunology. It is now considered a highly multifunctional cytokine involved in the regulation of the immune response, inflammation, hematopoiesis, regeneration, metabolism, endocrine and nervous system [10].

A special feature of IL-6 signaling is the existence of two different signaling pathways. In the classic one, IL-6 binds to its membrane bound IL-6 Receptor (mIL-6R) which has a transmembrane and intracellular region but its binding does not lead to signaling. The complex of IL-6 and IL-6R associates with a second protein, gp130, which thereafter dimerizes and initiates intracellular signaling [11]. IL-6R presence is restricted to few cell types including hepatocytes, leukocytes [12] and in some brain regions. Cells, which do not express IL-6R, cannot respond to the cytokine *via.* this pathway. However, in the more recently discovered trans-signaling pathway, IL-6 binds to a soluble form of the Receptor (sIL-6R), containing only the extracellular region and the complex binds to gp130 signaling subunits. As gp130 is ubiquitously expressed, trans-signaling confers IL-6 responsiveness to virtually all cells in the body, even the ones lacking IL-6R [13]. The sharing of gp130 partly explains the redundancy of the actions of these cytokines.

IL-6 plays a major role in the transition from innate immunity to acquired immunity [14] and it is implicated in the pathogenesis of numerous autoimmune disorders in humans, including Multiple Sclerosis (MS) [15,16]. Experimental Autoimmune Encephalomyelitis (EAE) is a well-known animal model of MS; it is induced directly by administration of a myelin antigen, such as Myelin Oligodendrocyte Glycoprotein (MOG), together with an adjuvant. A critical role of IL-6 in the animal model of MS, EAE, has been demonstrated by a number of studies: systemic IL-6 KO mice are resistant to EAE [17-21], and neutralization of IL-6 with antibodies leads to a reduced disease [22], in line with the blockade of IL-6 trans-signaling, which delays the onset of adoptively transferred EAE [23]. Oppositely, some studies show that the virus-mediated transgenic expression of IL-6 in the CNS reduces EAE [24] and that the systemic administration of IL-6 also reduces the symptomatology in a viral model of EAE [25]. Therefore, IL-6 has a dual role in EAE, both potentiating and inhibiting it, reflecting the system's complexity. The next logical step at that point was to elucidate the identity of the key cell types that produce and respond to IL-6 in the CNS and whether the critical actions of IL-6 are peripheral or central, as it is produced from both peripheral and central sources. Establishing the specific contribution of each source of IL-6 to the development of the disease has been one of the top priorities of many investigation groups.

Hidalgo, et al. demonstrated that mice with astrocyte-driven IL-6 production did not develop classical EAE with leukocyte infiltration and demyelination of the spinal cord, but instead, they redirected the response to the cerebellum, suffering severe ataxia while mice expressing only astrocyte-driven IL-6 production (GFAP-IL6-IL-6 KO mice) were not resistant to EAE like total IL-6 KO, instead, they developed the same cerebellar EAE symptomatology as GFAP-IL6 mice [21]. Additionally, adoptive transfer of Tcell lines from IL-6+/+ mice induced EAE in the mice with the intact IL-6 gene but less in the IL-6 KO mice, indicating that not only the encephalitogenic Tcells, but also local IL-6 in the brain, mediates the disease [18]. As astrocytic IL-6 have a key role in neuroinflammation [26,27] and astrocytes are the most abundant glial cell in the CNS, astrocytic IL-6 is an ideal candidate to be assessed. Mice lacking astrocytic IL-6 (Ast-IL-6 KO mice) exhibit a number of altered behaviors under normal (basal) conditions, including changes in activity, anxiety and learning [28,29]. It has been recently demonstrated that in contrast to results in total IL-6 KO mice, astrocytic-specific IL-6 deficiency is unable to prevent typical signs of EAE induction and has no prominent neuropathological effects. However, a delay in the onset of clinical signs was observed in Ast-IL-6 KO females, with fewer inflammatory infiltrates, decreased demyelination and some alterations in gliosis and vasogenesis compared to controls [30].

Majority of work has been done to characterize the role of local IL-6 in EAE but the CNS response to IL-6 is another critical issue to assess. Although trans-signaling appears to have a key role in EAE induction [23] it is extremely difficult to restrict the study only to central trans-signaling. However, mice with simultaneous astrocyte-driven production of both IL-6 and sgp130 (specific inhibitor of IL-6 and sIL6-R complex and thus the trans-signaling pathway) are expected to be a promising candidate to elucidate central trans-signaling role in EAE, as this model has already demonstrated to

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counteract astrocyte-driven IL-6 in basal situations [27]. Regarding the role of IL-6 classic pathway in CNS, different cell populations must be studied, animals with lack of astrocyte-derived IL-6 membrane receptor have been created and initially characterized in basal conditions [27] and they might provide some answers when challenged with EAE to assess if they are capable of increasing clinical EAE's symptoms, as it has already been shown for immunized mice lacking cell surface expression of astrocyte-derived gp130 (GFAP-Cre gp 130 KO); which not only developed chronic EAE, but also showed a significantly more severe symptomatology with worse recovery rate, mainly because of increased astrocyte apoptosis, increased numbers of CD4 T cells in the CNS and increased demyelination [31]. Increased severity is expected to be much more obvious in this GFAP-gp130 KO than in KO for specific cytoquines because lacking gp130 receptor impairs signal transducing of nearly all IL-6 cytokines family, not only IL-6, being therefore more difficult to compensate. As GFAP-Cre also affects a subpopulation of neurons, this group decided to delete gp130 in neurons to assess whether astrocytes or neurons were responsible for aggravation of EAE in GFAP-Cre gp130 KO mice, showing that only the absence of gp130 on astrocytes, but not on neurons, was the responsible for the increased susceptibility phenotype [31]. They further demonstrated that diminished activation of the gp130-SHP2/Ras/ERK pathway reproduced all pathological features observed in GFAP-Cre gp130 KO mice, including astrocyte loss, lack of Astrogliosis, a significantly more severe clinical course, increased T-cell infiltration, and severe demyelination; while mice with intact gp130-SHP2/Ras/ERK signaling but impaired STAT activation in astrocytes developed a similar clinical course compared to floxed controls and decreased compared to GFAP-Cre gp130 KO and GFAP-Cre gp130-SHP2/Ras/ERK KO, due to an astrocyte-dependent reduction of autoimmune t cells in the CNS [31].

IL-6 has also a major role in Th17 cell differentiation from naive CD4+ T-cells [32]; particularly in the EAE model [33,34]. Moreover, showing the importance of in filtrating cells in EAE pathology, EAE-resistant IL-6 KO mice demonstrated a deficiency in Th17 cells infiltrated in the CNS [35]. When responsiveness to IL-6 is eliminated only in T helper cells there is resistance to EAE, as IL-21 pathway is intact but not active in the absence of IL-6 [36]. Th17 cells produce IL-17 (among other cytokines) which enhances IL-6 production by astrocytes, which in turn induces differentiation of Th17, cells in a positive feedback loop between IL-17 and IL-6 *via*. activation of NF-kB and STAT-3 [37]. As Ast-IL-6 KO mice are not resistant to EAE induction, finally reaching the same score as WT, one can venture to say that astrocyte-derived loop is not necessary for the development of the disease as it is probable that neuronal, endothelial and microglial IL-6 allow this positive feed-back between IL-17 and IL-6. Now the efforts are directed to assess the role of IL-6 expression from other brain populations and to further characterized the inflammatory response in these models. After thirty years of study, the relevance of IL-6 is still growing.

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