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Editorial

IL-10 Signalling in Macrophage during Autoimmunity

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Received: April 04, 2016; **Accepted:** April 11, 2016; **Published:** April 12, 2016

Editorial

Over the last decade, despite macrophages have been identified as key regulator of innate immunity and also implicated in the pathogenesis of a variety of autoimmune diseases, including Rheumatoid Arthritis (RA), our current knowledge of targeting macrophages in the treatment of autoimmune diseases remains quite poor. In response to the pathological conditions, macrophages exhibited unsuspected flexibility and plasticity via two different polarized activations, the classical M1 activation (stimulated by TLRs and IFN-γ) and alternative M2 activation (controlled by IL-4 and IL-13) [1,2]. Several secreted factors such as proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12 and IL-23), Inducible Nitric Oxide Synthase (iNOS), and chemokines (CCL2) were specifically induced during M1 macrophages activation, which result in excessive inflammation during autoimmunity. In contrast, expressions of anti-inflammatory cytokines (IL-10 and IL-4), IL-1 receptor antagonist, mannose receptor CD206 and Arg1 (arginase 1) were involved in M2 activated phenotype [1,2]. Therefore, modulation of macrophages activation and function is a potential weapon for protect against autoimmune diseases.

Interleukin-10 (IL-10) has emerged as an essential and non-redundant anti-inflammatory cytokine of macrophages deactivation by down regulating MHC class II molecules, suppressing antigen presentation and inhibiting inflammation [3]. While IL-10 can derives macrophages polarization toward an M2 phenotypes and also can restrains the differentiation of M1 macrophages that inhibit the development of Th1 type responses [4]. Additionally, the expression of IL-10 is not specific expressed in adaptive immune cells such as T cells and B cells but instead that it is broadly expressed in macrophages and Dendritic Cells (DCs) [4]. Although much is known about the function of IL-10, which mainly dependent on IL-10 receptor (IL-10R) and activation of Signal Transducer and Activator of Transcription 3 (STAT3) [4], its role in modulating macrophages in autoimmunity has not been thoroughly defined.

To examine the involvement of IL-10 in macrophages during autoimmunity, IL-10 deficiency (IL-10-/-) mice were induced arthritis animal models by type II collagen (CII). CII induced arthritis is a stable and reproducible animal model that exhibits several pathological features of human RA. In this model, we found that IL-17 expressions and its transcript factor retinoid-related orphan receptor gamma-t (RORγt) were dramatically upregulated in IL-10-/-F4/80+ macrophages *in vitro* and *in vivo* [5]. Interestingly, IL-10-/- arthritic mice displayed high numbers of IL-17-producing F4/80+ macrophages in synovial tissues. IL-17, a signature cytokine of T helper cells (Th17) cells, which plays a crucial pathogenic role in the development of RA [6]. It was worth noting that inhibition of IL-17 production attenuates the event of experimental arthritis [7]. Thus, these findings indicate that the restriction of IL-17 mediated inflammatory response in RA at least or partially involving IL-10 signaling in macrophages [5]. Of note, IL-10 has also displayed potent anti-inflammatory property via regulating macrophage polarization. We thus investigated the phenotype of macrophages in the joint of IL-10-/- arthritic mice. While the proportion and the total number of M1 (F4/80+iNOS+) cells were significantly expanded in IL-10-/- arthritic mice, but M2 (F4/80+CD206+) cells were not changed [5]. Consistent with this results, All M1 associated genes such as TNF-α, IL-1β, IL-6 and iNOS were increased in IL-10-/- macrophages in arthritic mice, whereas M2 related markers were not affected in both IL-10-/- and wild type macrophages [5], indicating IL-10 exerts its anti-inflammatory action in RA through suppressing macrophage polarization toward M1 phenotype and down regulating proinflammatory cytokines production in M1 macrophages.

Moreover, the importance of IL-10 in modulating macrophages in autoimmunity is also supported by our unpublished data showing that IL-10 signaling involved in suppression of IL-33 in macrophages *in vitro* and *in vivo*. The deficiency of IL-10 not only exhibited high numbers of IL-33- producing F4/80+ macrophages in the local joint of arthritic mice but also induced IL-33 expression in macrophages. We further demonstrated that IL-10 regulates downstream molecule STAT3 phosphorylation to exert anti-inflammatory activity that inhibits IL-33 production in macrophages. Furthermore, IL-33 and IL-33 receptor (ST2) mediated inflammatory responses in macrophages were also restricted by IL-10 through suppression of activation of NF-κB. These events suggest that as one of the important innate immune cells, macrophages should be an interesting target to study in autoimmune diseases. Tracing IL-10 signaling in macrophages should be considered as an efficient approach for development of new immune therapeutics for controlling autoimmunity.

Funding

This work was supported by grants from the Basic Research Program of Science and Technology Plan of Shenzhen (Grant number: JCYJ20150324141711578).

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Citation: Liang YE and Huang Z. IL-10 Signalling in Macrophage during Autoimmunity. Austin Biol. 2016; 1(1): 1004.

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