Involvement of *IL-10* Signaling in Macrophages during Autoimmunity

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DESCRIPTION

Macrophages have been identified as a major regulator of innate immunity and are also involved in the pathogenesis of various autoimmune diseases, including Rheumatoid Arthritis (RA). 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-a)* and alternative M2 activation (controlled by *IL-4* and IL-13). Several secretory factors such as inflammatory cytokines *(TNF-a, IL-1β, IL-6, IL-12, IL-23)*, nitric oxide synthase, chemokines are M1, it was specifically induced during macrophage activation and causes excessive inflammation during autoimmunity. In contrast, expression of anti-inflammatory cytokines *(IL-10 and IL-4)*, IL-1 receptor antagonists, mannose receptor CD206, and Arg1 (arginase 1) has been associated with the M2 activation phenotype. Therefore, macrophage activation and regulation of function are potential weapons for protection against autoimmune diseases.

Interleukin-10 *(IL-10)* emerges as an essential and non-redundant anti-inflammatory cytokine for macrophage inactivation by down-regulating MHC class II molecules, suppressing antigen presentation, and suppressing inflammation. *IL-10* can induce macrophage polarization towards the M2 phenotype and can also limit the differentiation of M1 macrophages that inhibit the development of Th1-type responses. Furthermore, *IL-10* expression is not specifically expressed in adaptive immune cells such as T cells and B cells, but instead is widely expressed in macrophages and Dendritic Cells (DCs). 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), its role in modulating macrophages in autoimmunity has not been thoroughly defined.

To investigate the involvement of *IL-10* in autoimmune macrophages, *IL-10*-deficient *(IL-10-/-)* mice were induced by type II collagen (CII) in an animal model of arthritis. CII-induced arthritis is a stable and reproducible animal model that exhibits some pathological features of human RA. *IL-17* expression and its transcription factor retinoid-related orphan receptor gamma-t was dramatically upregulated in *IL-10-/-* F4/80+ macrophages *in vitro* and *in vivo*. *IL-10-/-*arthritic mice show a large number of *IL-17*-producing F4/80+ macrophages in synovial tissue. *IL-17,* a characteristic cytokine of helper T *(Th17)* cells, plays an important pathogenic role in the development of RA. It is noteworthy that inhibition of *IL-17* production reduces the incidence of experimental arthritis. This indicates that the limitation of *IL-17*-mediated inflammatory response in RA is at least or partially involved in *IL-10* signaling in macrophages.

In particular, *IL-10* has strong anti-inflammatory properties by regulating macrophage polarization. Researchers conducted a study on the phenotype of macrophages in the joints of *IL-10-/-* arthritic mice. The proportion and total number of M1 cells were significantly increased in *IL-10-/-*arthritic mice, but M2 cells were unchanged. Consistently, all M1-related genes such as *TNF-a, IL-1β, IL-6, iNOS* are increased in *IL-10-/-*macrophages in arthritis mice, and M2 related markers were not affected in both *IL-10-/-* and wild type macrophages, 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.

IL-10 deficiency not only showed a large number of *IL-33*-producing F4/80+ macrophages in the local joints of arthritic mice, but also induced *IL-33* expression in macrophages. In addition, *IL-10* regulates the phosphorylation of the downstream molecule STAT3 and exerts anti-inflammatory activity that inhibits IL-33 production in macrophages. In addition, *IL-33* and *IL-33* receptor (ST2) mediated inflammatory responses in macrophages were also reduced by *IL-10* by suppressing NF-κB activation. These events suggest that macrophages as one of the important innate immune cells should be interesting targets for studying autoimmune diseases. Tracking the *IL-10* signaling pathway in macrophages should be seen as an efficient approach to developing new immunotherapeutic to control autoimmunity.

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