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Review Article

Seeking balance: Potentiation and inhibition of multiple sclerosis autoimmune responses by IL-6 and IL-10

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ABSTRACT

The cytokines IL-6 and IL-10 are produced by cells of the adaptive and innate arms of the immune system and they appear to play key roles in genetically diverse autoimmune diseases such as relapsing remitting multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Whereas previous intense investigations focused on the generation of autoantibodies and their contribution to immune-mediated pathogenesis in these diseases; more recent attention has focused on the roles of cytokines such as IL-6 and IL-10. In response to pathogens, antigen presenting cells (APC), including B cells, produce IL-6 and IL-10 in order to up-or down-regulate immune cell activation and effector responses. Evidence of elevated levels of the proinflammatory cytokine IL-6 has been routinely observed during inflammatory responses and in a number of autoimmune diseases. Our recent studies suggest that MS peripheral blood B cells secrete higher quantities of IL-6 and less IL-10 than B cells from healthy controls. Persistent production of IL-6, in turn, contributes to T cell expansion and the functional hyperactivity of APC such as MS B cells. Altered B cell activity can have a profound impact on resultant T cell effector functions. Enhanced signaling through the IL-6 receptor can effectively inhibit cytolytic activity, induce T cell resistance to IL-10-mediated immunosuppression and increase skewing of autoreactive T cells to a pathogenic Th17 phenotype. Our recent findings and studies by others support a role for the indirect attenuation of B cell responses by Glatiramer acetate (GA) therapy. Our studies suggest that GA therapy temporarily permits homeostatic regulatory mechanisms to be reinstated. Future studies of mechanisms underlying dysregulated B cell cytokine production could lead to the identification of novel targets for improved immunoregulatory therapies for autoimmune diseases.

1. Introduction

Autoimmune diseases, including relapsing-remitting multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) demonstrate abnormalities in both innate and adaptive immune responses. In spite of the fact that MS has a distinct genetic susceptibility profile in comparison to RA and SLE, these diseases display altered regulation in similar mediators, such as the cytokines interleukin-6 (IL-6) and interleukin-10 (IL-10), involved in controlling inflammation and immunity [1,2]. Therapies modulating IL-6 and IL-10 activity have been examined in RA and models of SLE for two decades [3–8]. Anti-IL-6 targeted therapies have been FDA approved for the treatment of rheumatic diseases including RA, SLE, Castleman's disease and there are ongoing clinical trials for other autoimmune diseases [3,5,9]. Anti-IL-10 therapy is in clinical trials for RA [6]. Here, we review recent studies and our own work exploring the roles of IL-6 and IL-10 in MS [10]. These studies suggest that despite the differences in clinical and genetic profiles, understanding the mechanisms influencing IL-6 and IL-10 cytokine programs could lead to improved targeted therapies for MS and a number of other autoimmune diseases.

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2. Interleukin-6

Both IL-6 and IL-10 can be produced at inflammatory sites and several recent reviews have described the pleiotropic effects of IL-6 and IL-10 in detail [3–5,9]. IL-6 and the IL-6 receptor alpha chain (IL-6R) are expressed by monocytes, lymphocytes, fibroblasts, endothelial cells and a number of other cell types [11–14]. After IL-6 ligation, the IL-6R signals through homodimerization of gp130 (CD130) that is a ubiquitous common signal transducer for several cytokines. IL-6 signaling through gp130 activates the protein-tyrosine kinase, Janus kinase 1 (JAK1), and transiently activates signal transducer and activator of transcription 3 (STAT3) dimerization and phosphorylation, followed by STAT3 nuclear translocation and target gene transcription. IL-6 activates the mitogen activated protein kinase (MAPK) pathway, resulting in transcription of other genes. For example, in human monocyte-derived macrophages 39 genes were induced by exposure to IL-6 while 31 transcripts were down-modulated [15]. IL-6 activates the tyrosine phosphatase, SHP-2, while STAT3 induces protein inhibitors of activated STATs (PIAS), suppressor of cytokine signaling 1 (SOCS1) and SOCS3 as part of a complex auto-regulatory negative feedback loop. A soluble form of the IL-6R (sIL-6R) can be produced by enzymatic cleavage of the membrane form or by alternative splicing of the IL-6 receptor alpha transcript. IL-6 bound to the sIL-6R can form a complex with gp130 on cells and transduce a signal to the cell. Such IL-6 "trans-signaling" has been implicated in lupus renal pathology [13,14,16]. IL-6 has important roles in homeostatic mechanisms, such as inducing hepcidin which reduces serum iron levels and enhances the hepatocyte inflammatory response, inducing acute phase proteins, cell growth, cell survival and promotes differentiation of lymphocytes and many other cells [7,9].

3. Interleukin-10

IL-10 is predominantly produced by stimulated myeloid cells and lymphocytes and can be produced at lower levels by other cells during inflammation [17]. IL-10 dimerizes and binds to a tetramer consisting of two IL-10 receptor (IL-10R)1 subunits and two IL-10R2 subunits and with JAK1 and Tyk2. This induces the phosphorylation and activation of STAT1, STAT3, and, in some cells, STAT5 leading to an inhibition of NFκB-mediated signal transduction [17]. IL-10 induces a sustained activation of STAT3 and SOCS3 transcription which contribute to transcriptional regulation of pro-apoptotic genes, inhibition of cell activation, cytokine production and proliferation [18–21]. IL-10 inhibits production of a number of proinflammmatory cytokines, including IL-1β, IL-6, IL-12, IL-18, GM-CSF and TNFα and IL-10 promotes the production of other anti-inflammatory mediators, such as the IL-1β receptor antagonist and soluble TNFα receptors p55 and p75 [17]. The anti-inflammatory effects of IL-10 have been demonstrated in models of MS, RA, SLE, diabetes, inflammatory bowel disease and other autoimmune disorders [17]. In macrophages, IL-10 is expressed as a means to inhibit immune responses [22–24]. Although IL-10 has been reported to suppress CD40, CD80, CD86, IL-12 and T effector functions, IL-10 in the presence of other cytokines, enhances human B cell activation, proliferation and differentiation into immunoglobulin (Ig) secreting cells [22,25–28] Importantly, IL-6 and IL-10 expression and function can be regulated by a number of factors including other cytokines, genetics and noncoding RNAs as described below.

4. Cytokine regulation by genetic elements

4.1. Noncoding RNAs

MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs) can influence a single cytokine pathway or regulate a cassette of cytokines en bloc [29–32]. Multiple studies have identified dysregulated microRNAs (miRNAs) in MS patients and their potential roles in controlling gene expression in lymphocytes and CNS tissues [31–34]. In particular, miRNA-155 has been the most thoroughly studied and was found to confer susceptibility to experimental autoimmune encephalomyelitis (EAE) through regulation of dendritic cells (DC) cytokines, including IL-6, and T-cell intrinsic mechanisms that support Th17 development [34]. In humans, several observations support a role for miRNAs in controlling cytokine production. For instance, overexpression of miRNA-132, that targets surtuin-1, in B cells from MS patients is responsible for elevated TNFα and LTβ but had no impact on IL-10 secretion [35]. miRNA-142-3p inhibits IL-10 expression and is elevated in peripheral blood mononuclear cells (PBMC) from MS patients [36]. In the same study, they found that the immunomodulatory therapeutic glatiramer acetate (GA) reduced levels of miR-146a and miR-142-3p observed in PBMC from MS patients [36,37]. However, miR-146a negatively regulates IL-6 [38]. Other studies have demonstrated modulation of miRNAs by MS therapies such as IFN-β and Natilizumab [39,40].

4.2. Genetics

Beyond the known HLA risk loci, such as the HLA-DRB1 locus, approximately 52 risk loci for MS have been identified in GWAS studies, many known as key regulators of the immune response [41]. For example, notable Single Nucleotide Polymorphisms (SNPs) in costimulatory molecules, cytokines, cytokine receptors and signaling pathways that impact APC function and T cell migration, expansion and differentiation such as CD40, CD58, CD69, CD86, MERTK, CCR4, CXCR5, IL12A, IL12B, IL2RA, IL22RA, TYK2, STAT3, STAT4, NFKBI, EOMES, IRF8, BCL10 and BATF were identified and could be important in grouping MS patients into subsets for treatment [41–43]. Recent pathway analysis of GWAS datasets have identified cell adhesion molecules such as ITGAL, ICAM1, ICAM3 and validated VCAM1 as important potential targets for novel therapies [44]. IL-6, IL-10 and their downstream effectors can impact expression of many of the cell adhesion molecules, chemokine receptors and signaling pathways that have been associated with MS.

Although SNPs for IL-10, IL-6 and their receptors have not been identified in GWAS studies to date as risk alleles for MS, it is clear that some MS patients harbor systemic dysregulation of these cytokines. Of note, IL-6 cytokine responsiveness and inflammation are impaired in RA patients with a common IL-6R polymorphism [45]. Thus, it is likely that future studies of the IL-6R common variants along with other select genes will distinguish aggressive from indolent disease subgroups of MS patients. Importantly, SNPs in the STAT3 pathway have been described in MS and additional studies are needed to determine the impact of these variants on disease [41,42,46].

A recent large study of candidate causal genetic variants for 21 autoimmune diseases, including MS, indicated that approximately 90% of the causal variants were non-coding SNPs and that 60% could be mapped to immune-related enhancer-like elements, while only 10–20% appeared to alter known transcription factor binding motifs. These authors concluded that the non-coding variants might cause subtle key differences in transcription or epigenetics that influence immune responses, allowing variants to escape pressure from negative selection [47]. Of interest, some originally predicted "non-coding RNAs" have been found to code for small peptides with powerful influences on cell regulation [48].

5. A cytokine imbalance in MS

Relapsing-remitting MS is an immune-mediated inflammatory demyelinating disorder of the central nervous system [49–51]. In