Invited review

The therapeutic potential of interleukin-10 in neuroimmune diseases

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ABSTRACT

Neuroimmune diseases have diverse symptoms and etiologies but all involve pathological inflammation that affects normal central nervous system signaling. Critically, many neuroimmune diseases also involve insufficient signaling/bioavailability of interleukin-10 (IL-10). IL-10 is a potent anti-inflammatory cytokine released by immune cells and glia, which drives the regulation of a variety of anti-inflammatory processes. This review will focus on the signaling pathways and function of IL-10, the current evidence for insufficiencies in IL-10 signaling/bioavailability in neuroimmune diseases, as well as the implications for IL-10-based therapies to treating such problems. We will review in detail four pathologies as examples of the common etiologies of such disease states, namely neuropathic pain (nerve trauma), osteoarthritis (peripheral inflammation), Parkinson's disease (neurodegeneration), and multiple sclerosis (autoimmune). A number of methods to increase IL-10 have been developed (e.g. protein administration, viral vectors, naked plasmid DNA, plasmid DNA packaged in polymers to enhance their uptake into target cells, and adenosine 2A agonists), which will also be discussed. In general, IL-10-based therapies have been effective at treating both the symptoms and pathology associated with various neuroimmune diseases, with more sophisticated gene therapy-based methods producing sustained therapeutic effects lasting for several months following a single injection. These exciting results have resulted in IL-10-targeted therapeutics being positioned for upcoming clinical trials for treating neuroimmune diseases, including neuropathic pain. Although further research is necessary to determine the full range of effects associated with IL-10-based therapy, evidence suggests IL-10 may be an invaluable target for the treatment of neuroimmune disease.
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1. Introduction

Neuroimmune diseases are debilitating conditions, which involve substantial loss of quality of life. The key features of these diseases include ongoing inflammation, pain, fatigue, anxiety, and cognitive-impairments, although the etiologies and full range of symptoms of these diseases are quite diverse. Here, we will focus on four neuroimmune diseases as examples of the common etiologies of such pathologies [i.e. neuropathic pain (NP) (nerve trauma), osteoarthritis (OA) (peripheral inflammation), Parkinson's disease (PD) (neurodegeneration), and multiple sclerosis (MS) (autoimmune)]. Treatments for neuroimmune diseases have been developed, but notably, most patients remain either partially or fully refractory to treatment (Ali et al., 2013; Gutierrez et al., 2014; Tarazi et al., 2014b; Taruc-Uy and Lynch, 2013).

The purpose of this review is to explore the potential of interleukin-10 (IL-10)-based therapeutic strategies for the treatment of neuroimmune disease. IL-10 is a potent anti-inflammatory cytokine that is endogenously released by immune cells and glia as a process of negative feedback during inflammation (Kettenmann et al., 2011; Ledeboer et al., 2002; Moore et al., 2001). Importantly, insufficiencies in IL-10 signaling/bioavailability have been implicated in these disease states, and in animal studies, strategies aimed at increasing IL-10 have been effective in treating symptoms and pathology associated with neuroimmune diseases. The signaling pathways and function of IL-10, potential therapeutic benefits of IL-10 in neuroimmune disease, and various strategies aimed at increasing physiological levels of IL-10 will be discussed.

2. Interleukin-10 (IL-10)

2.1. Cellular sources of IL-10

IL-10 was first described by Fiorentino et al. (1989) as a novel immune mediator secreted by T helper 2 (T$_H$2) cells that could

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inhibit the synthesis of interleukin 2 (IL-2) and interferon-γ (IFN-γ) in T_H1 cells. In the periphery, IL-10 is secreted by innate immune cells, including dendritic cells, macrophages, mast cells, natural killer cells, eosinophils and neutrophils, and by adaptive immune cells, including T_H1, T_H2, T_H17 and regulatory T cells (T_{regs}), as well as B cell subsets (Moore et al., 2001; Nouel et al., 2014; Saraiva and O'Garra, 2010). In the central nervous system (CNS), IL-10 is expressed by microglia, astrocytes and neurons (Gutierrez et al., 2014; Hulshof et al., 2002; Kettenmann et al., 2011; Ledeboer et al., 2002; Tarazi et al., 2014b; Taruc-Uy and Lynch, 2013; Yan et al., 2014). IL-10 is induced in innate immune cells by signaling at CD209 and pattern recognition receptors, such as Toll-like receptors (TLRs) and Dectin-1, and can be enhanced by CD40 or Fc receptor ligation (Saraiva and O'Garra, 2010). Antigenic stimulation at the T cell receptor, cytokine stimulation (e.g. IL-12, IL-21 and IL-27), and Notch signaling are sufficient to induce IL-10 production in T cells (O'Garra and Vieira, 2007; Saraiva et al., 2009; Saraiva and O'Garra, 2010).

2.2. IL-10 structure

Mouse (m)IL-10 and human (h)IL-10 genes are encoded by five exons on the respective chromosomes 1, rat (r)IL-10 gene is encoded by 4 exons on chromosome 13, and each are under epigenetic control (Moore et al., 2001; Saraiva and O'Garra, 2010). A large number of polymorphisms have been identified, particularly in the hIL-10 promoter region, which may be associated with a range of diseases (Moore et al., 2001; Sabat et al., 2010). hIL-10 is a 35 kD homodimer that is composed of two non-covalently bonded monomers. The homodimer contains two distinct domains that are oriented at right angles to each other. Each of the domains is composed of helices, four on one (A–D), and two on the other (E, F) (Syto et al., 1998; Walter and Nagabhushan, 1995; Zdanov, 2010; Zdanov et al., 1995), with two disulfide bridges existing within the monomer (C30–C126 and C80–C132) (see Fig. 2 in Zdanov, 2010 for a diagram of IL-10 crystal structure; Syto et al., 1998; Windsor et al., 1993). This structure is essential to maintain the biological activity of IL-10, with two residues located at the bend in helix F (Lys- 138 and Glu-142) forming a binding pocket for IL-10R1 (Shrestha et al., 2014), while IL-10R2 likely binds to helices A and D (Yoon et al., 2010). mIL-10 and hIL-10 share 72% homology at the amino-acid level, while rIL-10 shares 83% homology with mIL-10 and 73% homology with hIL-10 (Ball et al., 2001). IL-10 protein is trafficked and secreted by constitutive exocytosis (Lacy and Stow, 2011).
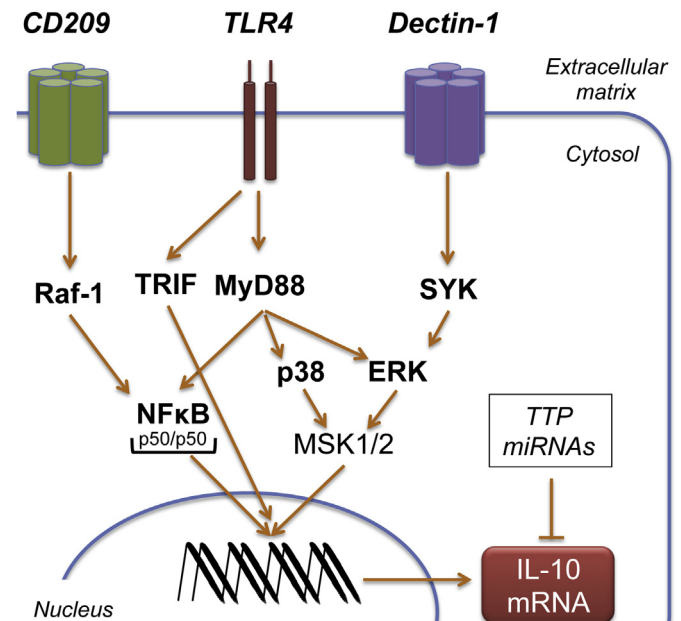
2.3. Regulation of IL-10 gene transcription

TLR-dependent IL-10 transcription is mediated though Toll/IL-1 receptor (TIR)-domain-containing adaptor molecules, such as myeloid differentiation primary-response protein 88 (MyD88) and TIR-domain-containing adaptor protein inducing IFNβ (TRIF) (Boonstra et al., 2006) (Fig. 1). Activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and the mitogen activated protein kinases (MAPKs) extracellular-signal-regulated kinase (ERK) and p38 follows recruitment of MyD88, leading to IL-10 transcription, together with proinflammatory cytokines (Kawai and Akira, 2007; Saraiva and O'Garra, 2010) (Fig. 1). However, distinct from proinflammatory cytokines, whose transcription is induced by the prototypical NFκB heterodimers (p65/p50), IL-10 transcription is only induced by p50 homodimers (Cao et al., 2006). IL-10 transcription is also differentially regulated by mitogen- and stress-activated protein kinase 1 (MSK1) and MSK2, which are downstream of ERK and p38 (Ananieva et al., 2008). Triggering of CD209 activates the kinase rapidly-

accelerated fibrosarcoma (Raf)-1, which leads to NFκB p65 sub-unit acetylation and IL-10 transcription after TLR-dependent activation (Gringhuis et al., 2007) (Fig. 1). Dectin-1 receptor-dependent IL-10 transcription follows recruitment of spleen tyrosine kinase (SYK) (Rogers et al., 2005). Despite being independent of TLR signaling, IL-10 production downstream of dectin-1 receptor signaling is also dependent on ERK (Slack et al., 2007) (Fig. 1). Most if not all macrophages produce IL-10 when activated. Polarized regulatory macrophages (M2; alternatively activated) produce IL-10, but not proinflammatory cytokines (released by M1 macrophages), though the intracellular mechanisms governing this selective regulation are not well understood (Murray and Wynn, 2011).

Alternatively activated macrophages are characterized, among other factors, by elevated IL-10 production and the absence of M1 cytokines (Sica and Mantovani, 2012). Several studies have implicated differential expression of suppressor of cytokine signaling (SOCS) 1, 2, and 3, depending on the signals driving polarization to various M2 phenotypes (Spence et al., 2013; Wang et al., 2010; Whyte et al., 2011). SOCS proteins negatively regulate JAK-STAT signaling leading to selective suppression of proinflammatory mediators, such as TNF, IFNγ, and nitric oxide, while retaining anti-inflammatory function, such as IL-10 production.

Signaling cascades controlling IL-10 transcription in T cells have not been as well studied as those of innate immune cells. IL-10 induction is ERK dependent in all T cell subsets, but in addition is dependent on signal transducer and activator of transcription 4 (STAT4) in T_H1 cells; STAT6 and GATA3 in T_H2 cells; and, STAT1 and STAT3 in T_H17 cells (Saraiva and O'Garra, 2010). While T_{regs} are known to express IL-10 in vivo, the signal transduction mechanisms

Fig. 1. Interleukin-10 (IL-10) gene transcription regulation. IL-10 transcription is initiated after a) CD209 signaling mediated via rapidly-accelerated fibrosarcoma (Raf)-1, which activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB); b) Toll-like receptor 4 (TLR4) signaling mediated via TIR-domain-containing adaptor protein inducing IFNβ (TRIF) and Myeloid differentiation primary response gene 88 (MyD88). MyD88 activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB). MyD88 also activates the mitogen activated protein kinases (MAPKs) p38 and extracellular related kinase (ERK), further activating mitogen- and stress-activated protein kinase (MSK) 1 and 2; c) Dectin-1 signaling mediated via the ERK pathway and upstream spleen tyrosine kinase (SYK) activation. IL-10 mRNA is post-transcriptionally regulated by a range of micro-RNAs and by tristetraprolin (TTP).