HHS Public Access

Author manuscript

Neuropharmacology. Author manuscript; available in PMC 2016 December 08.

Published in final edited form as:

Neuropharmacology. 2015 September ; 96(Pt A): 55–69. doi:10.1016/j.neuropharm.2014.10.020.

The therapeutic potential of interleukin-10 in neuroimmune diseases

A.J. Kwilasz[*], **P.M. Grace**, **P. Serbedzija**, **S.F. Maier**, and **L.R. Watkins**

Department of Psychology and Neuroscience, and the Center for Neuroscience, University of Colorado-Boulder, Boulder, CO 80309-0345, USA

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.

This article is part of a Special Issue entitled 'Neuroimmunology and Synaptic Function'.

Keywords

Interleukin-10; Interleukin-10 receptor; Neuropathic pain; Osteoarthritis; Parkinson's disease; Multiple sclerosis

[*]Corresponding author. Department of Psychology and Neuroscience, University of Colorado-Boulder, Muenzinger D244, 345 UCB, Boulder, CO 80309-0345, USA. Tel.: +1 303 492 2967. andrew.kwilasz@colorado.edu (A.J. Kwilasz).

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_H2) cells that could 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 h*IL-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 antiinflammatory 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 underlying this phenomenon remain elusive. For additional details on transcription factors that regulate production of IL-10 beyond those discussed herein, see the recent review (Saraiva and O'Garra, 2010).

There are also several mechanisms leading to enhancement or suppression of *IL-10* transcription, though the factors dictating the balance between these mechanisms are not well understood. For instance, STAT3 signaling induced by IL-10 elevates CD209 expression on M2 macrophages, which increases *IL-10* transcription (Dominguez-Soto et al., 2011). Conversely, *IL-10* transcription is negatively regulated by IFNγ, which suppresses AP1 binding (Hu et al., 2006). Autocrine IL-10 signaling also negatively regulates p38 phosphorylation and thus serves to dampen *IL-10* transcription (Hammer et al., 2005). IL-10 may be further regulated at a posttranscriptional level by factors that modulate mRNA stability and by microRNAs (Nemeth et al., 2005; Powell et al., 2000; Schulte et al., 2011; Sharma et al., 2009). For example, IL-10 mRNA contains adenine and uridine-rich elements (AREs) found in the 3′ untranslated regions of mRNA molecules that are targeted by the RNA binding protein tristetraprolin (TTP) for rapid degradation (Anderson, 2008). Adenosine A2B receptor and TLR4 signaling suppress ARE-mediated IL-10 mRNA degradation, the latter via p38-mediated suppression of TTP (Kiyota et al., 2012; Nemeth et al., 2005).

3. IL-10 receptor and consequences of IL-10 receptor signaling

As described above, IL-10 is produced in inflammatory cascades, together with classical proinflammatory cytokines, such as TNF and IL-1β. However, regulation of such proinflammatory processes is achieved as a consequence of subsequent IL-10 activity at its cognate receptor (summarized in Fig. 2).

IL-10 exerts its innate and adaptive immune effects through its cognate cell surface receptor complex, a heterotetramer consisting of two IL-10 receptor 1 (IL-10R1) chains and two IL-10 receptor 2 (IL-10R2) chains (Moore et al., 2001). While IL-10R1 is specific for the IL-10 receptor complex with a relatively high affinity, IL-10R2 is also part of the receptor complexes of other cytokines (IL-22, IL-26, IL-28a, IL-28b, and IL-29) (Zdanov, 2010). IL-10R2 is widely and strongly expressed in both immune and non-immune cells and tissues (Wolk et al., 2004, 2005). In contrast, IL-10R1 expression is restricted to innate and adaptive immune cells, is upregulated under inflammatory conditions, and is consequently the

determinant of the cellular response to IL-10 (Ding et al., 2001; Ledeboer et al., 2002; Sabat et al., 2010; Wolk et al., 2002). The IL-10/IL-10R1 interaction changes IL-10 conformation, thereby exposing the IL-10R2 binding site that allows association of the IL-10/IL-10R1 complex with IL-10R2 (Reineke et al., 1999;Wolk et al., 2005; Yoon et al., 2006). The ligation of IL-10 to IL-10R1 and IL-10R2 has diverse consequences, which are elaborated upon in the following sections.

3.1. Cytokine modulation

Activation of IL-10 receptors leads to the inhibition of tumor necrosis factor (TNF), IL-1β, IL-6, IL-8, IL-12 and IL-23 release and enhanced release of anti-inflammatory mediators such as IL-1 receptor antagonist and soluble TNF receptors (sTNFRs) from innate immune cells. Activation of IL-10 receptors also leads to the inhibition of both the proliferation and the cytokine synthesis of CD4+ T cells, including the T_H1 production of IL-2 and IFNγ, and T_H2 production of IL-4 and IL-5 (Sabat et al., 2010). However, IL-10 does not suppress the IL-17 production in T_H17 cells (Naundorf et al., 2009).

Ligation of IL-10 to its receptors induces dual activation of two members of the Janus kinase (Jak) family: Jak1 (associated with IL-10R1) and tyrosine kinase 2 (Tyk2) (associated with IL-10R2), which together induce the phosphorylation of IL-10R1, allowing binding and phosphorylation of STAT3 (as well as STAT1 and STAT5 in some cell types) (Finbloom and Winestock, 1995; Weber-Nordt et al., 1996; Wehinger et al., 1996). STAT3 migrates into the cell nucleus and/or is constitutively present in the nucleus but undergoes a conformational change to induce transcription of genes corresponding to effector proteins. These effector proteins, such as A20-binding inhibitor of NFκB activation (Abin-3) and dual specificity phosphatase-1 (DUSP-1), inhibit transcription of proinflammatory cytokines by inhibiting phosphorylation of the MAPK p38 and inducing nuclear translocation and DNA binding of p50/p50 homodimers of NFκB, which are insufficient to induce proinflammatory cytokine transcription (Sabat et al., 2010). IL-10 signaling also induces SOCS1 and SOCS3 production that suppresses proinflammatory cytokine production by targeting the p65 NFκB subunit for degradation, as well as controlling cytokine receptor signaling by marking activated JAK-STAT complexes for proteasomal degradation (Yoshimura et al., 2007). Several other factors induced by IL-10 have been described as suppressing NFκB activity including Bcl-3, IKBNS, ETV3 and SBNO2 (Sabat et al., 2010). IL-10 also induces expression of MAPK phosphatases, including MKP1, which inhibit MAPK signaling and hence transcription of proinflammatory cytokines (Chi et al., 2006; Hammer et al., 2005). For further reading, see Sabat et al. (2010).

3.2. Decreased antigen presentation

IL-10 inhibits antigen presentation of monocytes/macrophages. It reduces the constitutive and induced cell surface expression of major histocompatibility complex class II (MHC II) molecules by inducing membrane-associated RING-CH (MARCH) 1, which prevents MHC II trafficking to the cell membrane (Koppelman et al., 1997; Thibodeau et al., 2008). IL-10 also inhibits antigen presentation by inhibiting expression of co-stimulatory (e.g. CD86) and adhesion (e.g. CD54) molecules that drive a proinflammatory response (Grace et al., 2011; Sabat et al., 2010).

3.3. Cell polarization

IL-10 promotes the differentiation of anti-inflammatory macrophage phenotypes, such as IL-10 producing M2-like macrophages via induction of the transcription factors STAT3, c-MAF, as well as regulatory macrophages that promote T_H2 polarization (Locati et al., 2013; Mosser and Edwards, 2008). IL-10 attenuates development of T_H1 and T_H17 immunity by inhibiting the synthesis of proinflammatory cytokines (e.g. IL-12, IL-23; described above) (McKinstry et al., 2009; Schuetze et al., 2005). Decreased antigen presentation due to factors described above also shifts the balance away from T_H1 development. In addition, IL-10 inhibits phosphorylation of CD28, inducing a state of anergy (Groux et al., 1996; Joss et al., 2000). The presence of IL-10 also enhances the differentiation of T_{reg} cells (Barrat et al., 2002; Hawrylowicz and O'Garra, 2005; Roncarolo et al., 2006).

3.4. Neuroprotection

IL-10 has the capacity to act in a neuroprotective fashion. Inhibition of microglial proinflammatory mediator production by IL-10 halts astrocyte activation and directly inhibits p65 NFκB binding (Balasingam and Yong, 1996). Such a reduction in NFκB activity results in increased excitatory amino acid transporter-2 (EAAT2) expression, helping to prevent neurotoxic synaptic glutamate accumulation (Bachis et al., 2001; Kim et al., 2011). In addition, some neuronal populations have been shown to express functional IL-10 receptors, which when activated promote neuronal survival (Boyd et al., 2003). For example, IL-10 activation of the PI3K-AKT pathway, downstream of IL-10R1, protects neurons against glutamate-induced excitotoxicity and hypoxic and ischemic injury by inducing transcription of survival genes preventing and by normalizing intracellular Ca^{2+} levels (Sharma et al., 2011; Tukhovskaya et al., 2014; Turovskaya et al., 2012; Zhou et al., 2009). IL-10 has also been shown to prevent glutamate-induced neuronal apoptosis by restoring suppressed anti-apoptotic factors Bcl-2 and Bcl-xl, and by attenuating caspase-3 expression (Bachis et al., 2001; Zhou et al., 2009).

4. Diseases that implicate inflammation and impairments in IL-10 signaling

4.1. Neuropathic pain

Neuropathic pain (NP) is a debilitating disorder originating from mechanical/chemical tissue damage, infection, or disease to the peripheral and/or central nervous system (CNS), which affects approximately four million people in the United States alone (Taylor, 2006). The common features of NP involve sensory disturbances including spontaneous pain, increased sensitivity to painful stimuli (hyperalgesia), and painful sensitivity to innocuous stimuli (allodynia) (Jensen et al., 2007; Macleod et al., 2002; Rowbotham and Fields, 1996). NP generally remains at least partially refractory to currently available analgesics, and frontline opioid medications have been shown to exacerbate pain and inflammation with chronic use (Hansen et al., 2005; Hutchinson et al., 2007; Salengros et al., 2010; Trevino et al., 2013; van Gulik et al., 2012; Watkins et al., 2009). In both NP patients as well as in animal models of NP, IL-10 levels in blood, sciatic nerve, dorsal root ganglion (DRG), spinal cord and/or cerebrospinal fluid (CSF) tissues are decreased versus healthy controls (Backonja et al., 2008; Franchi et al., 2012; George et al., 2004; Jancalek et al., 2011; Liou et al., 2011; Uceyler et al., 2007; Wilkerson et al., 2012a). Moreover, in animal studies, decreased IL-10

occurs later after injury despite maintaining high IL-10 mRNA levels, and is preceded by an initial increase in IL-10 shortly after injury (Franchi et al., 2012; George et al., 2004; Jancalek et al., 2011; Liou et al., 2011; Mika et al., 2008; Okamoto et al., 2001; Taskinen et al., 2000; Wilkerson et al., 2012b). These findings suggest that either IL-10 mRNA is not translated sufficiently and/or IL-10 is produced endogenously at high levels but is also rapidly utilized during NP, thus remaining insufficient to control pain and inflammation associated with the disease. In this context, several animal studies have demonstrated antinociceptive effects with IL-10-based therapies, which will be covered below (see Table 1 for summary).

Direct IL-10 protein administration has been shown to produce antinociception after peripheral nerve injury. For example, IL-10 injected intrathecally (IT) following CCI produced transient reversal of mechanical allodynia for approximately 2 h that resolved by 24 h (Lee et al., 2013; Milligan et al., 2005b; Shen et al., 2013). This effect was correlated with decreased injury-induced TNF, IL-1β, and IL-6 in lumbar spinal cord (Lee et al., 2013). Contrastingly, IT injection of the same dose of IL-10 4×/day was effective for each day of treatment and 4 days thereafter. This sustained reversal of mechanical allodynia with repeated IL-10 injections was also associated with reversal of injury-induced increases in total, tetrodotoxin-sensitive, and voltage-gated sodium channel 1.8 current densities, as well as reversal of overall excitability of cultured lumbar DRG neurons (Shen et al., 2013). Moreover, the therapeutic effect of IL-10 is not limited to central administration, as peri-sciatic nerve injection of IL-10 at the time of sciatic nerve injury blocks thermal hyperalgesia and is correlated with decreased TNF in the sciatic nerve (Wagner et al., 1998).

Viral vector-mediated delivery of IL-10 is another strategy to increase IL-10, which produces a longer reversal of NP-related behaviors than direct protein administration given the short half-life of IL-10 (~2 h) (Li et al., 1994; Milligan et al., 2005a). IT viral-mediated delivery of IL-10 after nerve injury has resulted in sustained reversal of mechanical allodynia for as little as 6 days and as long as 4 weeks depending on dose and viral vector used, and these effects were associated with decreased injury-induced IL-1β in lumbosacral CSF and decreased TNF, IL-1β, and IL-6 protein in lumbar spinal cord (He et al., 2013; Lau et al., 2012; Milligan et al., 2005a, 2005b). As with protein, viral vectors are also effective when administered peripherally, as intraplantar administration of herpes simplex virus (HSV)-IL-10 decreased both mechanical allodynia/hyperalgesia and thermal hyperalgesia for at least 4 weeks while also decreasing operant mechanical allodynia-related conflict avoidance responses (Lau et al., 2012).

To date, the IL-10-based therapeutic strategy that has produced the longest-lasting reversal of NP-related behaviors has been to inject naked (unencapsulated) plasmid DNA encoding IL-10 (pDNA-IL-10) or pDNA-IL-10 encapsulated in microparticles composed of various polymers (see route of administration, below). Repeated intrathecal (IT) injections of pDNA-IL-10 after sciatic nerve injury (chronic constriction injury [CCI]) produced increasingly longer periods of anti-allodynia after each subsequent injection (Milligan et al., 2006a), and a second IT injection of pDNA-IL-10 three days after the first injection, produced sustained anti-allodynia and antihyperaglesia after nerve injury for up to 80+ days (Ledeboer et al., 2007; Milligan et al., 2007, 2006a, 2006b; Sloane et al., 2009a). This effect

was correlated with an increased ED1/ED2 ratio in lumbar CSF cells early after the first injection, followed by a decreased ED1/ED2 ratio 6 days after the second injection, demonstrating a shift from a predominately proinflammatory to predominately antiinflammatory phenotype in CSF cells over time (Sloane et al., 2009a). Administration of polyethylenimine (PEI) polymer-based microparticles encapsulating pDNA-IL-10 after CCI also required two injections for a maximally sustained antinociceptive effect (Milligan et al., 2006b). In contrast, a single injection of XT-101, an IL-10-based gene therapy from Xalud Therapeutics consisting of an IL-10 plasmid encapsulated in a biodegradable poly(lactic-co-glycolic) (PLGA) microparticle polymer, reversed CCI-induced mechanical allodynia for up to ~3 months and increased the number of ED2 positive cells in CSF at 72 h versus 24 h post-injection (Milligan et al., 2006b; Soderquist et al., 2010b). Importantly, reversal of allodynia by XT-101 was abolished by IT anti-IL-10 neutralizing antibody, confirming that the pain resolving effect of this therapeutic approach was due to ongoing IL-10 induction (Milligan et al., 2006b; Soderquist et al., 2010b). Excitingly, we and our collaborators have also found that a single IT injection of XT-101 produces sustained reversal of NP-related behaviors in dogs in an open-label study for up to 4 months (unpublished observations). As a result of these highly successful rodent and promising dog studies, phase I/II clinical trials with XT-101 for the treatment of NP in humans are currently planned to begin in 2015.

4.2. Ostoeoarthritis

Osteoarthritis (OA) is a peripherally-based neuroimmune disorder, which involves inflammation of tissues within the joints (e.g. synovial membrane and chondrocytes) and ongoing pain. Although the precise etiology of OA is unknown, it is thought to involve degradation of cartilage that leads to tissue damage, inflammation, and pain with resulting alterations in central nervous system function such as peripheral and central sensitization (for review, see Fernandes et al., 2002; Martel-Pelletier et al., 1999; Salaffi et al., 2014; Taruc-Uy and Lynch, 2013). OA is the leading cause of pain and disability in the world, most commonly affecting the elderly but also occurring in younger populations often following injury or intense physical activity (Sharma et al., 2006).

In human OA, elevated IL-10 levels in joint tissues and IL-10-associated anti-inflammatory effects have been demonstrated in several studies. For example, IL-10 mRNA is detected in synovial tissue and is spontaneously produced in synovial cell culture from OA patients (Katsikis et al., 1994). IL-10 and TNF are also inversely correlated in cartilage from OA patients within and around chondrocytes (Moos et al., 1999), and IL-10 incubation in synovial fibroblast culture from OA patients decreased prostaglandin E2-stimulated release of TNF, upregulated sTNFRs, and reduced TNF induction of cyclooxygenase 2 (Alaaeddine et al., 1999). Moreover, blood cells from OA patients that produced the least amount of IL-10 in response to LPS stimulation were correlated with greater disease symptoms (Riyazi et al., 2005). This finding is contradicted, however, by another study in which patients whose blood cells produced the most IL-10 were correlated with a 4-fold increased risk of joint space narrowing progression over a 2-year timespan (Botha-Scheepers et al., 2008). Lastly, moderate exercise, which increases intra-articular and peri-synovial IL-10, has been found to be beneficial for female patients with OA (Helmark et al., 2010).

Due to a lack of sufficient preclinical models for OA (Malfait et al., 2013), there have been few studies of OA involving IL-10 in animals (see Table 2 for summary). In OA dogs as in OA humans, IL-10 mRNA is detected in synovial tissue (Maccoux et al., 2007). In a rabbit model of OA, intra-articular injection of primary synoviocytes transfected with retroviral vector expressing hIL-10 was moderately effective at preventing cartilage breakdown (Zhang et al., 2004). Lastly, we and our collaborators have begun testing of XT-101 for the treatment of OA in dogs. Preliminary open-label studies have been promising, with a single intra-articular injection reversing pain-related behaviors for up to 4 months (unpublished observations). These studies are currently undergoing expansion and aim to provide further evidence that IL-10-based gene therapy may be an effective treatment for OA.

4.3. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder that causes death of dopaminergic neurons of the striatum. Neuroinflammation is also closely associated with PD, and has been identified an important mediator of PD-induced neurodegeneration (Shrestha et al., 2014; Yan et al., 2014). In the United States alone, there are approximately one million people currently affected by PD and approximately 40,000–50,000 new diagnoses for PD each year (Tarazi et al., 2014a). Although its etiology remains unknown, PD produces motor symptoms such as muscle tremors, stiffness, and loss of spontaneous movement (Jankovic, 2008; Tolosa et al., 2006). Non-motor symptoms of PD include cognitive/memory impairment, depression, sleep disturbances, hallucinations, and autonomic motor dysfunction (Chaudhuri et al., 2006). Common treatments for PD are mostly limited to supplementation with the precursor for dopamine, levodopa, and/or dopamine D2 receptor agonists, although these treatments tend to only be partially effective, can lose efficacy over time, and are associated with a variety of severe motor and cognitive side effects (Rao et al., 2006; Tarazi et al., 2014a). Although there is limited information on the relationship of IL-10 to PD, current studies do not rule out a potential role for IL-10-based therapy in PD and warrant further examination.

The majority of supporting studies for IL-10-based therapies in PD have been conducted in animals (see Table 2 for summary). In animal models of PD, IL-10-based therapies have been shown to reduce dopaminergic cell damage and related microglial activation and inflammation. For example, intra-substantia nigral injection of LPS causes a selective loss of dopaminergic neurons, and this effect can be attenuated by osmotic minipump infusion of IL-10 into the substantia nigra, producing decreased microglial activation in the same region (Arimoto et al., 2007). IL-10 is also protective against LPS-induced dopaminergic cell toxicity in rat primary mesencephalic neuron-glia co-cultures, and this effectwas also attributed to decreased microglial activation and microglial production of TNF, nitric oxide, reactive oxygen species, and superoxide free radicals (Qian et al., 2006a, 2006b). Lastly, in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, which causes striatal tyrosine hydroxylase depletion and subsequent dopaminergic cell death, AAV2-hIL-10 injected intracerebroventricularly (ICV) before MPTP injection provided neuroprotective effects by increasing striatal tyrosine hydroxylase (Schwenkgrub et al., 2013).

To date, there have been no studies examining the efficacy of IL-10-based therapies in PD patients. Several studies have investigated potential associations between IL-10 polymorphisms and risk for developing PD, and although most found no association (Bialecka et al., 2008, 2007; Chu et al., 2012; Infante et al., 2008; Nie et al., 2013; Pascale et al., 2011), two studies did find IL-10 promoter polymorphisms −819 and −1082 may be associated with early onset PD and PD risk in female Han Chinese populations (Hakansson et al., 2005; Li et al., 2012). Moreover, plasma IL-10 levels have been shown to be higher in PD patients with classical motor symptoms of PD versus healthy controls (Brodacki et al., 2008; Rentzos et al., 2009), although in a separate study, IL-10 was not found to be correlated to the non-motor symptoms of PD (Menza et al., 2010).

Overall, there is limited but promising evidence that IL-10-based therapies could be effective for PD. Future studies should focus on the potential of IL-10-based therapies to treat both the behavioral and cellular deficits associated with PD.

4.4. Multiple sclerosis

The hallmark of multiple sclerosis (MS) is chronic inflammation directed against oligodendrocyte-derived antigens comprising myelin sheaths. The resultant focal de-myelination and axonal damage leads to motor, sensory, and cognitive impairment (for review, see Compston and Coles, 2008). Patients suffer from a variety of neurological symptoms, most notably loss of normal gait, paresis, muscle atrophy, gradual paralysis, and pain. The majority of patients experience multiple episodes of autoimmune attacks interceded by temporary remissions, although succeeding attacks usually increase in severity and damage tends to be cumulative. More than two million people are estimated to be afflicted globally, with 2–3 times higher prevalence among women (Disanto and Ramagopalan, 2013). While the etiology is unknown, evidence suggests that both genetic (Kenealy et al., 2003) and environmental factors play a role (Marrie, 2004). Currently, there is no effective therapy that eliminates MS, although medications are available that slow disease progression (for review, see Ali et al., 2013).

Significant perturbations in cytokine homeostasis have been reported in MS patients, including levels of IL-10 (see Imitola et al., 2005 for review). In both relapsing-remitting and secondary-progressive MS patients, IL-10 mRNA levels are reduced in unstimulated peripheral blood mononuclear cells (Hesse et al., 2011; van Boxel-Dezaire et al., 1999), while B cells exhibit deficiency in IL-10-producing capacity, and $CD4^+$ cells show reduced IL-10R-mediated signaling compared to healthy controls (Duddy et al., 2007; Martinez-Forero et al., 2008). Importantly, IL-10 secretion by peripheral blood mononuclear cells is decreased prior to relapse and increased during remission (Rieckmann et al., 1994;Waubant et al., 2001), suggesting that IL-10 presence is required for recovery to occur.

Multiple autoimmune murine and rat models of MS have been developed, collectively known as experimental autoimmune encephalomyelitis (EAE) (for review, see Batoulis et al., 2011; Croxford et al., 2011). Elevated gene expression of proinflammatory cytokines is an early, lasting, and shared feature of rodent EAE models, while expression of the *IL-10* gene depends on the model and stage of disease progression. For example, the Dark Agouti (DA) EAE rat model is commonly used to mimic relapsing MS where spinal cord IL-10

mRNA levels increase as the disease progresses, particularly preceding symptoms and during remission (Issazadeh et al., 1996; Tanuma et al., 2000). Murine relapsing-remitting EAE models likewise show upregulated IL-10 mRNA during remission (Kennedy et al., 1992), whereas IL-10 mRNA in acute rat models of EAE is elevated throughout the monophasic episode and is thought to contribute to the resolution of the disease.

Continuing deterioration of symptoms in EAE may be the consequence of diminished bioavailability of IL-10. For example, IL-10-deficient mice develop a stronger proinflammatory T cell-mediated immune response with more severe EAE (Anderson et al., 2004; Bettelli et al., 1998) and accelerated disease progression that does not remit compared to wild-type mice (Samoilova et al., 1998), suggesting that IL-10 plays a crucial role in recovery. Likewise, mice overexpressing *IL-10* are highly resistant to EAE, an effect mediated at least in part by suppression of proinflammatory T_H1 cells. This effect was abolished following administration of anti-IL-10 antibody, demonstrating that resistance to disease development was IL-10-dependent (Bettelli et al., 1998; Cua et al., 1999).

Early interventions to abrogate disease development in EAE rodents using IL-10 protein have yielded conflicting results (Table 2). Systemic delivery of IL-10 was only modestly effective in suppressing EAE in an acute Lewis rat model (Rott et al., 1994) and in the relapsing-remitting SJL/J mouse model (Nagelkerken et al., 1997). Contrastingly, intranasal delivery of low concentrations of IL-10 strongly suppressed clinical signs of disease in both acute and chronic-progressive EAE rats (Xiao et al., 1998). This effect was associated with decreased microglial activation, T-cell proliferation, spinal cord infiltration by peripheral immune cells, and IFN-γ secretion. Likewise, successive ICV treatment of $CSJLF_1/J$ chronic EAE mice with IL-10 at disease onset improved clinical scores only over the period of intervention (Cua et al., 2001), with motor impairments emerging once daily treatment was discontinued. Importantly, intraperitoneal antibody-mediated sequestration of IL-10 was found to worsen the disease (Cannella et al., 1996). By contrast, intravenously-delivered IL-10 failed to improve histological outcomes and even exacerbated clinical score under some treatment regimens (Cannella et al., 1996). Similarly, systemically delivered IL-10 was reported ineffective in another murine EAE context (Croxford et al., 2001). A likely explanation for the varied success of IL-10 protein administration may be the short half-life of IL-10 (~2 h), its route of administration, and its inability to cross the blood–brain barrier (Kastin et al., 2003; Li et al., 1994).

More promising results have been noted with IL-10 gene therapy using viral vectors for delivery directly into the CNS (Table 2). ICV administration of adenovirus (AD)-IL-10 in SJL EAE mice at symptom onset prevented development of inflammation and clinical disease symptoms in a dose-dependent manner, including blocking relapse and accelerating remission (Cua et al., 2001). By contrast, a similar study involving lower doses of AD-IL-10 delivered ICV in ABH relapsing-remitting EAE mice was ineffective (Croxford et al., 2001), suggesting the need for greater IL-10 ligand bioavailability in ameliorating EAE symptoms. Preliminary results from our lab found both relapsing-remitting (non-obese diabetic) and chronic progressive (C57Bl/6) EAE mice show improvement of clinical scores following a single IT delivery of adeno-associated viral vector (AAV)-IL-10-F129S (a potent variant of

IL-10) at disease onset, as well as modest improvement following transgene delivery 12 days after manifestation of overt symptoms (unpublished observations).

IL-10 plasmid injections in EAE rodents have likewise yielded promising results (Table 2). Our lab found that two successive IT injections of naked IL-10-F129S plasmid arrested and reversed paralysis and extended remission of symptoms along with suppression of astrocyte and microglial activation in lumbar spinal cord of DA EAE rats. Similar to findings for NP, the disease-suppressing effects of T cells were observed only when a second IL-10 plasmid injection was administered within a regular time interval following the first, reinforcing the importance of time of intervention as a determinant of efficacy (Schif-Zuck et al., 2006; Sloane et al., 2009b). A more recent development in IL-10 gene delivery includes XT-101 (IL-10 plasmid DNA encapsulated in a biodegradable polymer). Preliminary studies in our lab show that IT delivery of XT-101 at symptom onset in relapsing-remitting DA rats enhanced survival and attenuated EAE-induced paralysis/paresis, anxiety-like behavior, and motor impairment (Grace, 2012). Similarly, we have found that XT-101 is most effective at suppressing motor deficits in chronic-progressive mouse EAE when administered before the onset of symptoms (unpublished observations).

Taken together, there is overwhelming evidence from rodent studies that IL-10-based therapies are effective to treat MS disease onset, severity, and progression (see Table 2 for summary). In general, IL-10 intervention has been most effective in suppressing EAE when administered centrally in the form of a gene therapy at disease onset. Disease suppression after the development of overt symptoms has also been demonstrated, however more work is needed to ascertain optimal timing and dosing of gene therapy.

4.5. Other

The most promising and extensive research to date with IL-10-based therapies has been done with the diseases described above, however other neuroimmune diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, and rheumatoid arthritis also share common properties with these diseases (e.g. inflammation/altered neuronal functioning), and thus could too benefit from IL-10-based therapy. For example, a single study has demonstrated the efficacy of IL-10 gene therapy in a mouse model of Alzheimer's disease (Kiyota et al., 2012). Moreover, IL-10-based therapies for rheumatoid arthritis have been explored but remain controversial. This discrepancy is founded primarily on two failed clinical studies in which rheumatoid arthritis patients were injected subcutaneously with recombinant human-IL-10 (Smeets et al., 1999; van Roon et al., 2003). One reason for the failure of these clinical studies may be that IL-10 protein was used, which is rapidly degraded upon systemic administration (Li et al., 1994). In contrast to clinical findings with IL-10 protein, IL-10-based gene therapy in animal models of rheumatoid arthritis has been mostly successful (Keravala et al., 2006; Lechman et al., 1999; Lubberts et al., 2000; Whalen et al., 1999), with some conflicting results when administered after the development of the disease (Apparailly et al., 1998; Kim et al., 2000;Ma et al., 1998). There have been no studies to date investigating the efficacy of IL-10-based therapy for amyotrophic lateral sclerosis or Huntington's disease in either humans or animals. Future

studies are thus needed to determine the full range of neuroimmune diseases for which IL-10-based therapies might be effective.

5. Therapeutic potential of IL-10-based therapies: setting the stage for interventions with IL-10

5.1. IL-10 protein

Systemic administration of IL-10 protein is generally not feasible due to the rapid breakdown of the protein and its large size, which renders it incapable of crossing the blood brain barrier (Kastin et al., 2003; Li et al., 1994). In contrast, studies involving direct IT or intranasal administration of IL-10 protein have been mostly successful. However, this route of administration still produces only transient effects due to the rapid clearance of IL-10 protein from intrathecal space (half-life ~2 h) (Milligan et al., 2005a). One advantage of IL-10 protein administration over IL-10-based gene-therapy is that it is effective immediately, whereas gene therapies have a delayed therapeutic onset. Direct IL-10 protein administration can thus be useful in clinical situations where immediate and transient relief is needed, and could also be used as an adjuvant to longer-term gene therapies to provide immediate relief during the period in which therapeutic onset of the gene therapy is delayed (Milligan et al., 2006a, 2006b; Soderquist et al., 2010a).

5.2. IL-10 gene-therapy

IL-10-based gene-therapies have been more successful at producing sustained therapeutic effects of IL-10 than protein administration. There are several methods of gene-therapy that are currently used. The IL-10 gene can be delivered by a variety of methods from viral vectors to naked pDNA to encapsulation of IL-10-pDNA in polymers designed to enhance the uptake of pDNA into appropriate cell types.

5.2.1. Viral vectors encoding IL-10—One method for producing sustained therapeutic effects of IL-10 is to deliver a viral vector that increases the expression of IL-10. To date, AD, AAV, retroviral, lentiviral, and HSV vectors encoding IL-10 have been effective at producing therapeutic effects in a variety of animal models of neuroimmune disease (Croxford et al., 2001; He et al., 2013; Lau et al., 2012; Milligan et al., 2005a, 2005b). Replication-deficient AD, AAV, and HSV are more favored methods of transgene delivery due to their specificity of infection as well as their ability to produce large quantities of the transgene product over an extended period of time, usually weeks for AD (Wood et al., 1996), weeks to months for AAV (Beutler and Reinhardt, 2009; Milligan et al., 2005b), and months for HSV (Lau et al., 2012). Although not completely understood, the effects of IL-10 increased by single viral vector have generally been more transient than effects from other methods of gene therapy such as optimized injections of naked pDNA or microparticles encapsulating pDNA, which have been shown to last up to 4 months. One explanation for this difference is exposure to viral proteins, which may ultimately be targeted for suppression by the immune system. Repeated dosing has also not been studied with viral vector administration, which has been shown with naked pDNA injections to increase the potency, efficacy, and duration of its therapeutic effect.

5.2.2. Naked pDNA-IL-10 injection—Direct IT injection of naked pDNA-IL-10 has also been a successful method for producing sustained therapeutic effects of IL-10. With this method of IL-10 delivery, the cellular environment at the time of neuroinflammation and subsequent pDNA injection is thought to play a critical role in the therapeutic effect. For example, shortly after nerve injury, macrophages infiltrate CSF and surrounding meningeal tissue (Gomez-Nicola et al., 2008), and following pDNA injection, additional macrophages are recruited to CSF (Sloane et al., 2009c). These infiltrating cells have been shown to be primarily ED1-positive (blood-derived macrophages or monocytes) (Dijkstra et al., 1985) and/or ED2-positive (mature tissue or resident macrophages) (Polfliet et al., 2001). Importantly, both of these cell populations are highly phagocytic (Duffield, 2003), which is thought to be a critical cell property for uptake of pDNA. Accordingly, pDNA-IL-10 has been most effective when administered IT as two injections separated over 5 h to 3 days, which is thought to be a result of a higher number of phagocytic cells to uptake pDNA at the time of the second injection as a result of the first injection. This argument is further supported by a study in which efficacy of treatment is similar whether the first injection included only the control pDNA or the actual IL-10 plasmid (Sloane et al., 2009a). Although some IL-10-transfected macrophages are likely to undergo apoptosis or be cleared to the lymph nodes (de Vos et al., 2002), many of the infiltrating macrophages may differentiate into ED2 positive resident macrophages (Honda et al., 1990) or microglia (Zhang et al., 2007), which could provide an ongoing source of IL-10 and subsequent therapeutic effects. Notably, itwas recently shown that the addition of D-mannose as an adjuvant to IT pDNA-IL-10 injection dramatically improves the potency of pDNA IL-10 and reduces the need for two injections to produce sustained antinociceptive efficacy (Dengler et al., 2014), providing a potentially revolutionary therapeutic strategy for pDNA-IL-10 delivery. Future studies will be necessary to explore the full capabilities of D-mannose as an adjuvant to pDNA-IL-10 injections.

5.2.3. Polymer-based microparticles encapsulating IL-10-pDNA—The most successful method to date for producing sustained therapeutic effects of IL-10 has been to encapsulate pDNA-IL-10 into biodegradable polymer-based microparticles that enhance the uptake of pDNA into phagocytic cells. One major advantage to this technique is that it protects the pDNA from extracellular and intracellular degradative enzymes (Kaneda, 2001; Sebestyen et al., 1998), thus greatly reducing the amount of pDNA that is required to produce a comparable effect with naked pDNA (Meuli-Simmen et al., 1999; Shi et al., 2003). To date, two polymers have been the most extensively studied in the context of IL-10 (i.e. PEI and PLGA). The increased potency of PEI-pDNA complexes over naked pDNA is thought to be mainly due to the efficiency of releasing pDNA from the complex (see Meuli-Simmen et al., 1999; Pack et al., 2005; Shi et al., 2003 for more information). PLGA is a copolymer of lactic and glycolic acid approved by the US Food and Drug Administration and has also been demonstrated as a successful method for slow release of peptides and proteins (Hedley, 2003). The advantage of PLGA-based microparticles is that they naturally stimulate the innate immune system, allowing increased infiltration of phagocytic cells, which readily phagocytize PLGA microparticles. Accordingly, a single IT injection of a PLGA-based IL-10 gene therapy (now called XT-101 and being forwarded toward clinical trials by Xalud Therapeutics), was as effective as two optimized IT injections of pDNA-

IL-10 in a model of NP at a tenth of the dose (Sloane et al., 2009a; Soderquist et al., 2010b). Also importantly, IT PLGA is non-toxic to cells of the meninges (Ayhan et al., 2002), and proteins released from PLGA microparticles have been shown to be non-toxic for up to 35 days after treatment (Lagarce et al., 2005a, 2005b; Sendil et al., 2003). Phase I/II clinical trials with XT-101 for the treatment of NP are expected to begin in 2015.

5.3. Adenosine 2A agonists

Adenosine 2A receptors (A2ARs) are typically activated by adenosine but can also be activated by various A2AR-selective agonists. A2ARs are found on both glial cells (Gyoneva et al., 2009) and neurons (Guntz et al., 2008) and activation following inflammation has been shown to increase IL-10 and decrease proinflammatory molecules released from a variety of different inflammatory cell types in culture (Grinberg et al., 2009; Hasko et al., 1996; Khoa et al., 2001; Link et al., 2000; Perez-Aso et al., 2013; Vincenzi et al., 2013a, 2013b). Interestingly, the A2AR is upregulated on macrophages and microglia following inflammatory signals such as LPS, CpG, lipoteichoic acid, or TNF, and on lymphocytes from MS and ALS patients, providing a unique pharmacological target for immune cells and glia exclusively activated by prior proinflammatory signals (Grinberg et al., 2009; Gyoneva et al., 2009; Vincenzi et al., 2013a, 2013b). As with IL-10-based gene therapies, a single administration of A2AR agonist after the onset of CCI-induced allodynia or collagen-induced arthritis resulted in sustained suppression of disease symptoms (Loram et al., 2009, 2013; Mazzon et al., 2011). A2AR agonist effects on allodynia appear to furthermore be dependent on sustained IL-10 release, although the mechanisms underlying this effect are not fully understood (Loram et al., 2009, 2013). Genetic inactivation of the A2AR has also been shown to exacerbate brain damage in the experimental autoimmune encephalomyelitis (EAE) model of MS, providing further evidence for a protective effect of A2ARs in neuroimmune diseases (Yao et al., 2012).

6. Conclusion

In conclusion, IL-10 is implicated in neuroimmune diseases of varying etiologies such as NP (nerve trauma), OA (peripheral inflammation), PD (neurodegeneration), and MS (autoimmune). A common feature of these disorders is an insufficiency in IL-10 signaling/bioavailability and ongoing inflammation. In animal studies, increasing physiological levels of IL-10 in the context of these diseases has generally been a successful strategy to reduce disease symptoms and associated inflammation. Various methodologies to increase physiological levels of IL-10 have been employed (i.e. direct protein administration, viral vectors, naked plasmid delivery, plasmid delivery in microparticles, A2AR agonist administration), which have grown increasingly sophisticated in their ability to produce sustained therapeutic effects following a single injection. Future studies including clinical trials planned for XT-101 will critically evaluate the efficacy of IL-10-based therapies for the treatment of neuroimmune diseases in both animals and humans.

References

Alaaeddine N, Di Battista JA, Pelletier JP, Kiansa K, Cloutier JM, Martel-Pelletier J. Inhibition of tumor necrosis factor alpha-induced prostaglandin E2 production by the antiinflammatory cytokines

interleukin-4, interleukin-10, and interleukin-13 in osteoarthritic synovial fibroblasts: distinct targeting in the signaling pathways. Arthritis Rheum. 1999; 42:710–718. [PubMed: 10211885]

Ali R, Nicholas RS, Muraro PA. Drugs in development for relapsing multiple sclerosis. Drugs. 2013; 73:625–650. [PubMed: 23609782]

Ananieva O, Darragh J, Johansen C, Carr JM, McIlrath J, Park JM, Wingate A, Monk CE, Toth R, Santos SG, Iversen L, Arthur JS. The kinases MSK1 and MSK2 act as negative regulators of Toll-like receptor signaling. Nat Immunol. 2008; 9:1028–1036. [PubMed: 18690222]

Anderson AC, Reddy J, Nazareno R, Sobel RA, Nicholson LB, Kuchroo VK. IL-10 plays an important role in the homeostatic regulation of the autoreactive repertoire in naive mice. J Immunol. 2004; 173:828–834. [PubMed: 15240669]

Anderson P. Post-transcriptional control of cytokine production. Nat Immunol. 2008; 9:353–359. [PubMed: 18349815]

Apparailly F, Verwaerde C, Jacquet C, Auriault C, Sany J, Jorgensen C. Adenovirus-mediated transfer of viral IL-10 gene inhibits murine collagen-induced arthritis. J Immunol. 1998; 160:5213–5220. [PubMed: 9605116]

Arimoto T, Choi DY, Lu X, Liu M, Nguyen XV, Zheng N, Stewart CA, Kim HC, Bing G. Interleukin-10 protects against inflammation-mediated degeneration of dopaminergic neurons in substantia nigra. Neurobiol Aging. 2007; 28:894–906. [PubMed: 21887889]

Ayhan S, Tugay C, Ortak T, Prayson R, Parker M, Siemionow M, Papay FA. Effect of bioabsorbable osseous fixation materials on dura mater and brain tissue. Plastic Reconstr Surg. 2002; 109:1333–1337.

Bachis A, Colangelo AM, Vicini S, Doe PP, De Bernardi MA, Brooker G, Mocchetti I. Interleukin-10 prevents glutamate-mediated cerebellar granule cell death by blocking caspase-3-like activity. J Neurosci. 2001; 21:3104–3112. [PubMed: 11312295]

Backonja MM, Coe CL, Muller DA, Schell K. Altered cytokine levels in the blood and cerebrospinal fluid of chronic pain patients. J Neuroimmunol. 2008; 195:157–163. [PubMed: 18325600]

Balasingam V, Yong VW. Attenuation of astroglial reactivity by interleukin-10. J Neurosci. 1996; 16:2945–2955. [PubMed: 8622125]

Ball C, Vigues S, Gee CK, Poole S, Bristow AF. Rat interleukin-10: production and characterisation of biologically active protein in a recombinant bacterial expression system. Eur Cytokine Netw. 2001; 12:187–193. [PubMed: 11282564]

Barrat FJ, Cua DJ, Boonstra A, Richards DF, Crain C, Savelkoul HF, de Waal-Malefyt R, Coffman RL, Hawrylowicz CM, O'Garra A. In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. J Exp Med. 2002; 195:603–616. [PubMed: 11877483]

Batoulis H, Recks MS, Addicks K, Kuerten S. Experimental autoimmune encephalomyelitis – achievements and prospective advances. APMIS Acta Pathol Microbiol Immunol Scand. 2011; 119:819–830.

Bettelli E, Das MP, Howard ED, Weiner HL, Sobel RA, Kuchroo VK. IL-10 is critical in the regulation of autoimmune encephalomyelitis as demonstrated by studies of IL-10- and IL-4-deficient and transgenic mice. J Immunol. 1998; 161:3299–3306. [PubMed: 9759845]

Beutler AS, Reinhardt M. AAV for pain: steps towards clinical translation. Gene Ther. 2009; 16:461–469. [PubMed: 19262609]

Bialecka M, Klodowska-Duda G, Kurzawski M, Slawek J, Gorzkowska A, Opala G, Bialecki P, Sagan L, Drozdzik M. Interleukin-10 (IL10) and tumor necrosis factor alpha (TNF) gene polymorphisms in Parkinson's disease patients. Park Relat Disord. 2008; 14:636–640.

Bialecka M, Klodowska-Duda G, Kurzawski M, Slawek J, Opala G, Bialecki P, Safranow K, Drozdzik M. Interleukin-10 gene polymorphism in Parkinson's disease patients. Arch Med Res. 2007; 38:858–863. [PubMed: 17923267]

Boonstra A, Rajsbaum R, Holman M, Marques R, Asselin-Paturel C, Pereira JP, Bates EE, Akira S, Vieira P, Liu YJ, Trinchieri G, O'Garra A. Macrophages and myeloid dendritic cells, but not plasmacytoid dendritic cells, produce IL-10 in response to MyD88- and TRIF-dependent TLR signals, and TLR-independent signals. J Immunol. 2006; 177:7551–7558. [PubMed: 17114424]

Botha-Scheepers S, Watt I, Slagboom E, de Craen AJ, Meulenbelt I, Rosendaal FR, Breedveld FC, Huizinga TW, Kloppenburg M. Innate production of tumour necrosis factor alpha and interleukin 10 is associated with radiological progression of knee osteoarthritis. Ann Rheum Dis. 2008; 67:1165–1169. [PubMed: 18029383]

Boyd ZS, Kriatchko A, Yang J, Agarwal N, Wax MB, Patil RV. Interleukin-10 receptor signaling through STAT-3 regulates the apoptosis of retinal ganglion cells in response to stress. Invest Ophthalmol Vis Sci. 2003; 44:5206–5211. [PubMed: 14638718]

Brodacki B, Staszewski J, Toczylowska B, Kozlowska E, Drela N, Chalimoniuk M, Stepien A. Serum interleukin (IL-2, IL-10, IL-6, IL-4), TNFalpha, and INFgamma concentrations are elevated in patients with atypical and idiopathic parkinsonism. Neurosci Lett. 2008; 441:158–162. [PubMed: 18582534]

Cannella B, Gao YL, Brosnan C, Raine CS. IL-10 fails to abrogate experimental autoimmune encephalomyelitis. J Neurosci Res. 1996; 45:735–746. [PubMed: 8892085]

Cao S, Zhang X, Edwards JP, Mosser DM. NF-kappaB1 (p50) homodimers differentially regulate pro- and anti-inflammatory cytokines in macrophages. J Biol Chem. 2006; 281:26041–26050. [PubMed: 16835236]

Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006; 5:235–245. [PubMed: 16488379]

Chi H, Barry SP, Roth RJ, Wu JJ, Jones EA, Bennett AM, Flavell RA. Dynamic regulation of pro- and anti-inflammatory cytokines by MAPK phosphatase 1 (MKP-1) in innate immune responses. Proc Natl Acad Sci U S A. 2006; 103:2274–2279. [PubMed: 16461893]

Chu K, Zhou X, Luo BY. Cytokine gene polymorphisms and Parkinson's disease: a meta-analysis. The Canadian journal of neurological sciences. Le J Can Sci Neurol. 2012; 39:58–64.

Compston A, Coles A. Multiple sclerosis. Lancet. 2008; 372:1502–1517. [PubMed: 18970977]

Croxford AL, Kurschus FC, Waisman A. Mouse models for multiple sclerosis: historical facts and future implications. Biochim Biophys Acta. 2011; 1812:177–183. [PubMed: 20600870]

Croxford JL, Feldmann M, Chernajovsky Y, Baker D. Different therapeutic outcomes in experimental allergic encephalomyelitis dependent upon the mode of delivery of IL-10: a comparison of the effects of protein, adenoviral or retroviral IL-10 delivery into the central nervous system. J Immunol. 2001; 166:4124–4130. [PubMed: 11238662]

Cua DJ, Groux H, Hinton DR, Stohlman SA, Coffman RL. Transgenic interleukin 10 prevents induction of experimental autoimmune encephalomyelitis. J Exp Med. 1999; 189:1005–1010. [PubMed: 10075984]

Cua DJ, Hutchins B, LaFace DM, Stohlman SA, Coffman RL. Central nervous system expression of IL-10 inhibits autoimmune encephalomyelitis. J Immunol. 2001; 166:602–608. [PubMed: 11123343]

de Vos AF, van Meurs M, Brok HP, Boven LA, Hintzen RQ, van der Valk P, Ravid R, Rensing S, Boon L, t Hart BA, Laman JD. Transfer of central nervous system autoantigens and presentation in secondary lymphoid organs. J Immunol. 2002; 169:5415–5423. [PubMed: 12421916]

Dengler EC, Alberti LA, Bowman BN, Kerwin AA, Wilkerson JL, Moezzi DR, Limanovich E, Wallace JA, Milligan ED. Improvement of spinal non-viral IL-10 gene delivery by D-mannose as a transgene adjuvant to control chronic neuropathic pain. J Neuroinflammation. 2014; 11:92. [PubMed: 24884664]

Dijkstra CD, Dopp EA, Joling P, Kraal G. The heterogeneity of mononuclear phagocytes in lymphoid organs: distinct macrophage subpopulations in the rat recognized by monoclonal antibodies ED1, ED2 and ED3. Immunology. 1985; 54:589–599. [PubMed: 3882559]

Ding Y, Qin L, Zamarin D, Kotenko SV, Pestka S, Moore KW, Bromberg JS. Differential IL-10R1 expression plays a critical role in IL-10-mediated immune regulation. J Immunol. 2001; 167:6884–6892. [PubMed: 11739506]

Disanto G, Ramagopalan SV. Similar genetics of adult and pediatric MS: age is just a number. Neurology. 2013; 81:1974–1975. [PubMed: 24198289]

Dominguez-Soto A, Sierra-Filardi E, Puig-Kroger A, Perez-Maceda B, Gomez-Aguado F, Corcuera MT, Sanchez-Mateos P, Corbi AL. Dendritic cell-specific ICAM-3-grabbing nonintegrin expression on M2-polarized and tumor-associated macrophages is macrophage-CSF dependent

and enhanced by tumor-derived IL-6 and IL-10. J Immunol. 2011; 186:2192–2200. [PubMed: 21239715]

Duddy M, Niino M, Adatia F, Hebert S, Freedman M, Atkins H, Kim HJ, Bar-Or A. Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. J Immunol. 2007; 178:6092–6099. [PubMed: 17475834]

Duffield JS. The inflammatory macrophage: a story of Jekyll and Hyde. Clin Sci. 2003; 104:27–38. [PubMed: 12519085]

Fernandes JC, Martel-Pelletier J, Pelletier JP. The role of cytokines in osteoarthritis pathophysiology. Biorheology. 2002; 39:237–246. [PubMed: 12082286]

Finbloom DS, Winestock KD. IL-10 induces the tyrosine phosphorylation of tyk2 and Jak1 and the differential assembly of STAT1 alpha and STAT3 complexes in human T cells and monocytes. J Immunol. 1995; 155:1079–1090. [PubMed: 7543512]

Fiorentino DF, Bond MW, Mosmann TR. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J Exp Med. 1989; 170:2081–2095. [PubMed: 2531194]

Franchi S, Valsecchi AE, Borsani E, Procacci P, Ferrari D, Zalfa C, Sartori P, Rodella LF, Vescovi A, Maione S, Rossi F, Sacerdote P, Colleoni M, Panerai AE. Intravenous neural stem cells abolish nociceptive hypersensitivity and trigger nerve regeneration in experimental neuropathy. Pain. 2012; 153:850–861. [PubMed: 22321918]

George A, Kleinschnitz C, Zelenka M, Brinkhoff J, Stoll G, Sommer C. Wallerian degeneration after crush or chronic constriction injury of rodent sciatic nerve is associated with a depletion of endoneurial interleukin-10 protein. Exp Neurol. 2004; 188:187–191. [PubMed: 15191815]

Gomez-Nicola D, Valle-Argos B, Suardiaz M, Taylor JS, Nieto-Sampedro M. Role of IL-15 in spinal cord and sciatic nerve after chronic constriction injury: regulation of macrophage and T-cell infiltration. J Neurochem. 2008; 107:1741–1752. [PubMed: 19014377]

Grace PM, Rolan PE, Hutchinson MR. Peripheral immune contributions to the maintenance of central glial activation underlying neuropathic pain. Brain Behav Immun. 2011; 25:1322–1332. [PubMed: 21496480]

Grace, PMLLC.; Strand, KA.; Christianson, JP.; Flyer, JG.; Penzkover, KR.; Zhang, Y.; Maier, SF.; van Dam, A.; Mahoney, MJ.; Watkins, LR. Intrathecal IL-10 gene therapy (XT-101) attenuates multiple sclerosis-like symptoms in a rat model of experimental autoimmune encephalomyelitis (EAE). The Society for Neuroscience Annual Meeting; New Orleans, LA. 2012. p. 767p. 703/U711

Grinberg S, Hasko G, Wu D, Leibovich SJ. Suppression of PLCbeta2 by endotoxin plays a role in the adenosine A(2A) receptor-mediated switch of macrophages from an inflammatory to an angiogenic phenotype. Am J Pathol. 2009; 175:2439–2453. [PubMed: 19850892]

Gringhuis SI, den Dunnen J, Litjens M, van Het Hof B, van Kooyk Y, Geijtenbeek TB. C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. Immunity. 2007; 26:605–616. [PubMed: 17462920]

Groux H, Bigler M, de Vries JE, Roncarolo MG. Interleukin-10 induces a long-term antigen-specific anergic state in human CD4+ T cells. J Exp Med. 1996; 184:19–29. [PubMed: 8691133]

Guntz E, Dumont H, Pastijn E, de d'Exaerde AK, Azdad K, Sosnowski M, Schiffmann SN, Gall D. Expression of adenosine A 2A receptors in the rat lumbar spinal cord and implications in the modulation of N-methyl-d-aspartate receptor currents. Anesth Analg. 2008; 106:1882–1889. [PubMed: 18499627]

Gutierrez J, Raju S, Riley JP, Boulis NM. Introduction to neuropathic pain Syndromes. Neurosurg Clin N Am. 2014; 25:639–662. [PubMed: 25240654]

Gyoneva S, Orr AG, Traynelis SF. Differential regulation of microglial motility by ATP/ADP and adenosine. Park Relat Disord. 2009; 15(Suppl 3):S195–S199.

Hakansson A, Westberg L, Nilsson S, Buervenich S, Carmine A, Holmberg B, Sydow O, Olson L, Johnels B, Eriksson E, Nissbrandt H. Investigation of genes coding for inflammatory components in Parkinson's disease. Mov Disord Off J Mov Disord Soc. 2005; 20:569–573.

Hammer M, Mages J, Dietrich H, Schmitz F, Striebel F, Murray PJ, Wagner H, Lang R. Control of dual-specificity phosphatase-1 expression in activated macrophages by IL-10. Eur J Immunol. 2005; 35:2991–3001. [PubMed: 16184516]

Hansen EG, Duedahl TH, Romsing J, Hilsted KL, Dahl JB. Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. Acta Anaesthesiol Scand. 2005; 49:1464–1470. [PubMed: 16223391]

Hasko G, Szabo C, Nemeth ZH, Kvetan V, Pastores SM, Vizi ES. Adenosine receptor agonists differentially regulate IL-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice. J Immunol. 1996; 157:4634–4640. [PubMed: 8906843]

Hawrylowicz CM, O'Garra A. Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. Nat Rev Immunol. 2005; 5:271–283. [PubMed: 15775993]

He Z, Guo Q, Xiao M, He C, Zou W. Intrathecal lentivirus-mediated transfer of interleukin-10 attenuates chronic constriction injury-induced neuropathic pain through modulation of spinal high-mobility group box 1 in rats. Pain Physician. 2013; 16:E615–E625. [PubMed: 24077211]

Hedley ML. Formulations containing poly(lactide-co-glycolide) and plasmid DNA expression vectors. Expert Opin Biol Ther. 2003; 3:903–910. [PubMed: 12943449]

Helmark IC, Mikkelsen UR, Borglum J, Rothe A, Petersen MC, Andersen O, Langberg H, Kjaer M. Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Res Ther. 2010; 12:R126. [PubMed: 20594330]

Hesse D, Krakauer M, Lund H, Sondergaard HB, Limborg SJ, Sorensen PS, Sellebjerg F. Disease protection and interleukin-10 induction by endogenous interferon-beta in multiple sclerosis? Eur J Neurol Off J Eur Fed Neurol Soc. 2011; 18:266–272.

Honda H, Kimura H, Rostami A. Demonstration and phenotypic characterization of resident macrophages in rat skeletal muscle. Immunology. 1990; 70:272–277. [PubMed: 2197218]

Hu X, Paik PK, Chen J, Yarilina A, Kockeritz L, Lu TT, Woodgett JR, Ivashkiv LB. IFN-gamma suppresses IL-10 production and synergizes with TLR2 by regulating GSK3 and CREB/AP-1 proteins. Immunity. 2006; 24:563–574. [PubMed: 16713974]

Hulshof S, Montagne L, De Groot CJ, Van Der Valk P. Cellular localization and expression patterns of interleukin-10, interleukin-4, and their receptors in multiple sclerosis lesions. Glia. 2002; 38:24–35. [PubMed: 11921201]

Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, Watkins LR. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. ScientificWorldJournal. 2007; 7:98–111.

Imitola J, Chitnis T, Khoury SJ. Cytokines in multiple sclerosis: from bench to bedside. Pharmacol Ther. 2005; 106:163–177. [PubMed: 15866318]

Infante J, Garcia-Gorostiaga I, Sanchez-Juan P, Sanchez-Quintana C, Gurpegui JL, Rodriguez-Rodriguez E, Mateo I, Berciano J, Combarros O. Inflammation-related genes and the risk of Parkinson's disease: a multilocus approach. Eur J Neurol Off J Eur Fed Neurol Soc. 2008; 15:431–433.

Issazadeh S, Lorentzen JC, Mustafa MI, Hojeberg B, Mussener A, Olsson T. Cytokines in relapsing experimental autoimmune encephalomyelitis in DA rats: persistent mRNA expression of proinflammatory cytokines and absent expression of interleukin-10 and transforming growth factor-beta. J Neuroimmunol. 1996; 69:103–115. [PubMed: 8823381]

Jancalek R, Svizenska I, Klusakova I, Dubovy P. Bilateral changes of IL-10 protein in lumbar and cervical dorsal root ganglia following proximal and distal chronic constriction injury of peripheral nerve. Neurosci Lett. 2011; 501:86–91. [PubMed: 21763399]

Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008; 79:368–376. [PubMed: 18344392]

Jensen MP, Kuehn CM, Amtmann D, Cardenas DD. Symptom burden in persons with spinal cord injury. Arch Phys Med Rehabilitation. 2007; 88:638–645.

Joss A, Akdis M, Faith A, Blaser K, Akdis CA. IL-10 directly acts on T cells by specifically altering the CD28 co-stimulation pathway. Eur J Immunol. 2000; 30:1683–1690. [PubMed: 10898505]

Kaneda Y. Gene therapy: a battle against biological barriers. Curr Mol Med. 2001; 1:493–499. [PubMed: 11899093]

Kastin AJ, Akerstrom V, Pan W. Interleukin-10 as a CNS therapeutic: the obstacle of the blood-brain/blood-spinal cord barrier. Brain Res Mol brain Res. 2003; 114:168–171. [PubMed: 12829328]

Katsikis PD, Chu CQ, Brennan FM, Maini RN, Feldmann M. Immunoregulatory role of interleukin 10 in rheumatoid arthritis. J Exp Med. 1994; 179:1517–1527. [PubMed: 8163935]

Kawai T, Akira S. TLR signaling. Semin Immunol. 2007; 19:24–32. [PubMed: 17275323]

Kenealy SJ, Pericak-Vance MA, Haines JL. The genetic epidemiology of multiple sclerosis. J Neuroimmunol. 2003; 143:7–12. [PubMed: 14575907]

Kennedy MK, Torrance DS, Picha KS, Mohler KM. Analysis of cytokine mRNA expression in the central nervous system of mice with experimental autoimmune encephalomyelitis reveals that IL-10 mRNA expression correlates with recovery. J Immunol. 1992; 149:2496–2505. [PubMed: 1527389]

Keravala A, Lechman ER, Nash J, Mi Z, Robbins PD. Human, viral or mutant human IL-10 expressed after local adenovirus-mediated gene transfer are equally effective in ameliorating disease pathology in a rabbit knee model of antigen-induced arthritis. Arthritis Res Ther. 2006; 8:R91. [PubMed: 16704745]

Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiol Rev. 2011; 91:461–553. [PubMed: 21527731]

Khoa ND, Montesinos MC, Reiss AB, Delano D, Awadallah N, Cronstein BN. Inflammatory cytokines regulate function and expression of adenosine A(2A) receptors in human monocytic THP-1 cells. J Immunol. 2001; 167:4026–4032. [PubMed: 11564822]

Kim K, Lee SG, Kegelman TP, Su ZZ, Das SK, Dash R, Dasgupta S, Barral PM, Hedvat M, Diaz P, Reed JC, Stebbins JL, Pellecchia M, Sarkar D, Fisher PB. Role of excitatory amino acid transporter-2 (EAAT2) and glutamate in neurodegeneration: opportunities for developing novel therapeutics. J Cell Physiol. 2011; 226:2484–2493. [PubMed: 21792905]

Kim KN, Watanabe S, Ma Y, Thornton S, Giannini EH, Hirsch R. Viral IL-10 and soluble TNF receptor act synergistically to inhibit collagen-induced arthritis following adenovirus-mediated gene transfer. J Immunol. 2000; 164:1576–1581. [PubMed: 10640777]

Kiyota T, Ingraham KL, Swan RJ, Jacobsen MT, Andrews SJ, Ikezu T. AAV serotype 2/1-mediated gene delivery of anti-inflammatory interleukin-10 enhances neurogenesis and cognitive function in APP+PS1 mice. Gene Ther. 2012; 19:724–733. [PubMed: 21918553]

Koppelman B, Neefjes JJ, de Vries JE, de Waal Malefyt R. Interleukin-10 down-regulates MHC class II alphabeta peptide complexes at the plasma membrane of monocytes by affecting arrival and recycling. Immunity. 1997; 7:861–871. [PubMed: 9430231]

Lacy P, Stow JL. Cytokine release from innate immune cells: association with diverse membrane trafficking pathways. Blood. 2011; 118:9–18. [PubMed: 21562044]

Lagarce F, Faisant N, Desfontis JC, Marescaux L, Gautier F, Richard J, Menei P, Benoit JP. Baclofen-loaded microspheres in gel suspensions for intrathecal drug delivery: in vitro and in vivo evaluation. Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Pharm Verfahr eV. 2005a; 61:171–180.

Lagarce F, Renaud P, Faisant N, Nicolas G, Cailleux A, Richard J, Menei P, Benoit JP. Baclofen-loaded microspheres: preparation and efficacy testing in a new rabbit model. Eur J Pharm Biopharm Off J Arbeitsgemein-schaft Pharm Verfahr eV. 2005b; 59:449–459.

Lau D, Harte SE, Morrow TJ, Wang S, Mata M, Fink DJ. Herpes simplex virus vector-mediated expression of interleukin-10 reduces below-level central neuropathic pain after spinal cord injury. Neurorehabilitation Neural Repair. 2012; 26:889–897. [PubMed: 22593113]

Lechman ER, Jaffurs D, Ghivizzani SC, Gambotto A, Kovesdi I, Mi Z, Evans CH, Robbins PD. Direct adenoviral gene transfer of viral IL-10 to rabbit knees with experimental arthritis ameliorates disease in both injected and contralateral control knees. J Immunol. 1999; 163:2202–2208. [PubMed: 10438962]

Ledeboer A, Breve JJ, Wierinckx A, van der Jagt S, Bristow AF, Leysen JE, Tilders FJ, Van Dam AM. Expression and regulation of interleukin-10 and interleukin-10 receptor in rat astroglial and microglial cells. Eur J Neurosci. 2002; 16:1175–1185. [PubMed: 12405978]

Ledeboer A, Jekich BM, Sloane EM, Mahoney JH, Langer SJ, Milligan ED, Martin D, Maier SF, Johnson KW, Leinwand LA, Chavez RA, Watkins LR. Intrathecal interleukin-10 gene therapy attenuates paclitaxel-induced mechanical allodynia and proinflammatory cytokine expression in dorsal root ganglia in rats. Brain Behav Immun. 2007; 21:686–698. [PubMed: 17174526]

Lee BS, Jun IG, Kim SH, Park JY. Intrathecal gabapentin increases interleukin-10 expression and inhibits pro-inflammatory cytokine in a rat model of neuropathic pain. J Korean Med Sci. 2013; 28:308–314. [PubMed: 23399960]

Li D, He Q, Li R, Xu X, Chen B, Xie A. Interleukin-10 promoter polymorphisms in Chinese patients with Parkinson's disease. Neurosci Lett. 2012; 513:183–186. [PubMed: 22387064]

Li L, Elliott JF, Mosmann TR. IL-10 inhibits cytokine production, vascular leakage, and swelling during T helper 1 cell-induced delayed-type hypersensitivity. J Immunol. 1994; 153:3967–3978. [PubMed: 7930605]

Link AA, Kino T, Worth JA, McGuire JL, Crane ML, Chrousos GP, Wilder RL, Elenkov IJ. Ligand-activation of the adenosine A2a receptors inhibits IL-12 production by human monocytes. J Immunol. 2000; 164:436–442. [PubMed: 10605040]

Liou JT, Liu FC, Mao CC, Lai YS, Day YJ. Inflammation confers dual effects on nociceptive processing in chronic neuropathic pain model. Anesthesiology. 2011; 114:660–672. [PubMed: 21307767]

Locati M, Mantovani A, Sica A. Macrophage activation and polarization as an adaptive component of innate immunity. Adv Immunol. 2013; 120:163–184. [PubMed: 24070384]

Loram LC, Harrison JA, Sloane EM, Hutchinson MR, Sholar P, Taylor FR, Berkelhammer D, Coats BD, Poole S, Milligan ED, Maier SF, Rieger J, Watkins LR. Enduring reversal of neuropathic pain by a single intrathecal injection of adenosine 2A receptor agonists: a novel therapy for neuropathic pain. J Neurosci. 2009; 29:14015–14025. [PubMed: 19890011]

Loram LC, Taylor FR, Strand KA, Harrison JA, Rzasalynn R, Sholar P, Rieger J, Maier SF, Watkins LR. Intrathecal injection of adenosine 2A receptor agonists reversed neuropathic allodynia through protein kinase (PK)A/PKC signaling. Brain Behav Immun. 2013; 33:112–122. [PubMed: 23811314]

Lubberts E, Joosten LA, Van Den Bersselaar L, Helsen MM, Bakker AC, Xing Z, Richards CD, Van Den Berg WB. Intra-articular IL-10 gene transfer regulates the expression of collagen-induced arthritis (CIA) in the knee and ipsilateral paw. Clin Exp Immunol. 2000; 120:375–383. [PubMed: 10792391]

Ma Y, Thornton S, Duwel LE, Boivin GP, Giannini EH, Leiden JM, Bluestone JA, Hirsch R. Inhibition of collagen-induced arthritis in mice by viral IL-10 gene transfer. J Immunol. 1998; 161:1516–1524. [PubMed: 9686619]

Maccoux LJ, Salway F, Day PJ, Clements DN. Expression profiling of select cytokines in canine osteoarthritis tissues. Veterinary Immunol Immunopathol. 2007; 118:59–67.

Macleod MA, Stewart GE, Zeidler M, Will R, Knight R. Sensory features of variant Creutzfeldt-Jakob disease. J Neurol. 2002; 249:706–711. [PubMed: 12111303]

Malfait AM, Little CB, McDougall JJ. A commentary on modelling osteoarthritis pain in small animals. Osteoarthr Cartilage/OARS Osteoarthr Res Soc. 2013; 21:1316–1326.

Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol. 2004; 3:709–718. [PubMed: 15556803]

Martel-Pelletier J, Alaaeddine N, Pelletier JP. Cytokines and their role in the pathophysiology of osteoarthritis. Front Biosci J Virtual Libr. 1999; 4:D694–D703.

Martinez-Forero I, Garcia-Munoz R, Martinez-Pasamar S, Inoges S, Lopez-Diaz de Cerio A, Palacios R, Sepulcre J, Moreno B, Gonzalez Z, Fernandez-Diez B, Melero I, Bendandi M, Villoslada P. IL-10 suppressor activity and ex vivo Tr1 cell function are impaired in multiple sclerosis. Eur J Immunol. 2008; 38:576–586. [PubMed: 18200504]

Mazzon E, Esposito E, Impellizzeri D, DI Paola R, Melani A, Bramanti P, Pedata F, Cuzzocrea S. CGS 21680, an agonist of the adenosine (A2A) receptor, reduces progression of murine type II collagen-induced arthritis. J Rheumatol. 2011; 38:2119–2129. [PubMed: 21765105]

McKinstry KK, Strutt TM, Buck A, Curtis JD, Dibble JP, Huston G, Tighe M, Hamada H, Sell S, Dutton RW, Swain SL. IL-10 deficiency unleashes an influenza-specific Th17 response and

enhances survival against high-dose challenge. J Immunol. 2009; 182:7353–7363. [PubMed: 19494257]

Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Bienfait K, Dicke A, Kusnekov A. The role of inflammatory cytokines in cognition and other non-motor symptoms of Parkinson's disease. Psychosomatics. 2010; 51:474–479. [PubMed: 21051678]

Meuli-Simmen C, Liu Y, Yeo TT, Liggitt D, Tu G, Yang T, Meuli M, Knauer S, Heath TD, Longo FM, Debs RJ. Gene expression along the cerebral-spinal axis after regional gene delivery. Hum Gene Ther. 1999; 10:2689–2700. [PubMed: 10566897]

Mika J, Korostynski M, Kaminska D, Wawrzczak-Bargiela A, Osikowicz M, Makuch W, Przewlocki R, Przewlocka B. Interleukin-1 alpha has antiallodynic and antihyperalgesic activities in a rat neuropathic pain model. Pain. 2008; 138:587–597. [PubMed: 18374486]

Milligan ED, Langer SJ, Sloane EM, He L, Wieseler-Frank J, O'Connor K, Martin D, Forsayeth JR, Maier SF, Johnson K, Chavez RA, Leinwand LA, Watkins LR. Controlling pathological pain by adenovirally driven spinal production of the anti-inflammatory cytokine, interleukin-10. Eur J Neurosci. 2005a; 21:2136–2148. [PubMed: 15869510]

Milligan, ED.; Ledeboer, A.; Sloane, EM.; Busha, DA.; Maier, SF.; Watkins, LR. Glially driven enhancement of pain and its control by anti-inflammatory cytokines. In: DeLeo, JA.; Sorkin, LS.; Watkins, LR., editors. Immune and Glial Regulation of Pain. IASP Press; Seattle: 2007. p. 319-340.

Milligan ED, Sloane EM, Langer SJ, Cruz PE, Chacur M, Spataro L, Wieseler-Frank J, Hammack SE, Maier SF, Flotte TR, Forsayeth JR, Leinwand LA, Chavez R, Watkins LR. Controlling neuropathic pain by adeno-associated virus driven production of the anti-inflammatory cytokine, interleukin-10. Mol Pain. 2005b; 1:9. [PubMed: 15813997]

Milligan ED, Sloane EM, Langer SJ, Hughes TS, Jekich BM, Frank MG, Mahoney JH, Levkoff LH, Maier SF, Cruz PE, Flotte TR, Johnson KW, Mahoney MM, Chavez RA, Leinwand LA, Watkins LR. Repeated intrathecal injections of plasmid DNA encoding interleukin-10 produce prolonged reversal of neuropathic pain. Pain. 2006a; 126:294–308. [PubMed: 16949747]

Milligan ED, Soderquist RG, Malone SM, Mahoney JH, Hughes TS, Langer SJ, Sloane EM, Maier SF, Leinwand LA, Watkins LR, Mahoney MJ. Intrathecal polymer-based interleukin-10 gene delivery for neuropathic pain. Neuron Glia Biol. 2006b; 2:293–308. [PubMed: 18079973]

Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001; 19:683–765. [PubMed: 11244051]

Moos V, Fickert S, Muller B, Weber U, Sieper J. Immunohistological analysis of cytokine expression in human osteoarthritic and healthy cartilage. J Rheumatol. 1999; 26:870–879. [PubMed: 10229409]

Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008; 8:958–969. [PubMed: 19029990]

Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol. 2011; 11:723–737. [PubMed: 21997792]

Nagelkerken L, Blauw B, Tielemans M. IL-4 abrogates the inhibitory effect of IL-10 on the development of experimental allergic encephalomyelitis in SJL mice. Int Immunol. 1997; 9:1243–1251. [PubMed: 9310827]

Naundorf S, Schroder M, Hoflich C, Suman N, Volk HD, Grutz G. IL-10 interferes directly with TCR-induced IFN-gamma but not IL-17 production in memory T cells. Eur J Immunol. 2009; 39:1066–1077. [PubMed: 19266486]

Nemeth ZH, Lutz CS, Csoka B, Deitch EA, Leibovich SJ, Gause WC, Tone M, Pacher P, Vizi ES, Hasko G. Adenosine augments IL-10 production by macrophages through an A2B receptor-mediated posttranscriptional mechanism. J Immunol. 2005; 175:8260–8270. [PubMed: 16339566]

Nie K, Zhang Y, Gan R, Wang L, Zhao J, Huang Z, Tang H. Polymorphisms in immune/inflammatory cytokine genes are related to Parkinson's disease with cognitive impairment in the Han Chinese population. Neurosci Lett. 2013; 541:111–115. [PubMed: 23485736]

Nouel A, Simon Q, Jamin C, Pers JO, Hillion S. Regulatory B cells: an exciting target for future therapeutics in Transplantation. Front Immunol. 2014; 5:11. [PubMed: 24478776]

O'Garra A, Vieira P. T(H)1 cells control themselves by producing interleukin-10. Nat Rev Immunol. 2007; 7:425–428. [PubMed: 17525751]

Okamoto K, Martin DP, Schmelzer JD, Mitsui Y, Low PA. Pro- and antiinflammatory cytokine gene expression in rat sciatic nerve chronic constriction injury model of neuropathic pain. Exp Neurol. 2001; 169:386–391. [PubMed: 11358451]

Pack DW, Hoffman AS, Pun S, Stayton PS. Design and development of polymers for gene delivery. Nature Rev Drug Discov. 2005; 4:581–593. [PubMed: 16052241]

Pascale E, Passarelli E, Purcaro C, Vestri AR, Fakeri A, Guglielmi R, Passarelli F, Meco G. Lack of association between IL-1beta, TNF-alpha, and IL-10 gene polymorphisms and sporadic Parkinson's disease in an Italian cohort. Acta Neurol Scand. 2011; 124:176–181. [PubMed: 20880267]

Perez-Aso M, Feig JL, Mediero A, Cronstein BN. Adenosine A2A receptor and TNF-alpha regulate the circadian machinery of the human monocytic THP-1 cells. Inflammation. 2013; 36:152–162. [PubMed: 22923002]

Polfliet MM, Goede PH, van Kesteren-Hendrikx EM, van Rooijen N, Dijkstra CD, van den Berg TK. A method for the selective depletion of perivascular and meningeal macrophages in the central nervous system. J Neuroimmunol. 2001; 116:188–195. [PubMed: 11438173]

Powell MJ, Thompson SA, Tone Y, Waldmann H, Tone M. Posttranscriptional regulation of IL-10 gene expression through sequences in the 3′-untranslated region. J Immunol. 2000; 165:292–296. [PubMed: 10861064]

Qian L, Block ML, Wei SJ, Lin CF, Reece J, Pang H, Wilson B, Hong JS, Flood PM. Interleukin-10 protects lipopolysaccharide-induced neurotoxicity in primary midbrain cultures by inhibiting the function of NADPH oxidase. J Pharmacol Exp Ther. 2006a; 319:44–52. [PubMed: 16807359]

Qian L, Hong JS, Flood PM. Role of microglia in inflammation-mediated degeneration of dopaminergic neurons: neuroprotective effect of interleukin 10. J Neural Transm Suppl. 2006b: 367–371. [PubMed: 17017555]

Rao SS, Hofmann LA, Shakil A. Parkinson's disease: diagnosis and treatment. Am Fam Physician. 2006; 74:2046–2054. [PubMed: 17186710]

Reineke U, Schneider-Mergener J, Glaser RW, Stigler RD, Seifert M, Volk HD, Sabat R. Evidence for conformationally different states of interleukin-10: binding of a neutralizing antibody enhances accessibility of a hidden epitope. J Mol Recognit. 1999; 12:242–248. [PubMed: 10440995]

Rentzos M, Nikolaou C, Andreadou E, Paraskevas GP, Rombos A, Zoga M, Tsoutsou A, Boufidou F, Kapaki E, Vassilopoulos D. Circulating interleukin-10 and interleukin-12 in Parkinson's disease. Acta Neurol Scand. 2009; 119:332–337. [PubMed: 18976327]

Rieckmann P, Albrecht M, Kitze B, Weber T, Tumani H, Broocks A, Luer W, Poser S. Cytokine mRNA levels in mononuclear blood cells from patients with multiple sclerosis. Neurology. 1994; 44:1523–1526. [PubMed: 8058164]

Riyazi N, Slagboom E, de Craen AJ, Meulenbelt I, Houwing-Duistermaat JJ, Kroon HM, van Schaardenburg D, Rosendaal FR, Breedveld FC, Huizinga TW, Kloppenburg M. Association of the risk of osteoarthritis with high innate production of interleukin-1beta and low innate production of interleukin-10 ex vivo, upon lipopolysaccharide stimulation. Arthritis Rheum. 2005; 52:1443–1450. [PubMed: 15880595]

Rogers NC, Slack EC, Edwards AD, Nolte MA, Schulz O, Schweighoffer E, Williams DL, Gordon S, Tybulewicz VL, Brown GD, Reis e Sousa C. Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. Immunity. 2005; 22:507–517. [PubMed: 15845454]

Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK. Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol Rev. 2006; 212:28–50. [PubMed: 16903904]

Rott O, Fleischer B, Cash E. Interleukin-10 prevents experimental allergic encephalomyelitis in rats. Eur J Immunol. 1994; 24:1434–1440. [PubMed: 7515815]

Rowbotham MC, Fields HL. The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia. Brain J Neurol. 1996; 119(Pt 2):347–354.

Sabat R, Grutz G, Warszawska K, Kirsch S, Witte E, Wolk K, Geginat J. Biology of interleukin-10. Cytokine Growth Factor Rev. 2010; 21:331–344. [PubMed: 21115385]

Salaffi F, Ciapetti A, Carotti M. The sources of pain in osteoarthritis: a pathophysiological review. Reumatismo. 2014; 66:57–71. [PubMed: 24938198]

Salengros JC, Huybrechts I, Ducart A, Faraoni D, Marsala C, Barvais L, Cappello M, Engelman E. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. J Cardiothorac Vasc Anesth. 2010; 24:608–616. [PubMed: 20005744]

Samoilova EB, Horton JL, Chen Y. Acceleration of experimental autoimmune encephalomyelitis in interleukin-10-deficient mice: roles of interleukin-10 in disease progression and recovery. Cell Immunol. 1998; 188:118–124. [PubMed: 9756642]

Saraiva M, Christensen JR, Veldhoen M, Murphy TL, Murphy KM, O'Garra A. Interleukin-10 production by Th1 cells requires interleukin-12-induced STAT4 transcription factor and ERK MAP kinase activation by high antigen dose. Immunity. 2009; 31:209–219. [PubMed: 19646904]

Saraiva M, O'Garra A. The regulation of IL-10 production by immune cells. Nat Rev Immunol. 2010; 10:170–181. [PubMed: 20154735]

Schif-Zuck S, Wildbaum G, Karin N. Coadministration of plasmid DNA constructs encoding an encephalitogenic determinant and IL-10 elicits regulatory T cell-mediated protective immunity in the central nervous system. J Immunol. 2006; 177:8241–8247. [PubMed: 17114502]

Schuetze N, Schoeneberger S, Mueller U, Freudenberg MA, Alber G, Straubinger RK. IL-12 family members: differential kinetics of their TLR4-mediated induction by Salmonella enteritidis and the impact of IL-10 in bone marrow-derived macrophages. Int Immunol. 2005; 17:649–659. [PubMed: 15837713]

Schulte LN, Eulalio A, Mollenkopf HJ, Reinhardt R, Vogel J. Analysis of the host microRNA response to Salmonella uncovers the control of major cytokines by the let-7 family. EMBO J. 2011; 30:1977–1989. [PubMed: 21468030]

Schwenkgrub J, Joniec-Maciejak I, Sznejder-Pacholek AWawer A, Ciesielska A, Bankiewicz K, Czlonkowska A, Czlonkowski A. Effect of human interleukin-10 on the expression of nitric oxide synthases in the MPTP-based model of Parkinson's disease. Pharmacol Reports P R. 2013; 65:44–49.

Sebestyen MG, Ludtke JJ, Bassik MC, Zhang G, Budker V, Lukhtanov EA, Hagstrom JE, Wolff JA. DNA vector chemistry: the covalent attachment of signal peptides to plasmid DNA. Nat Biotechnol. 1998; 16:80–85. [PubMed: 9447599]

Sendil D, Bonney IM, Carr DB, Lipkowski AW, Wise DL, Hasirci V. Antinociceptive effects of hydromorphone, bupivacaine and biphalin released from PLGA polymer after intrathecal implantation in rats. Biomaterials. 2003; 24:1969–1976. [PubMed: 12615487]

Sharma A, Kumar M, Aich J, Hariharan M, Brahmachari SK, Agrawal A, Ghosh B. Posttranscriptional regulation of interleukin-10 expression by hsa-miR-106a. Proc Natl Acad Sci U S A. 2009; 106:5761–5766. [PubMed: 19307576]

Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. Curr Opin Rheumatol. 2006; 18:147–156. [PubMed: 16462520]

Sharma S, Yang B, Xi X, Grotta JC, Aronowski J, Savitz SI. IL-10 directly protects cortical neurons by activating PI-3 kinase and STAT-3 pathways. Brain Res. 2011; 1373:189–194. [PubMed: 21138740]

Shen KF, Zhu HQ, Wei XH, Wang J, Li YY, Pang RP, Liu XG. Interleukin-10 down-regulates voltage gated sodium channels in rat dorsal root ganglion neurons. Exp Neurol. 2013; 247:466–475. [PubMed: 23357618]

Shi L, Tang GP, Gao SJ, Ma YX, Liu BH, Li Y, Zeng JM, Ng YK, Leong KW, Wang S. Repeated intrathecal administration of plasmid DNA complexed with polyethylene glycol-grafted polyethylenimine led to prolonged transgene expression in the spinal cord. Gene Ther. 2003; 10:1179–1188. [PubMed: 12833127]

Shrestha R, Shakya Shrestha S, Millingtona O, Brewer J, Bushell T. Immune responses in neurodegenerative diseases. Kathmandu Univ Med J. 2014; 12:67–76.

Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Investig. 2012; 122:787–795. [PubMed: 22378047]

Slack EC, Robinson MJ, Hernanz-Falcon P, Brown GD, Williams DL, Schweighoffer E, Tybulewicz VL, Reis e Sousa C. Syk-dependent ERK activation regulates IL-2 and IL-10 production by DC stimulated with zymosan. Eur J Immunol. 2007; 37:1600–1612. [PubMed: 17458858]

Sloane E, Langer S, Jekich B, Mahoney J, Hughes T, Frank M, Seibert W, Huberty G, Coats B, Harrison J, Klinman D, Poole S, Maier S, Johnson K, Chavez R, Watkins LR, Leinwand L, Milligan E. Immunological priming potentiates non-viral anti-inflammatory gene therapy treatment of neuropathic pain. Gene Ther. 2009a; 16:1210–1222. [PubMed: 19571887]

Sloane E, Ledeboer A, Seibert W, Coats B, van Strien M, Maier SF, Johnson KW, Chavez R, Watkins LR, Leinwand L, Milligan ED, Van Dam AM. Anti-inflammatory cytokine gene therapy decreases sensory and motor dysfunction in experimental Multiple Sclerosis: MOG-EAE behavioral and anatomical symptom treatment with cytokine gene therapy. Brain Behav Immun. 2009b; 23:92–100. [PubMed: 18835435]

Sloane EM, Soderquist RG, Maier SF, Mahoney MJ, Watkins LR, Milligan ED. Long-term control of neuropathic pain in a non-viral gene therapy paradigm. Gene Ther. 2009c; 16:470–475. [PubMed: 19262611]

Smeets TJ, Kraan MC, Versendaal J, Breedveld FC, Tak PP. Analysis of serial synovial biopsies in patients with rheumatoid arthritis: description of a control group without clinical improvement after treatment with interleukin 10 or placebo. J Rheumatol. 1999; 26:2089–2093. [PubMed: 10529122]

Soderquist RG, Milligan ED, Harrison JA, Chavez RA, Johnson KW, Watkins LR, Mahoney MJ. PEGylation of interleukin-10 for the mitigation of enhanced pain states. J Biomed Mater Res Part A. 2010a; 93:1169–1179.

Soderquist RG, Sloane EM, Loram LC, Harrison JA, Dengler EC, Johnson SM, Amer LD, Young CS, Lewis MT, Poole S, Frank MG, Watkins LR, Milligan ED, Mahoney MJ. Release of plasmid DNA-encoding IL-10 from PLGA microparticles facilitates long-term reversal of neuropathic pain following a single intrathecal administration. Pharm Res. 2010b; 27:841–854. [PubMed: 20224990]

Spence S, Fitzsimons A, Boyd CR, Kessler J, Fitzgerald D, Elliott J, Gabhann JN, Smith S, Sica A, Hams E, Saunders SP, Jefferies CA, Fallon PG, McAuley DF, Kissenpfennig A, Johnston JA. Suppressors of cytokine signaling 2 and 3 diametrically control macrophage polarization. Immunity. 2013; 38:66–78. [PubMed: 23177319]

Syto R, Murgolo NJ, Braswell EH, Mui P, Huang E, Windsor WT. Structural and biological stability of the human interleukin 10 homodimer. Biochemistry. 1998; 37:16943–16951. [PubMed: 9836587]

Tanuma N, Shin T, Matsumoto Y. Characterization of acute versus chronic relapsing autoimmune encephalomyelitis in DA rats. J Neuroimmunol. 2000; 108:171–180. [PubMed: 10900351]

Tarazi FI, Sahli Z, Wolny M, Mousa SA. Emerging therapies for Parkinson's disease: from bench to bedside. Pharmacol Ther. 2014a; 144:123–133. [PubMed: 24854598]

Tarazi FI, Sahli ZT, Wolny M, Mousa SA. Emerging therapies for Parkinson's disease: from bench to bedside. Pharmacol Ther. 2014b; 144:123–133. [PubMed: 24854598]

Taruc-Uy RL, Lynch SA. Diagnosis and treatment of osteoarthritis. Prim Care. 2013; 40:821–836. (vii). [PubMed: 24209720]

Taskinen HS, Olsson T, Bucht A, Khademi M, Svelander L, Roytta M. Peripheral nerve injury induces endoneurial expression of IFN-gamma, IL-10 and TNF-alpha mRNA. J Neuroimmunol. 2000; 102:17–25. [PubMed: 10626662]

Taylor RS. Epidemiology of refractory neuropathic pain. Pain Pract Off J World Inst Pain. 2006; 6:22–26.

Thibodeau J, Bourgeois-Daigneault MC, Huppe G, Tremblay J, Aumont A, Houde M, Bartee E, Brunet A, Gauvreau ME, de Gassart A, Gatti E, Baril M, Cloutier M, Bontron S, Fruh K, Lamarre D, Steimle V. Interleukin-10-induced MARCH1 mediates intracellular sequestration of MHC class II in monocytes. Eur J Immunol. 2008; 38:1225–1230. [PubMed: 18389477]

Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. Lancet Neurol. 2006; 5:75–86. [PubMed: 16361025]

Trevino CM, de Roon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? J Pain Off J Am Pain Soc. 2013; 14:424–430.

Tukhovskaya EA, Turovsky EA, Turovskaya MV, Levin SG, Murashev AN, Zinchenko VP, Godukhin OV. Anti-inflammatory cytokine interleukin-10 increases resistance to brain ischemia through modulation of ischemia-induced intracellular Ca response. Neurosci Lett. 2014; 571:55–60. [PubMed: 24796809]

Turovskaya MV, Turovsky EA, Zinchenko VP, Levin SG, Godukhin OV. Interleukin-10 modulates [Ca2+]i response induced by repeated NMDA receptor activation with brief hypoxia through inhibition of InsP(3)-sensitive internal stores in hippocampal neurons. Neurosci Lett. 2012; 516:151–155. [PubMed: 22498075]

Uceyler N, Rogausch JP, Toyka KV, Sommer C. Differential expression of cytokines in painful and painless neuropathies. Neurology. 2007; 69:42–49. [PubMed: 17606879]

van Boxel-Dezaire AH, Hoff SC, van Oosten BW, Verweij CL, Drager AM, Ader HJ, van Houwelingen JC, Barkhof F, Polman CH, Nagelkerken L. Decreased interleukin-10 and increased interleukin-12p40 mRNA are associated with disease activity and characterize different disease stages in multiple sclerosis. Ann Neurol. 1999; 45:695–703. [PubMed: 10360761]

van Gulik L, Ahlers SJ, van de Garde EM, Bruins P, van Boven WJ, Tibboel D, van Dongen EP, Knibbe CA. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth. 2012; 109:616–622. [PubMed: 22831889]

van Roon J, Wijngaarden S, Lafeber FP, Damen C, van de Winkel J, Bijlsma JW. Interleukin 10 treatment of patients with rheumatoid arthritis enhances Fc gamma receptor expression on monocytes and responsiveness to immune complex stimulation. J Rheumatol. 2003; 30:648–651. [PubMed: 12672180]

Vincenzi F, Corciulo C, Targa M, Casetta I, Gentile M, Granieri E, Borea PA, Popoli P, Varani K. A2A adenosine receptors are up-regulated in lymphocytes from amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener. 2013a; 14:406–413. [PubMed: 23679925]

Vincenzi F, Corciulo C, Targa M, Merighi S, Gessi S, Casetta I, Gentile M, Granieri E, Borea PA, Varani K. Multiple sclerosis lymphocytes upregulate A2A adenosine receptors that are antiinflammatory when stimulated. Eur J Immunol. 2013b; 43:2206–2216. [PubMed: 23661562]

Wagner R, Janjigian M, Myers RR. Anti-inflammatory interleukin-10 therapy in CCI neuropathy decreases thermal hyperalgesia, macrophage recruitment, and endoneurial TNF-alpha expression. Pain. 1998; 74:35–42. [PubMed: 9514558]

Walter MR, Nagabhushan TL. Crystal structure of interleukin 10 reveals an interferon gamma-like fold. Biochemistry. 1995; 34:12118–12125. [PubMed: 7547951]

Wang YC, He F, Feng F, Liu XW, Dong GY, Qin HY, Hu XB, Zheng MH, Liang L, Feng L, Liang YM, Han H. Notch signaling determines the M1 versus M2 polarization of macrophages in antitumor immune responses. Cancer Res. 2010; 70:4840–4849. [PubMed: 20501839]

Wang ZH, Zeng XY, Han SP, Fan GX, Wang JY. Interleukin-10 of red nucleus plays anti-allodynia effect in neuropathic pain rats with spared nerve injury. Neurochem Res. 2012; 37:1811–1819. [PubMed: 22584848]

Watkins LR, Hutchinson MR, Rice KC, Maier SF. The “toll” of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. Trends Pharmacol Sci. 2009; 30:581–591. [PubMed: 19762094]

Waubant E, Gee L, Bacchetti P, Sloan R, Cotleur A, Rudick R, Goodkin D. Relationship between serum levels of IL-10, MRI activity and interferon beta-1a therapy in patients with relapsing remitting MS. J Neuroimmunol. 2001; 112:139–145. [PubMed: 11108942]

Weber-Nordt RM, Riley JK, Greenlund AC, Moore KW, Darnell JE, Schreiber RD. Stat3 recruitment by two distinct ligand-induced, tyrosine-phosphorylated docking sites in the interleukin-10 receptor intracellular domain. J Biol Chem. 1996; 271:27954–27961. [PubMed: 8910398]

Wehinger J, Gouilleux F, Groner B, Finke J, Mertelsmann R, Weber-Nordt RM. IL-10 induces DNA binding activity of three STAT proteins (Stat1, Stat3, and Stat5) and their distinct combinatorial assembly in the promoters of selected genes. FEBS Lett. 1996; 394:365–370. [PubMed: 8830676]

Whalen JD, Lechman EL, Carlos CA, Weiss K, Kovesdi I, Glorioso JC, Robbins PD, Evans CH. Adenoviral transfer of the viral IL-10 gene periarticularly to mouse paws suppresses development of collagen-induced arthritis in both injected and uninjected paws. J Immunol. 1999; 162:3625–3632. [PubMed: 10092823]

Whyte CS, Bishop ET, Ruckerl D, Gaspar-Pereira S, Barker RN, Allen JE, Rees AJ, Wilson HM. Suppressor of cytokine signaling (SOCS)1 is a key determinant of differential macrophage activation and function. J Leukoc Biol. 2011; 90:845–854. [PubMed: 21628332]

Wilkerson JL, Gentry KR, Dengler EC, Wallace JA, Kerwin AA, Armijo LM, Kuhn MN, Thakur GA, Makriyannis A, Milligan ED. Intrathecal cannabilactone CB(2)R agonist, AM1710, controls pathological pain and restores basal cytokine levels. Pain. 2012a; 153:1091–1106. [PubMed: 22425445]

Wilkerson JL, Gentry KR, Dengler EC, Wallace JA, Kerwin AA, Kuhn MN, Zvonok AM, Thakur GA, Makriyannis A, Milligan ED. Immunofluorescent spectral analysis reveals the intrathecal cannabinoid agonist, AM1241, produces spinal anti-inflammatory cytokine responses in neuropathic rats exhibiting relief from allodynia. Brain Behav. 2012b; 2:155–177. [PubMed: 22574283]

Windsor WT, Syto R, Tsarbopoulos A, Zhang R, Durkin J, Baldwin S, Paliwal S, Mui PW, Pramanik B, Trotta PP, et al. Disulfide bond assignments and secondary structure analysis of human and murine interleukin 10. Biochemistry. 1993; 32:8807–8815. [PubMed: 8364028]

Wolk K, Kunz S, Asadullah K, Sabat R. Cutting edge: immune cells as sources and targets of the IL-10 family members? J Immunol. 2002; 168:5397–5402. [PubMed: 12023331]

Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. Immunity. 2004; 21:241–254. [PubMed: 15308104]

Wolk K, Witte E, Reineke U, Witte K, Friedrich M, Sterry W, Asadullah K, Volk HD, Sabat R. Is there an interaction between interleukin-10 and interleukin-22? Genes Immun. 2005; 6:8–18. [PubMed: 15526001]

Wood MJ, Charlton HM, Wood KJ, Kajiwara K, Byrnes AP. Immune responses to adenovirus vectors in the nervous system. Trends Neurosci. 1996; 19:497–501. [PubMed: 8931276]

Xiao BG, Bai XF, Zhang GX, Link H. Suppression of acute and protracted-relapsing experimental allergic encephalomyelitis by nasal administration of low-dose IL-10 in rats. J Neuroimmunol. 1998; 84:230–237. [PubMed: 9628468]

Yan J, Fu Q, Cheng L, Zhai M, Wu W, Huang L, Du G. Inflammatory response in Parkinson's disease (Review). Mol Med Reports. 2014; 10:2223–2233.

Yao SQ, Li ZZ, Huang QY, Li F, Wang ZW, Augusto E, He JC, Wang XT, Chen JF, Zheng RY. Genetic inactivation of the adenosine A(2A) receptor exacerbates brain damage in mice with experimental autoimmune encephalomyelitis. J Neurochem. 2012; 123:100–112. [PubMed: 22639925]

Yoon SI, Jones BC, Logsdon NJ, Harris BD, Deshpande A, Radaeva S, Halloran BA, Gao B, Walter MR. Structure and mechanism of receptor sharing by the IL-10R2 common chain. Structure. 2010; 18:638–648. [PubMed: 20462497]

Yoon SI, Logsdon NJ, Sheikh F, Donnelly RP, Walter MR. Conformational changes mediate interleukin-10 receptor 2 (IL-10R2) binding to IL-10 and assembly of the signaling complex. J Biol Chem. 2006; 281:35088–35096. [PubMed: 16982608]

Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signalling and immune regulation. Nat Rev Immunol. 2007; 7:454–465. [PubMed: 17525754]

Zdanov A. Structural analysis of cytokines comprising the IL-10 family. Cytokine Growth Factor Rev. 2010; 21:325–330. [PubMed: 20846897]

Zdanov A, Schalk-Hihi C, Gustchina A, Tsang M, Weatherbee J, Wlodawer A. Crystal structure of interleukin-10 reveals the functional dimer with an unexpected topological similarity to interferon gamma. Structure. 1995; 3:591–601. [PubMed: 8590020]

Zhang J, Shi XQ, Echeverry S, Mogil JS, De Koninck Y, Rivest S. Expression of CCR2 in both resident and bone marrow-derived microglia plays a critical role in neuropathic pain. J Neurosci. 2007; 27:12396–12406. [PubMed: 17989304]

Zhang X, Mao Z, Yu C. Suppression of early experimental osteoarthritis by gene transfer of interleukin-1 receptor antagonist and interleukin-10. J Orthop Res Off Publ Orthop Res Soc. 2004; 22:742–750.

Zhou Z, Peng X, Insolera R, Fink DJ, Mata M. Interleukin-10 provides direct trophic support to neurons. J Neurochem. 2009; 110:1617–1627. [PubMed: 19575707]

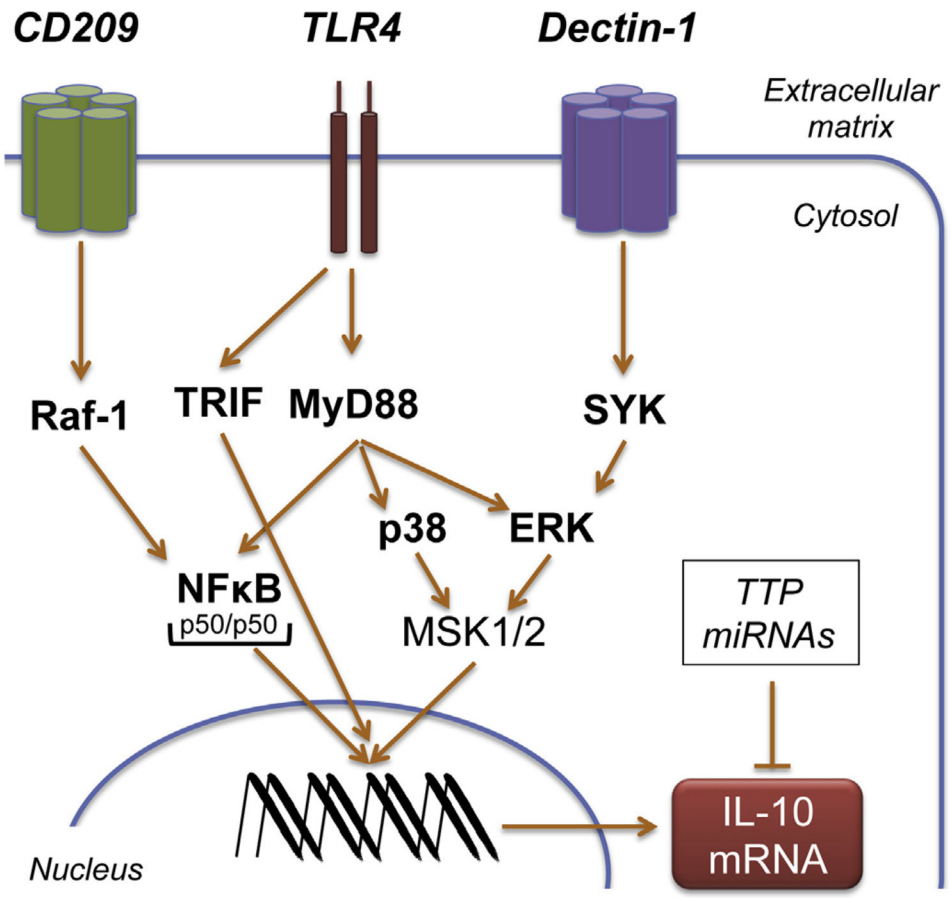

Fig. 1.

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).

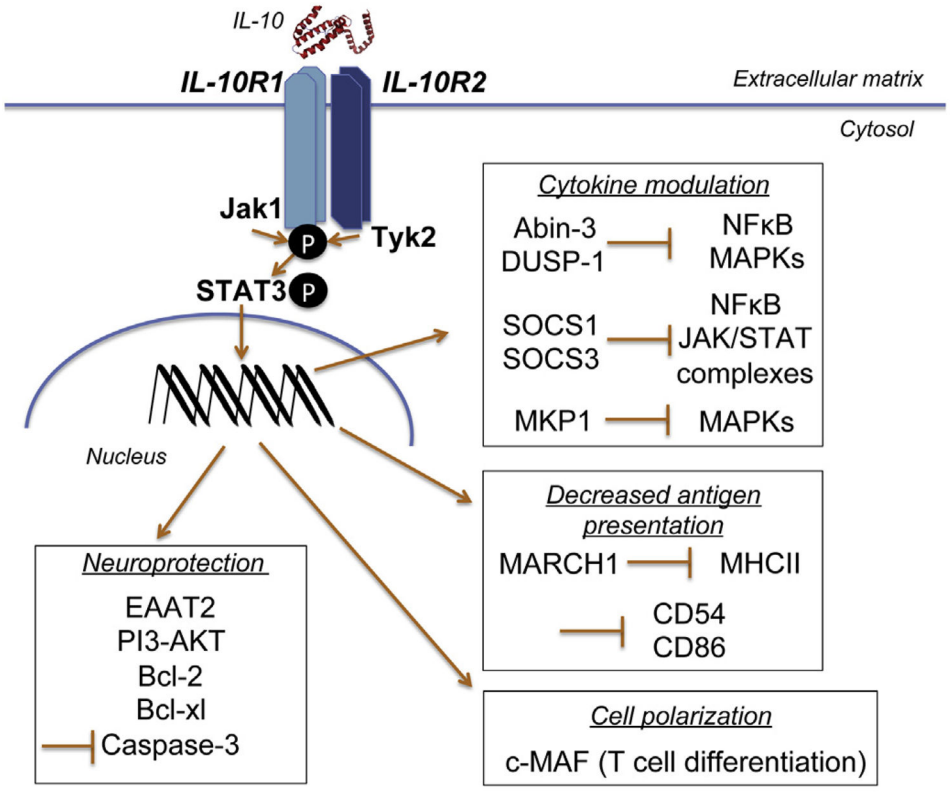

Fig. 2.

Interleukin-10 (IL-10) receptor signaling. IL-10 exerts effects through a heterotetramer consisting of two IL-10 receptor 1 (IL-10R1) chains and two IL-10 receptor 2 (IL-10R2) chains. IL-10R1 activates Janus kinase 1 (Jak1), while IL-10R2 activates tyrosine kinase 2 (Tyk2), leading to phosphorylation of IL-10R1 followed by phosphorylation of STAT3 (other STAT proteins have also been implicated including STAT4 in T_H1 cells; STAT6 and GATA3 in T_H2 cells; and, STAT1 and STAT3 in T_H17 cells). Such signaling results in diverse consequences, such as a) cytokine modulation by the induction of A20-binding inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) (Abin-3) and dual specificity phosphatase-1 (DUSP-1) that inhibit mitogen activated protein kinase (MAPK) phosphorylation as well as NFkB. Suppressor of cytokine signaling (SOCS) 1 and 3 are also produced which target the p65 NFκB subunit for degradation and mark activated JAK-STAT complexes for degradation. Mitogen activated protein kinase (MAPK) phosphatase (MKP) expression, including MKP1, is elevated to inhibit MAPK signaling; b) decreased antigen presentation by reducing expression of major histocompatibility complex class II (MHC II) molecules by inducing membrane-associated RING-CH (MARCH) 1 and by inhibiting expression of adhesion (e.g. CD54) and co-stimulatory (e.g. CD86) molecules c) cell polarization via induction of transcription factors such as c-MAF, and d) neuroprotection by normalizing expression of excitatory amino acid transporter-2 (EAAT2), by releasing intracellular calcium stores via PI3K-AKT, by preventing apoptosis through restoration of suppressed anti-apoptotic factors Bcl-2 and Bcl-xl, and by attenuating caspase-3 expression.

Table 1

Summary of studies in which IL-10-based therapy was used in animal models of neuropathic pain.

Neuropathic Pain							
Model	**Sex**	**Treatment**	**Dose/route**	**Time of treatment**	**Effect**	**Duration of effect**	**Reference**
SD rats (CCI)	Female	IL-10 (n/s)	250 ng, peri-sciatic nerve	0 DPI	↓ Thermal hyperalgesia	~7 days	Wagner et al., 1998
SD rats (CCI)	Male	hIL-10	50 –> 500 – > 500 ng, IT	10 –> 11 –> 12 DPI	↓ Mechanical allodynia (each injection) ↓ Thermal hyperalgesia (2nd/3rd injection)	~2 h	Milligan et al., 2005a
SD rats (CCI)	Male	AD-hIL-10	5 × 10^7 PFU, IT	10 DPI	↓ Mechanical allodynia ↓ Thermal hyperalgesia	~10 days (mechanical allodynia) ~3–5 days (thermal hyperalgesia)	Milligan et al., 2005a
SD rats (SIN)	Male	AD-hIL-10	5 × 10^7 PFU, IT	Immediately pre-zymosan injection	↓Mechanical allodynia	24 h (ET)	Milligan et al., 2005a
SD rats (SIN)	Male	AD-hIL-10	5 × 10^7 PFU, IT	1 day post-zymosan injection	↓Mechanical allodynia	~3 days (ET)	Milligan et al., 2005a
SD rats (CCI)	Male	AAV2-rIL-10	8.5 × 10^8 IPs, IT	10 DPI	↓Mechanical allodynia/thermal hyperalgesia	~12 days (allodynia) ~14 days (thermal hyperalgesia)	Milligan et al., 2005b
SD rats (SIN)	Male	AAV2-rIL-10	8.5 × 10^8 IPs, IT	2 days pre-zymosan	↓Mechanical allodynia	~7–8 days	Milligan et al., 2005b
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 μg × 4, IT	10 –> 14 –> 22 – > 64 DPI	↓Mechanical allodynia	Each injection lasted until subsequent injection, final injection 5 days (ET)	Milligan et al., 2006a
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 μg × 2, IT	10 –> 13 DPI	↓Mechanical allodynia	~45–47 days (ET)	Milligan et al., 2006a
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 μg × 2, IT	58 –> 61 DPI	↓Mechanical allodynia	~7–35 days (unreliable effect)	Milligan et al., 2006a
SD rats (CCI)	Male	pDNA-rIL-10-F129S	1 μg × 2, IT	10 –> 13 DPI	No effect	N/A	Milligan et al., 2006b
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 μg × 2, IT	10 –> 13 DPI	↓Mechanical allodynia	~31 days	Milligan et al., 2006b
SD rats (CCI)	Male	PEI-pDNA-rIL-10-F129S	5 μg, IT	10 DPI	↓Mechanical allodynia	~11 days	Milligan et al., 2006b
SD rats (CCI)	Male	PEI-pDNA-rIL-10-F129S	5 μg × 2, IT	10 –> 13 DPI	↓Mechanical allodynia	~27–30 days	Milligan et al., 2006b
SD rats (CCI)	Male	XT-101	400 ng, IT	10 DPI	↓Mechanical allodynia	~28–29 days (ET)	Milligan et al., 2006b
SD rats (PIN)	Male	pDNA-rIL-10-F129S	100 –> 25 μg, IT	35 –> 38 DPI	↓Mechanical allodynia	~32–37 days	Ledeboer et al., 2007
SD rats (CCI)	Male	Control pDNA – > pDNA-rIL-10-F129S	100–>25 μg, IT	10 –> 13 DPI	↓Mechanical allodynia	~89 days (ET)	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S – > Control pDNA	100 –> 25 μg, IT	10 –> 13 DPI	↓Mechanical allodynia	~3–4 days	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 –> 25 μg, IT	10 –> 13 DPI	↓Mechanical allodynia	~93 days (ET)	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 –> 1 μg, IT	10 –> 13 DPI	↓Mechanical allodynia	~77–85 days	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 –> 25 μg, IT	10 DPI–>2 h post 1st injection	↓Mechanical allodynia	~6 days	Sloane et al., 2009

Neuropathic Pain							
Model	**Sex**	**Treatment**	**Dose/route**	**Time of treatment**	**Effect**	**Duration of effect**	**Reference**
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 –> 25 μg, IT	10 DPI–>5 h post 1st injection	↓Mechanical allodynia	~58 days (ET)	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	125 μg, IT	10 DPI	↓Mechanical allodynia	~6 days	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 (pDNA) –> 0.2 (anti-IL-10) –> 25 (pDNA) μg, IT	10 DPI–>1 h after 1st injection –>13 DPI	↓Mechanical allodynia (pDNA) reversed acute/sustained pDNA antinociception (anti-IL-10)	~1 day after each injection (pDNA) ~1 day/~29 days (ET) (anti-IL-10)	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	100 –> 25 μg (pDNA) –> 0.2 μg (anti-IL-10), IT	10 –> 13 (pDNA) – > 23 (anti-IL-10) DPI	↓Mechanical allodynia (pDNA) reversed sustained pDNA antinociception (anti-IL-10)	~23 days (pDNA) ~31 days (ET) (anti-IL-10)	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	25 –> 25 –> 25 μg, IT	10 –> 13–> 45 DPI	↓Mechanical allodynia	Each injection lasted until subsequent injection, final injection 47 days (ET)	Sloane et al., 2009
SD rats (CCI)	Male	pDNA-rIL-10-F129S	25 –> 25 –> 25 μg, IT	10 –> 13–> 61 DPI	↓Mechanical allodynia	1st and 2nd injections lasted ~28 days, final injection had no effect	Sloane et al., 2009
SD rats (CCI)	Male	XT-101 (rat)	8.8 μg, IT	10 DPI	↓Mechanical allodynia	~73–81 days	Soderquist et al., 2010
SD rats (SNI)	Male	rIL-10	0.5–5 μg, intra-red nucleus	21 DPI	↓Mechanical allodynia	30–60 min	Wang et al., 2012
SD rats (SCI)	Male	HSV-rIL-10	2×10^8 PFU, IPL	7 DPI	↓Mechanical allodynia/hyperalgesia and thermal hyperalgesia ↓Operant conflict avoidance	~28 days (allodynia/hyperalgesia) (ET) *only tested on day 35 (operant conflict avoidance)	Lau et al., 2012
SD rats (L5/L6 SNL)	Male	rIL-10	0.1–1 μg, IT	1–7 DPI (daily) (each injection 1 h before testing)	↓Mechanical allodynia	N/A	Lee et al., 2013
SD rats (L5/L6 SNL)	Male	rIL-10	7 μg, IT	7 DPI (injection 1 h before testing)	No effect	N/A	Lee et al., 2013
SD rats (L5 SNL)	Male	rIL-10	500 ng × 3, IT	7 –> 8 –> 9 DPI (1×/day)	↓Mechanical allodynia	~2 h after each injection	Shen et al., 2013
SD rats (L5 SNL)	Male	rIL-10	500 ng × 12, IT	7 –> 8 –> 9 DPI (4×/day)	↓Mechanical allodynia	~8 days (ET)	Shen et al., 2013
SD rats (CCI)	Male	D-mannose –> pDNA-rIL-10-F129S	50 ug (D-mannose) –> 1 μg (pDNA)	10 (D-mannose) – > 13 (pDNA) DPI	↓Mechanical allodynia	~10 days	Dengler et al., 2014
SD rats (CCI)	Male	D-mannose –> pDNA-rIL-10-F129S	50 ug (D-mannose) –> 25 μg (pDNA)	10 (D-mannose) – > 13 (pDNA) DPI	↓Mechanical allodynia	~92 days (ET)	Dengler et al., 2014
SD rats (CCI)	Male	D-mannose + pDNA-rIL-10-F129S	50 ug (D-mannose) + 1 μg (pDNA)	10 DPI	↓Mechanical allodynia	~23 days (ET)	Dengler et al., 2014
Dog (N/S NP)	Mixed	XT-101 (human)	500 μg, IT	Various	↓Pain-related behaviors	~4 months	Unpublished observations

Abbreviations: ↓: suppression, –>: denotes sequence of injections, AAV: adeno-associated virus, AD: adenovirus, CCI: chronic constriction injury, DPI: days post-injury, ET: experiment terminated before resolution of antinociceptive effect, hIL-10: human IL-10, HSV: herpes simplex virus, IPs: infectious particles, IPL: intraplantar, IT: intrathecal, N/S NP: non-specified neuropathic pain, pDNA: plasmid DNA, PEI: polyethylenimine, PIN: paclitaxel-induced neuropathy, PFU: plaque-forming units, PLGA: poly(lactic-co-glycolic), SCI: T12 blunt laminectomy, SD rat: Sprague–Dawley rat, SIN: sciatic inflammatory neuropathy, SNI: spared nerve-injury, SNL: spinal nerve ligation, rIL-10: rat IL-10 rIL-10-F129S: point mutation rIL-10 variant, xT-101 (rat): PLGA-rat IL-10-F129S, xT-101 (human): PLGA-human IL-10-F129S.

Table 2

Summary of studies in which IL-10-based therapy was used in animal models of osteoarthritis, Parkinson's Disease, and multiple sclerosis.

Model	Sex	Treatment	Dose/route	Time of treatment	Effect	Duration of effect	Reference
Osteoarthritis							
Rabbit (bilateral excision of MCL/medial meniscectomy)	N/S	Synoviocytes transduced with RV-hIL-10	5^7 cells, intra-articular	5 DPI	↓Cartilage breakdown	Only determined at 19 DPI	Zhang et al., 2004
Dogs (N/S OA)	Mixed	XT-101 (human)	800 ug, intra-articular	Various	↓Pain-related behaviors	~4 months	Unpublished observations
Parkinson's disease							
SD rats (intra-substantia nigral LPS)	Male	rIL-10	50 ng/day continuous infusion, intra-substantia nigral	0–14 DPI	↓Dopaminergic cell loss ↓Microglial activation	Only determined 14 DPI	Arimoto et al., 2007
C57/Bl6 mice (IP MPTP)	Male	AAV2-hIL-10	2×10^{10} VGs, intrastriatal	−28 days DPI	↓Striatal tyrosine hydroxylase expression loss	Only determined on days 7 and 21 DPI	Schwenkgrub et al., 2013
Multiple sclerosis							
Lewis rats (MBP, acute)	N/S	hIL-10	5000 units × 3, SC	0, 3, 6 DPI	↓Clinical score ↓Body weight loss	~12 days (clinical score) ~14 days (ET) body weight	Rott et al., 1994
SJL/J mice (MBP lymphocyte transfer, acute)	Female	mIL-10	1 μg, IV	Various	No Effect/↑Clinical score	N/A	Cannella et al., 1996
SJL/J mice (MBP lymphocyte transfer, acute)	Female	anti-IL-10 antibody	100 μg × 3, IP	4–6 DPI	↑Clinical score	N/A	Cannella et al., 1996
SJL/J mice (PLP, acute)	Female	hIL-10	2 μg, IP × 13	0–12 DPI (daily)	↓Clinical score ↓Body weight loss	~21 days (ET) (clinical score/body weight)	Nagelkerken et al., 1997
SJL/J mice (PLP, acute)	Female	hIL-10	2–20 μg, IP × 8	−2–5 DPI (daily)	No Effect	N/A	Nagelkerken et al., 1997
C57Bl/6 mice (MOG_{35-55}, chronic progressive)	Female	IL-10−/−	N/A	N/A	↑Clinical score	~32 days (ET)	Bettelli et al., 1998
$(SJLxFVB)F_1$ mice (PLP, acute)	N/S	IL-10 over-expression under CD2 promoter	N/A	N/A	↓Clinical score	~22 days (ET)	Bettelli et al., 1998
Lewis rats (SCH, acute)	N/S	hIL-10	150 ng × 10, IN	0–9 DPI (daily)	↓Clinical score	~7 days	Xiao et al., 1998
DA Rats (SCH, relapsing-remitting)	N/S	hIL-10	150 ng × 10, IN	0–9 DPI (daily)	↓Clinical score	~35 days (ET)	Xiao et al., 1998
BALB/cAnN (SCH, acute)	N/S	IL-10 over-expression under MHCII promoter	N/A	N/A	↓Clinical score	~120 days (ET)	Cua et al., 1999

Model	Sex	Treatment	Dose/route	Time of treatment	Effect	Duration of effect	Reference
(SJL/J x BALB/cAnN)F_1 (SCH, acute)	N/S	IL-10 over-expression under MHCII promoter	N/A	N/A	↓Clinical score	~16 days (ET)	Cua et al., 1999
Biozzi ABH mice (SCH)	N/S	mIL-10	1 ng/ml ICV	12 DPI	No effect	N/A	Croxford et al., 2001
Biozzi ABH mice (SCH)	N/S	AD5-mIL-10	5×10^4–5×10^6, ICV	12 DPI	No effect	N/A	Croxford et al., 2001
$CSJLF_1$/J (SCH, chronic)	N/S	hIL-10	10 μg × 5, ICV	10–14 DPI (daily)	↓Clinical score	8 days (ET)	Cua et al., 2001
$CSJLF_1$/J (SCH, chronic)	N/S	AD-hIL-10	3×10^9 VPs, ICV	10	↓Clinical score	~15–26 days (ET)	Cua et al., 2001
$CSJLF_1$/J (SCH, chronic)	N/S	AD-hIL-10	3×10^7–3×10^9, IV	10 DPI	No effect	N/A	Cua et al., 2001
$CSJLF_1$/J (SCH, chronic)	N/S	AD-hIL-10	3×10^7–3×10^9 VPs, IN	10 DPI	No effect	N/A	Cua et al., 2001
$CSJLF_1$/J (SCH, chronic)	N/S	AD-hIL-10	3×10^9 VPs, ICV	−2 DPI or 15 DPI	↓Clinical score ↑Survival	~46 days (ET)	Cua et al., 2001
$CSJLF_1$/J (SCH, chronic)	N/S	AD-hIL-10	3×10^9 VPs, ICV	24 DPI	↓Relapse	~21 days (ET)	Cua et al., 2001
DA rats (MOG_{1-125}, relapsing-remitting)	Male	pDNA-rIL-10-F129S	100 μg –> 25 μg, IT	0 DPI –> 3 DPI	↓Clinical score ↓Mechanical allodynia ↓Body weight loss	~19 days (ET) (clinical score) ~15 days (ET) (allodynia) ~3 days (ET) (body weight)	Sloane et al., 2009
DA rats (MOG_{1-125}, relapsing-remitting)	Male	XT-101 (rat)	8 μg, IT	12 DPI	↓Clinical score ↑Survival ↑Wheel-running ↓Social exploration	~18 days (ET) (clinical score) ~14 days (ET) (survival) ~11 days (ET) (wheel-running) Only tested on day 12 (social exploration)	Grace et al., 2012

Abbreviations: ↓ : suppression, ↑: enhancement, –>: denotes sequence of injections, AD: adenovirus, AAV: adeno-associated virus, DA: Dark Agouti rats, DPI: days post-immunization with myelin peptide or homogenate to induce EAE. Plus and minus signify interventions before and after immunization, respectively, ET: experiment terminated before resolution of therapeutic effect, hIL-10: human IL-10, ICV: intracerebroventricular, mIL-10: murine IL-10, IN: intranasal, IP: intraperitoneal, IT: intrathecal, LPS: lipopolysaccharide, MBP: myelin basic protein, MOG: myelin oligodendrocyte glycoprotein, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, N/A: not applicable, NOD mice: non-obese diabetic mice, N/S: not specified, PFU: plaque-forming units, PLGA: poly(lactic-co-glycolic), PLP: proteolipid protein, rIL-10: rat IL-10, rIL-10-F129S: point mutation rat IL-10 variant, SC: subcutaneous, SCH: spinal cord homogenate, SD rat: Sprague–Dawley rat, VGs: Viral/Vector genomes, VPs: viral particles, xT-101 (rat): PLGA-rat IL-10-F129S, xT-101 (human): PLGA-human IL-10-F129S.