Biochimica et Biophysica Acta 1863 (2016) 1218–1227

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

The role of interleukin-6 signaling in nervous tissue

Michelle Rothaug, Christoph Becker-Pauly [1], Stefan Rose-John [*,1]

Institute of Biochemistry, Christian-Albrechts-Universität zu Kiel, Olshausenstrasse 40, D-24098 Kiel, Germany

ARTICLE INFO

Article history:
Received 19 January 2016
Received in revised form 18 March 2016
Accepted 21 March 2016
Available online 23 March 2016

Keywords:
IL-6 signaling
gp130
Multiple sclerosis
Sleep
Neurodegeneration
Trans-signaling

ABSTRACT

The cytokine interleukin-6 (IL-6) plays a critical role in the pathogenesis of inflammatory disorders and in the physiological homeostasis of neural tissue. Profound neuropathological changes, such as multiple sclerosis (MS), Parkinson's and Alzheimer's disease are associated with increased IL-6 expression in brain. Increased nocturnal concentrations of serum IL-6 are found in patients with impaired sleep whereas IL-6-deficient mice spend more time in rapid eye movement sleep associated with dreaming. IL-6 is crucial in the differentiation of oligodendrocytes, regeneration of peripheral nerves and acts as a neurotrophic factor. It exerts its cellular effects through two distinct pathways which include the anti-inflammatory pathway involving the membrane-bound IL-6 receptor (IL-6R) expressed on selective cells, including microglia, in a process known as classical signaling that is also critical for bacterial defense. In classical signaling binding of IL-6 to the membrane-bound IL-6R activates the β-receptor glycoprotein 130 (gp130) and subsequent down-stream signaling. The alternative, rather pro-inflammatory pathway, shown to mediate neurodegeneration in mice, termed trans-signaling, depends on a soluble form of the IL-6R that is capable of binding IL-6 to stimulate a response on distal cells that express gp130. A naturally occurring soluble form of gp130 (sgp130) has been identified that can specifically bind and neutralize the IL-6R/IL-6 complex. Thus, trans-signaling is blocked but classical signaling is completely unaffected. A modified, recombinant dimerized version of sgp130 (sgp130Fc) has successfully been used to block inflammatory processes in mice and may also be used in the clarification of IL-6 trans-signaling in neurological diseases.

1. Introduction

Cytokines are proteins secreted by various cell types, which signal through specific receptors in the regulation of the intensity and duration of the immune response as well as acting as mediators in cellular communication. Some cytokines play a role in signaling within the central nervous system (CNS) in the regulation of sleep, the generation and recall of long-term memory, the focus of attention as well as in neurodegenerative diseases and the integrity of the blood–brain-barrier [1,2]. In this review we focus on the role of IL-6 classical and trans-signaling in nervous tissue, its impact on the onset and progression of neurological disorders, and on potential therapeutic strategies to specifically block either single or both signaling pathways.

2. The pleiotropic nature of interleukin-6

In the mid-eighties several groups reported on cytokines important for the stimulation of B-cells (B-cell stimulatory factor type-2, BSF-2) [3], the growth of virus-infected B cells (interferon-β-2, INFβ-2) [4], regulation of fibrinogen expression in hepatocytes (hepatocyte-stimulating factor, HSF-2) [5] and as a factor released from fibroblasts upon a viral stimulus (the 26-kDa protein) [6]. Almost simultaneous molecular cloning of the cDNA for BSF-2 [7], INFβ-2 [4], HSF-2 [8] and the 26-kDa protein [9] revealed that they represent one identical molecule, now referred to as interleukin-6 (IL-6) [10]. Since then, IL-6 was identified to be involved in tissue regeneration [11–14], inflammation [15–17] and pathogen defense [18]. However, IL-6 signaling is also a major trigger for the onset and progression of many pathological conditions, such as rheumatoid arthritis [19,20], inflammatory bowel disease [21] or sepsis [22], and is therefore a chief focus of pharmaceutical research [23].

IL-6 belongs to a group of four-helical bundle cytokines that includes IL-11, IL-27, leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), neuropoietin and cardiotrophin-like cytokine factor-1 (also known as new neurotrophin 1 and B cell stimulatory factor-3) [24–28]. A cytokine may bind to its corresponding non-signaling α-receptor. This receptor/cytokine complex in turn binds to a β-receptor that sequentially creates a signal. Consequently, cytokines can also be categorized into families based on their target β-receptors. Thus, IL-6 and other cytokines, such as OSM, LIF IL-11 and CT-1, have been grouped into one family as, when in complex with their corresponding α-receptor, they bind a common signal-transducing β-receptor glycoprotein 130 (gp130) [29,30].

* Corresponding author.
E-mail address: rosejohn@biochem.uni-kiel.de (S. Rose-John).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.bbamcr.2016.03.018
0167-4889/

IL-6 is a potent inducer of the hepatic acute phase response [31], is involved in lymphocyte and monocyte differentiation and acts on B-cells, T-cells, hepatocytes and hematopoietic progenitor cells [32]. It also plays a critical role in the normal homeostasis of neuronal tissue as its absence leads to reduced glial activation in traumatic brain injury as well as changes in sleeping behavior [33–35]. On the other hand, IL-6 overproduction in the brain leads to neurodegeneration [36,37].

IL-6 can be secreted by both immune (T-cells, B-cells, macrophages and microglia) [38–41] and non-immune cells (muscle cells, adipocytes, fibroblasts, endothelial cells, neurons) [32,42–45]. In contrast, the IL-6 receptor (IL-6R) is only found on a restricted subset of cell types, including hepatocytes [46], some leukocytes [47] and microglia [48,49] but not on oligodendrocytes [50] or astrocytes [48]. However, the IL-6R also exists as a soluble protein (sIL-6R) either generated via alternative splicing [51,52] or limited proteolysis [53] by metalloproteases [54] including A Disintegrin And Metalloproteinase (ADAM) family members ADAM10 and ADAM17 [55,56] (Fig. 1a). The IL-6R lacks intrinsic signal transduction capacity. Therefore, signaling is induced through the binding of the IL-6/IL-6R complex to its β-receptor gp130, which prevents unwanted, non-specific cellular activation (Fig. 1). In order for the binding of this complex to elicit a cellular response, through the phosphorylation of downstream targets such as JAK/STAT, ERK and PI3 kinase, gp130 must be present at the cell surface [57]. Thus, regulation of signaling is mediated by the availability of the sIL-6R.

3. IL-6 classical versus trans-signaling

IL-6 may stimulate a response in a target cell in two different manners. Classical signaling involves the binding of IL-6 to the membrane-bound IL-6R which initiates dimerization of gp130 and subsequent downstream signaling [58,59] (Fig. 1a). Alternatively, the sIL-6R may form a complex with IL-6 and stimulate distant cells that express gp130 but not surface-bound IL-6R, including most neuronal types, endothelial cells, oligodendrocytes and many other cell types, in a process that is termed trans-signaling [60] (Fig. 1b). Such cells, in the absence of the sIL-6R, would not be able to respond to IL-6. In contrast to the expression of the IL-6R, gp130 is ubiquitously expressed on almost all cell types [61] including astroglial cells [62] and neurons [42]. As we know now, the majority of cells that respond to IL-6 during inflammation do not express the IL-6R and are thus not directly responsive to the cytokine. Therefore, trans-signaling allows cells distal to the source of sIL-6R release to be targeted. As mentioned above, classical signaling is critical for anti-inflammatory signals in contrast to pro-inflammatory trans-signaling. IL-6 trans-signaling differs from classic signaling in its kinetics, often leading to fundamentally different cellular responses [63]. Hepatocytes seem to require IL-6 trans-signaling for tissue regeneration after acute injury [11,12,64]. However, IL-6-mediated neurodegeneration [65], inflammatory colon cancer [15], arthritis [66,67] and inflammatory bowel disease [21,68] are mediated by trans-signaling. Interestingly, a soluble differentially spliced form of gp130 is expressed under normal physiological conditions and is capable of binding the complex of sIL-6R/IL-6 and thus selectively blocking trans-signaling [69,70]. This provides the basis for a therapeutic strategy to block trans-signaling-dependent pro-inflammatory conditions described in Section 7 under “therapeutic targets”.

4. Targets of IL-6 signaling in the nervous system

Low levels of IL-6 are present in brain under physiological conditions. A dramatic increase in expression and secretion of IL-6 is observed during various neurological disorders including Alzheimer's (AD) and Parkinson's disease (PD) [71], brain cancer [72], multiple sclerosis (MS) [73,74] and brain ischemia [75]. Lack of IL-6 signaling plays a critical role in inflammation as well as neuroprotection, demonstrated by decreased glial activation in IL-6-deficient mice in response to traumatic CNS injury [33,35]. However, IL-6 also promotes the differentiation of oligodendrocytes [76–78], acts as a neurotrophic factor [79–82] and is important in the regeneration of peripheral nerves [83]. These functions highlight the pro-survival effect of IL-6 in CNS pathology.

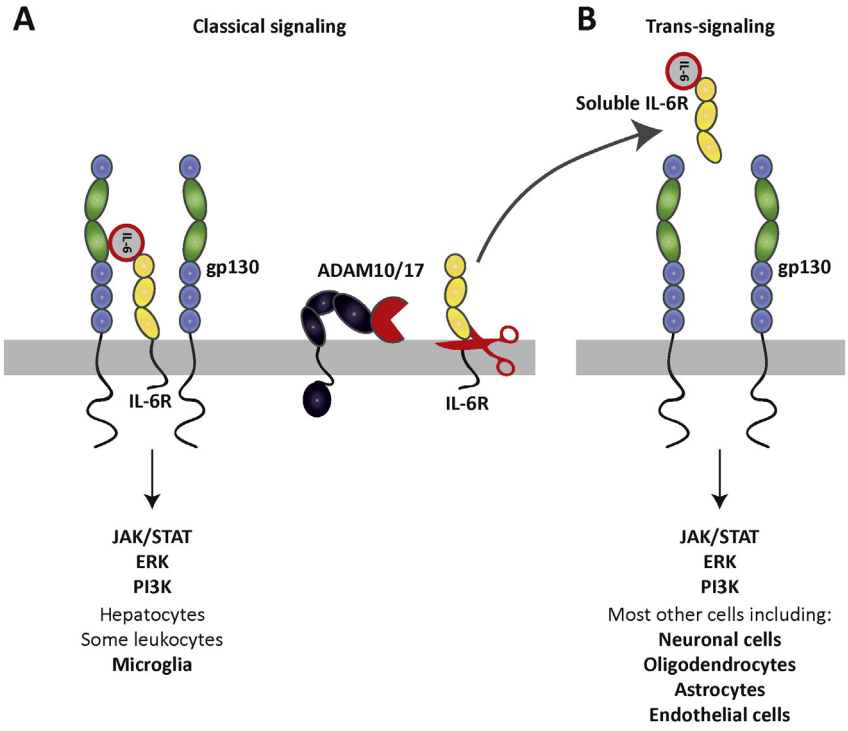

Fig. 1. Overview of IL-6 classical and trans-signaling. (A) In classical signaling, binding of IL-6 to the membrane-bound α-receptor IL-6R causes the dimerization of its β-receptor gp130 which leads to down-stream JAK/STAT signaling in a restricted subset of cells. Shedding of the IL-6R by the ADAMs leads to the liberation of sIL-6R which can bind free IL-6. (B) This complex may then elicit JAK/STAT signaling in distal cells that express gp130 but lack the membrane-bound IL-6R in a process termed trans-signaling.

Interestingly, IL-6-mediated neuronal degeneration [37] depends on trans-signaling in the CNS [65] whereas classical signaling has a regenerative role in neural tissue. This emphasizes the importance of distinguishing between the two pathways when designing drugs for the treatment of neurological diseases. IL-6R mRNA was detected in cultured microglia, astrocytes and neurons [50]. However, IL-6R protein could only be detected in microglial cells [48]. This may be due to the production of the spliced version of the IL-6R that gives rise to soluble receptor [51] and would correlate with reports that sIL-6R transcripts can be detected in human brain [84]. Thus, astrocytes and neurons appear to exclusively express the sIL-6R, which is excreted from the cell and is therefore undetectable in cell lysates. Although IL-6 alone can elicit gp130-mediated signaling in microglial cells, they are also responsive to hyper-IL-6 (a recombinant chimera of IL-6 and the sIL-6R that molecularly mimics trans-signaling) [48,85]. Importantly, classical signaling does not appear to cause the activation of microglial cells in pathological states as they only become pro-inflammatory when exposed to hyper-IL-6 when compared to IL-6 alone [49] highlighting the functional differences between classical and trans-signaling. In fact, classical signaling via IL-6 is hypothesized to have a protective role within the CNS [86] by accelerating nerve regeneration following trauma [83] as well as being neuroprotective following spinal cord injury [87].

5. Neurodegenerative diseases

5.1. Geriatric neurodegenerative diseases

IL-6 is generally altered in the CNS where neuro-inflammation appears to play a role in neurodegenerative disorders such as PD [88,89] and AD [90–92], the most common neurodegenerative disorders in an ageing population. Both conditions are caused by the accumulation of what are believed to be neurotoxic proteins leading ultimately to neuronal death [93,94]. AD is characterized by progressive loss of memory finally culminating in dementia. Neuropathologically, it is described as the accumulation of the β-amyloid peptide (Aβ) (a proteolytic cleavage product of the amyloid precursor protein (APP)) as well as intraneuronal inclusion of phosphorylated Tau [95] where the hippocampus and cortical regions are particularly affected. Both environmental and genetic risk factors play a role in its presentation [96,97]. To date, no treatment is available to prevent the progression of disease.

Aβ can activate glial cells in culture thereby inducing the production of a variety of inflammatory products including IL-6 [98,99]. In fact, intracerebroventricular (ICV) administration of Aβ is enough to elevate IL-6 levels in the periphery [100]. Interestingly, the transcription of APP is stimulated via IL-6 trans-signaling [101]. Furthermore, the addition of IL-6 to culture media significantly increased neurotoxicity caused by Aβ in cortical neurons [102]. However, despite the clear synergistic effect of IL-6 expression and Aβ toxicity shown *in vitro*, the cytokine was shown to be beneficial early in the disease process by potentially enhancing plaque clearance through the activation of astrocytes and microglia *in vivo* [103].

Similarly, IL-6 was previously shown to be neurotrophic [104] in pure cultures of dopaminergic neurons as well as protective against neurotoxic effects elicited by 1-methyl-4-phenylpyridinium (MPP^+), a compound used to mimic the selective neuronal loss observed in PD [79]. In this case signaling is probably mediated via secreted sIL-6R in the media, as discussed in Section 3. PD is pathologically characterized by the loss of dopaminergic motor neurons within the substantia nigra as well as the intraneuronal accumulation of α-synuclein [105]. IL-6-deficient mice were significantly more susceptible to neuronal death in a mouse model where MPP^+ was also used [106], highlighting the importance of IL-6 signaling for the maintenance of healthy neurons. Further studies are necessary to elucidate the role of trans-signaling in the pathogenicity of PD and AD.

5.2. Multiple sclerosis

MS is an inflammatory autoimmune disease with unknown etiology [107] where insulating myelin sheaths are successively destroyed leading to an array of neuropathological symptoms including pain, mental and sometimes psychiatric problems [108]. To date, treatment consists of alleviation of symptoms as well as physical therapy as there is no known cure for the disease. IL-6 signaling was demonstrated to be absolutely essential for the presentation of disease. This was highlighted in IL-6-deficient mice that are completely resistant to induction of MS-like symptoms in a mouse model of experimental autoimmune encephalomyelitis (EAE) [109–111]. Whereas other knockout rodents have shown reduced scores in EAE [112,113], IL-6-deficiency is one of the few knockout mouse strains that shows defective (T-helper) Th_{17} differentiation [114,115]. In fact, Th_{17} responses are also impaired in the absence of IL-6 [116]. Interestingly, IL-6-deficient mice exhibit reduced signs of inflammation at the onset of disease in other autoimmune mouse models such as arthritis [19,20] and irritable bowel syndrome [117] where trans-signaling was blocked.

There are two separate pathological processes that sequentially take place in order for IL-6-dependent EAE symptoms to occur. The initial phase begins in the periphery of the mouse before traversing the blood–brain barrier and entering the CNS (Fig. 2). To establish the contribution of the sources of IL-6 to the development of the disease, Quintana and colleagues analyzed the role of such tissue-localized production of IL-6 in the induction and evolution of EAE, using transgenic mice with astrocyte-targeted production of IL-6 (under the control of a GFAP, glial fibrillary acid protein, promoter) [65]. These GFAP-IL-6 transgenic mice develop neuropathological manifestations including degeneration of the gray and white matter [118]. However, due to strong expression of IL-6 in the cerebellum, ataxia symptoms overshadowed further potential roles of IL-6 in the neuropathology of EAE in other brain regions [37,118]. Additionally, mice expressing IL-6 under the control of a neuron-specific promoter exhibited reactive gliosis as observed in GFAP-IL-6 mice but no neurodegeneration [36] potentially due to dose-dependent effects. GFAP-IL-6 mice have been crossed into the IL-6-deficient background. These GFAP-IL6/IL-6-deficient mice did not show resistance to EAE as observed in IL-6-deficient mice [119]. Rather, they clearly developed symptoms of neurological disease despite restricted expression of IL-6 in nervous tissue. These findings suggest that production of IL-6 in the brain alone may promote an autoimmune response to a CNS antigen in the absence of peripheral IL-6.

Trans-signaling within the CNS is the prevailing mechanism responsible for IL-6-mediated neuropathology in mice [65]. Mice crossed from the GFAP-IL-6 strain with recently generated transgenic mice dubbed GFAP-sgp130Fc (where IL-6 trans-signaling can be distinguished from classic signaling within the CNS (Fig. 3A)) exhibit almost complete abolishment of neurodegenerative changes showing that trans-signaling in the brain is the destructive force behind IL-6-dependent neurodegeneration observed in the GFAP-IL-6 mice [65]. However, we have observed that GFAP-sgp130Fc mice (Fig. 3A) are completely vulnerable to induction of EAE, comparable to wild-type controls (Fig. 3B/C). GFAP-sgp130Fc mice and wild-type controls were immunized with a myelin oligodendrocyte glycoprotein peptide ($MOG_{35–55}$) with complete Freund's adjuvant (CFA) (Hooke laboratories, Lawrence, MA, USA) over a period of 16 days. Disease severity and weight fluctuation was measured for the duration of the experiment. Both genotypes showed the same progression of disease (Fig. 3B) as well as variations in weight (Fig. 3C). Furthermore, an extended experiment where mice were scored for 30 days after immunization showed a similar recovery pattern when comparing both genotypes (data not shown). Therefore, trans-signaling does not play a major role in the pathogenic progression of MS-like symptoms in mice.

Consequently, it is likely that IL-6-dependent signaling (classical and trans-) within the periphery is the main driving force behind the

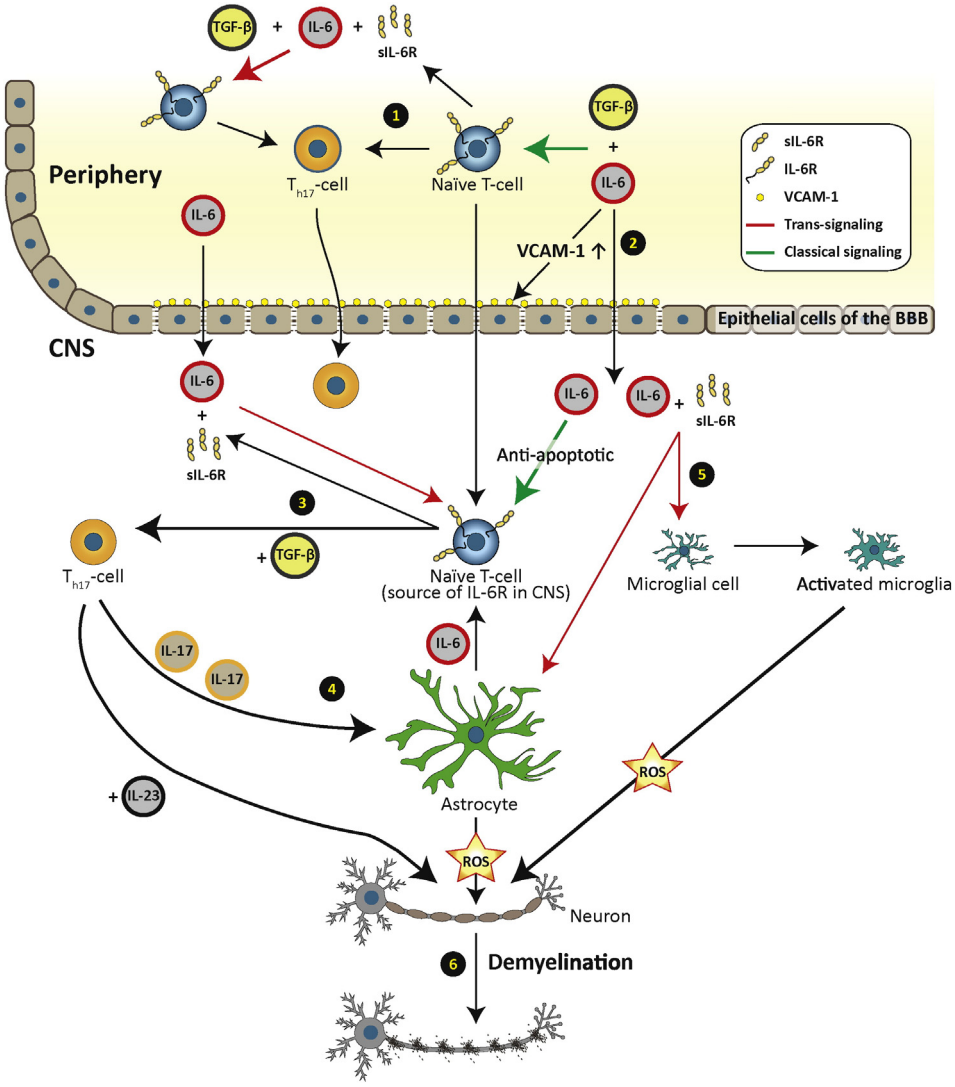

Fig. 2. Overview of the pathogenesis in MS. (1) T-cell response: naïve T-cells are differentiated into Th_{17}-cells after stimulation with IL-6, in combination with TGF-β, in the periphery. During the process of differentiation of naïve T-cells to Th_{17}-cells, sIL-6R is released from the surface. Additionally, trans-signaling (via IL-6 and IL-6R) leads to increased activation of naïve T-cells. (2) Crossing the blood–brain barrier (BBB) via increasing VCAM-1 on endothelial cells: increased levels of IL-6 directly influence the surface expression of the cell adhesion molecule VCAM-1, allowing T-cells to traverse the endothelial layer along with IL-6. (3) T-cell differentiation and secretion of sIL-6R: elevated IL-6 levels leads to differentiation of naïve T-cells that have crossed the BBB. (4) Feed-back activation loop: IL-17 released from Th_{17}-cells leads to activation of astrocytes which release more IL-6 causing a pathological feed-back loop of activated T-cells. (5) Microglial/astrocyte activation: elevated sIL-6R and IL-6 within the CNS also cause the activation of microglia cells and enhance the expression and secretion of IL-6 from astrocytes. (6) Attack of myelin and demyelination of axons: reactive oxygen species (ROS), released from activated astrocytes, in combination with activated microglial and Th_{17}-cells, ultimately leads to demyelination of the axon resulting in descending paralysis. Trans-signaling pathways are highlighted with red arrows. Trans-signaling within the CNS is not critical for progression of disease.

pathogenesis of MS. In fact, during the pathological course of MS T-cells differentiate into Th_{17} cells in a TGF-β/IL-6-dependent manner within the periphery (Fig. 2) [116]. IL-6 controls the balance between regulatory T-cells and Th_{17}-cells [120]. In the absence of IL-6, TGF-β alone induces T-cell differentiation into regulatory T-cells, thus promoting an anti-inflammatory rather than a pro-inflammatory response [110]. Furthermore, the induction of Th_{17}-cells by IL-6 is strongly increased by the presence of sIL-6R indicating a role for trans-signaling in this process [121].

Additionally, injection of an anti-IL-6R monoclonal antibody (clone MR16-1, which blocks both classical and trans-signaling) into the periphery of EAE-induced wild-type mice greatly diminished onset and progression of disease when compared to IgG treated control mice [122]. Furthermore, a study by Linker and colleagues used peripheral treatment of mice with recombinant sgp130Fc (thereby effectively blocking trans-signaling outside of the CNS) while concomitantly inducing EAE. Mice treated with peripheral injection of sgp130Fc exhibited a significantly later onset of symptoms [123]. However, in both EAE studies the symptoms were not completely abolished as was seen in IL-6-deficient mice pointing to a potential minor role of trans-signaling in the CNS (Fig. 2).

In the next step of pathogenesis in MS, the blood–brain-barrier integrity is disrupted via IL-6-mediated upregulation of VCAM-1 [111], allowing T-cells to infiltrate the brain. Interestingly, sIL-6R is produced by activated T-cells [124], thus providing a pool of soluble receptor for trans-signaling within the periphery and within the CNS from cells that have crossed the blood–brain barrier. The IL-6R expressed on microglia [48] also provides a potential source of sIL-6R as evidenced from elevated levels of trans-signaling in aged mice that have higher levels of the receptor and its sheddase ADAM17 than their younger counterparts after neurotoxic insult [125]. However, as mentioned earlier, trans-signaling within the brain does not appear to be critical for the progression of disease (Fig. 3B/C). In a further pathogenic step, IL-17, produced by Th_{17}-cells, stimulates IL-6 expression in astrocytes in a positive feedback-loop [126,127]. Trans-signaling is reported to activate astrocytes [128] and contribute further to elevation of IL-6

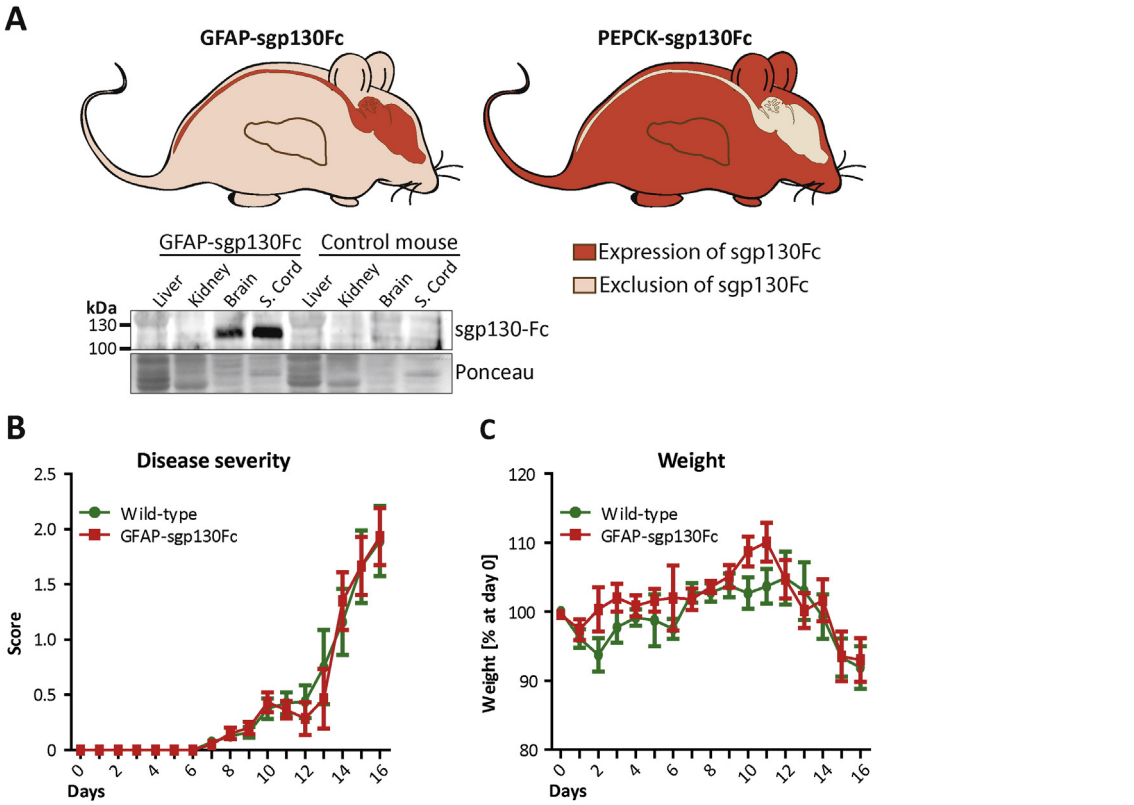

Fig. 3. Transgenic mice with sgp130Fc expressed under the control of a GFAP or PEPCK promoter. Trans-signaling is not essential for progression of symptoms of EAE in mice. (A) Within GFAP-sgp130 mice the protein is restricted to the CNS (brain and spinal cord) as confirmed by immunoblotting (ponceau was used to control loading). Conversely, within PEPCK-sgp130 transgenic mice the protein is excluded from the CNS but can penetrate all peripheral tissues of the mouse. (B) Both wild-type controls and mice where trans-signaling has specifically been blocked within the CNS respond identically to induction of EAE (mice were immunized with a myelin oligodendrocyte glycoprotein peptide ($MOG_{35–55}$) with complete Freund's adjuvant (CFA) according to the manufacturer's instructions, Hooke laboratories, Lawrence, MA, USA) over a period of 16 days. Disease severity was measured on a numerical scale from 0 to 4 as follows: 0: no symptoms; 0.5: absence of tail curling; 1: completely paralyzed tail; 1.5: hind limb paresis with affected walk; 2: affected walk due to initial paralysis of hind limbs; 2.5: full paralysis of one hind limb; 3: full paralysis of both hind limbs; 3.5 hind and forelimb paralysis; 4: moribund. Paralyzed mice were given easy access food and water. Animals were maintained in a conventional animal facility. All procedures performed in this study involving animals were in accordance with the ethical standards set by the National Animal Care Committee of Germany. (C) Likewise, both genotypes show similar fluctuation in weight for the duration of the study after $MOG_{35–55}$/CFA immunization. Data were analyzed for significance using a two-way ANOVA with a Bonferroni post-hoc test where the null hypothesis was rejected at $p < 0.05$ and $n \geq 14$ per genotype.

expression and secretion in these cells [129]. Reactive oxygen species released from activated astrocytes [130] and microglia [131] also contribute to myelin sheath damage due to their toxic effects on oligodendrocytes [132]. Furthermore, trans-signaling plays a role in the activation of microglia cells that also contribute to the destruction of myelin fibers. In fact, interferon-γ-dependent elevation of CD40 in microglia cells was elevated when primary cultures were exposed to hyper-IL-6 when compared to IL-6 alone [49]. This is in contrast to the proposed neuroprotective properties of microglia shown after stimulation with IL-6 alone in classical signaling [86]. Finally, demyelination leads to ascending paralysis and eventually, after repeated demyelination events, to destruction of the axon causing lesions within the CNS [133,134].

6. Sleep

The immune system, under physiologic and pathophysiologic condition, exerts control over the pattern of sleep [135,136]. It is believed that this control is mediated by cytokines such as TNFα, IL-1β and IL-6. It is, however, not well understood, whether this control is executed within the CNS or within the periphery. In the case of IL-6 such experiments have been recently conducted and therefore contribute to the understanding of the biology of this cytokine.

Sleep deprivation is associated with reduced antibody titers after immunization [137]. In fact, sleep was shown to modulate the rate of IL-6 trans-signaling. Dimitrov and colleagues measured the plasma concentrations of sIL-6R in healthy individuals during a regular sleep–wake cycle and compared their results to samples taken during 24 h of wakefulness. They clearly showed that the proteolytically cleaved form of the IL-6R rather than the differentially spliced form was significantly elevated during sleep [138]. Additionally, the sheddase of the IL-6R, ADAM17 is expressed in a sleep-dependent manner, at least in macrophages [139].

In rats, IL-6 augments NREM (non-rapid eye movement sleep, a transitional role in sleep cycling) [140], and more specifically, slow wave activity during SWS (slow-wave sleep which includes later stages of sleep often known as “deep sleep” that is important for cerebral restoration and recovery [141,142]) in humans [143]. Paradoxically, impaired sleep was reported to correlate with elevated nocturnal IL-6 levels in humans [144–146]. In agreement with this, IL-6-deficient mice spend more time in REM (the final stage of sleep associated with dreaming [147]) when compared to control mice [34]. Such studies highlight the cryptic role of IL-6 signaling in sleep. The heterogeneity of results from the observed IL-6-dependent effects on sleep can be partially explained by the fact that IL-6 can act on different cell types via classical or trans-signaling. Alternatively, differences in concentration as well as binding affinity between animal and human models may contribute to variances in results. In fact, some sleep-inducing cytokines have an anti-somnogenic activity at higher concentrations that resembles sleep that occurs during severe infectious disease states.

A previous study showed that an increase in trans-signaling enhanced REM but did not influence NREM in mice after ICV injection of hyper-IL-6 [148]. Interestingly, using the (phosphoenolpyruvate carboxykinase) PEPCK-sgp130Fc [16] and GFAP-sgp130Fc mice (Fig. 3A) that block trans-signaling in the periphery and CNS respectively, it could

be concluded that peripheral and CNS trans-signaling influence sleep in a different manner [16,65]. The mechanism of how sgp130Fc blocks trans-signaling is described in Section 7. In fact, trans-signaling in the periphery plays a more profound role than signaling within the CNS as PEPCK-gp130 transgenic mice spent less time in all stages of sleep (NREM as well as SWS and REM) than their control mice. In contrast, trans-signaling blockage in the CNS led only to a slight decrease in time spent in REM [149]. Thus, therapy that targets trans-signaling in the brain would have very little predictable side-effects in relation to sleep.

7. Therapeutic targets

IL-6 has been shown to play a fundamental role in neurological disorders as discussed in this review. Therefore, it seems reasonable that a blockade of IL-6 signaling could be a treatment option for neuroinflammatory conditions. The majority of IL-6-related treatments focus on preventing inflammation and target total signaling but not specifically trans-signaling (Fig. 4) [23]. Blocking IL-6 with neutralizing anti-IL-6 monoclonal antibodies (B-E4 and B-E8) have been used in clinical trials for the treatment of multiple myeloma with minimal side-effects [150]. However, treatment proved ineffective in the long term due to exaggerated increased levels of circulated IL-6 that override the neutralizing activity of the antibody [151]. As an alternative method to block IL-6 signaling a monoclonal antibody against the IL-6R (Tocilizumab), which binds to the membrane-bound and soluble IL-6R (Fig. 4) thereby blocking binding of IL-6, has been developed. Tocilizumab is approved for the treatment of rheumatoid arthritis as well as systemic and polyarticular juvenile inflammatory arthritis. [152]. The efficiency of this treatment in prevention of inflammation has been successfully shown in patients with juvenile idiopathic arthritis [153,154] as well as in a mouse model of MS [122]. However, as we have already highlighted, a problem with such therapies is that the primary pro-inflammatory nature of trans-signaling as well as the regenerative, anti-pathogenic function of classical signaling are simultaneously targeted leading to a higher propensity for infections in treated patients [154].

Another strategy is based on the capacity of the physiological soluble form of gp130 (sgp130) capable of blocking trans-signaling [69,70]. In fact ICV injection of sgp130 accelerated recovery and reduced neuropathological changes in response to lipopolysaccharide-induced endotoxemia in mice [125]. Furthermore, studies in animal models of stress observed that an IL-6-dependent reduction in prefrontal cortex synaptic inhibition, associated with stress, could be blocked using ICV application of sgp130 [155] and was absent in GFAP-sgp130Fc mice [156]. Another approach to expand on this idea is the generation of a designer protein sgp130Fc with increased affinity for the IL-6R/IL-6 complex. It is a fusion protein of the extracellular part of sgp130 and the constant Fc portion of human IgG1 antibody [70] (Fig. 4), identical to that overexpressed in GFAP-sgp130Fc [65] and PEPCK-sgp130Fc [16] mice. In fact, recombinant gp130Fc has already undergone evaluation in phase I clinical trials [157,158]. This protein specifically binds to the complex of IL-6 and its receptor, but not to IL-6 or the IL-6R alone. Importantly, due to the fact that soluble sgp130Fc selectively inhibits IL-6 trans-signaling, this provides a means to molecularly distinguish between IL-6 classical and trans-signaling. However, with regard to neuropathological conditions where IL-6 trans-signaling may play a role, this protein is not capable of crossing the blood–brain-barrier as it is exclusively detected within the CNS of GFAP-sgp130Fc mice (Fig. 3A). Receptors on the blood–brain barrier bind ligands to facilitate their transport, thus, recombinant proteins can be modified in order to mimic this selective process thereby facilitating its entry into the CNS via receptor-mediated transcytosis [159]. Well characterized blood–brain barrier receptors suitable for exploitation in the reengineering of proteins for such a task include the transferrin receptor (TfR) and insulin receptor (IR) [160]. Re-engineered TfR/IR IgG-fusion proteins that are capable of penetrating the CNS and eliciting a therapeutic effect have successfully been used in models of neurological disease [160]. Fusion proteins with the constant region of antibodies directed against the TfR for mice [161,162] or the IR (IRmAb) in humans [163,164] have been shown to traverse the blood–brain barrier and represent promising

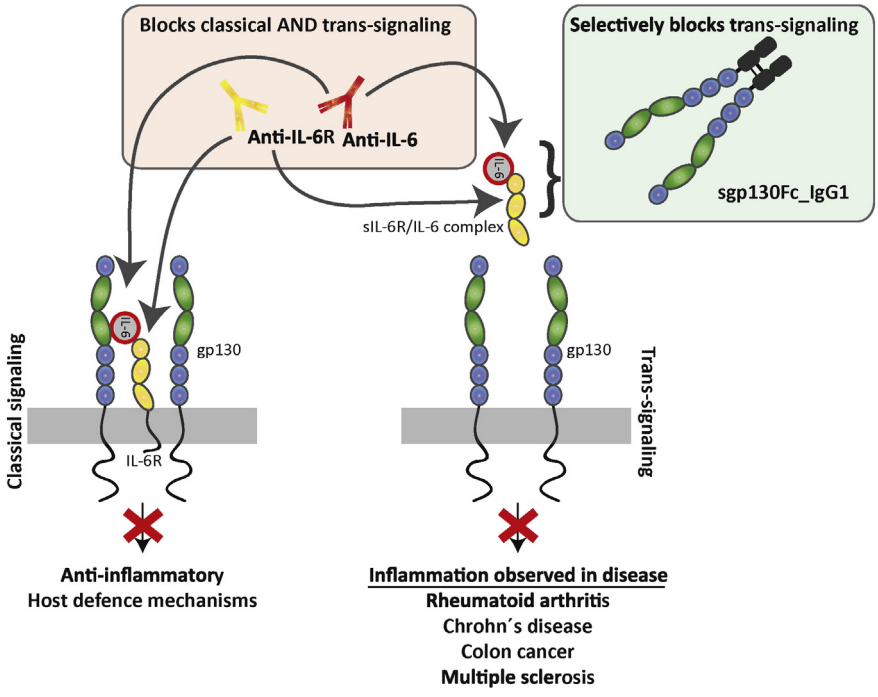

Fig. 4. Summary of available therapeutic options for the treatment of IL-6-mediated inflammatory diseases. Current monoclonal antibodies directed against either the IL-6R or IL-6 itself target both classical and trans-signaling, thereby preventing T-cell-mediated inflammation. However, such antibodies also bind to membrane-bound IL-6R as well as the sIL-6R, thereby preventing anti-inflammatory as well as pathogenic defence processes. In contrast sgp130Fc can selectively block trans-signaling leading to a reduction in potential side-effects of treatment.

technology in the development of therapies for neurological disease. In this respect, generation of an IRmAb-sgp130Fc chimera may, in theory, aid in its transport over the blood–brain barrier. Alternatively, addition of a biotin label to the Fc part of sgp130Fc would allow it to be recognized by an adivin tagged IRmAb as described for other proteins. Binding of avidin labelled proteins in this manner has been shown to dramatically increase transport into the CNS [165,166]. Naturally, further studies are necessary to test the efficiency of such chimeras to penetrate the blood–brain barrier and their ability to block trans-signaling.

8. Concluding remarks

IL-6 is a central player in physiological neuronal and glial function as well as neuroinflammatory pathways observed in diseases of the CNS. The significance of IL-6 signaling is appreciated in a wide range of diseases [19,21,72,74,167] highlighted by the development of therapies aimed at counteracting this pathway [23,150,153,154]. Due to the critical role of IL-6 in host defense and glial/neuronal homeostasis further studies are necessary to clarify the individual cellular consequences of IL-6 signaling within the CNS. While the pro-inflammatory trans-signaling pathway in the periphery is essential for susceptibility of mice to MS-like symptoms, we have shown that it only plays a minor role within the CNS. Nevertheless, this is probably different for other neurodegenerative diseases, as IL-6 trans-signaling has been shown to cause neuronal damage in mice. Such research is essential to help in the identification of effective therapies and their possible side-effects in the targeting of the grossly pro-inflammatory trans-signaling pathway in neuroinflammatory disorders.

Transparency document

The Transparency document associated with this article can be found, in online version.

Abbreviations

IL-6	interleukin-6
IL-6R	IL-6 receptor
MS	multiple sclerosis
ADAM	A Disintegrin And Metalloproteinase
CNS	central nervous system
PEPCK	phosphoenolpyruvate carboxykinase
GFAP	glial fibrillary acid protein
EAE	experimental autoimmune encephalomyelitis
AD	Alzheimer's disease
PD	Parkinson's disease
VCAM-1	vascular cell adhesion molecule 1
NREM	non-rapid eye movement
REM	rapid eye movement
SWS	slow-wave sleep
ICV	intracerebroventricular

Acknowledgments

The authors would like to thank Dr. Anna Otte, Frederike Schmidt, Dr. Philipp Arnold, Inez Götting, Neele Schumacher, Dr. Katja Möller-Hackbarth, Dr. Ute Pickhinke, Olga Matveeva and Wiona Burmeister for their help with the EAE experiments. This work was supported by Deutsche Forschungsgemeinschaft in SFB 654 (Plasticity and Sleep; project C05) and in SFB 877 (Proteolysis as a Regulatory Event in Pathophysiology; projects A1 and A9).

References

[1] J.G. Walsh, D.A. Muruve, C. Power, Inflammasomes in the CNS, Nat. Rev. Neurosci. 15 (2014) 84–97.
[2] M.J. Hofer, I.L. Campbell, Immunoinflammatory diseases of the central nervous system — the tale of two cytokines, Br. J. Pharmacol. (2015).
[3] T. Hirano, T. Taga, N. Nakano, K. Yasukawa, S. Kashiwamura, K. Shimizu, K. Nakajima, K.H. Pyun, T. Kishimoto, Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2), Proc. Natl. Acad. Sci. U. S. A. 82 (1985) 5490–5494.
[4] A. Zilberstein, R. Ruggieri, J.H. Korn, M. Revel, Structure and expression of cDNA and genes for human interferon-beta-2, a distinct species inducible by growth-stimulatory cytokines, EMBO J. 5 (1986) 2529–2537.
[5] G.M. Fuller, J.M. Otto, B.M. Woloski, C.T. McGary, M.A. Adams, The effects of hepatocyte stimulating factor on fibrinogen biosynthesis in hepatocyte monolayers, J. Cell Biol. 101 (1985) 1481–1486.
[6] J. Content, L. De Wit, D. Pierard, R. Derynck, E. De Clercq, W. Fiers, Secretory proteins induced in human fibroblasts under conditions used for the production of interferon beta, Proc. Natl. Acad. Sci. U. S. A. 79 (1982) 2768–2772.
[7] T. Hirano, K. Yasukawa, H. Harada, T. Taga, Y. Watanabe, T. Matsuda, S. Kashiwamura, K. Nakajima, K. Koyama, A. Iwamatsu, et al., Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin, Nature 324 (1986) 73–76.
[8] J. Gauldie, C. Richards, D. Harnish, P. Lansdorp, H. Baumann, Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells, Proc. Natl. Acad. Sci. U. S. A. 84 (1987) 7251–7255.
[9] G. Haegeman, J. Content, G. Volckaert, R. Derynck, J. Tavernier, W. Fiers, Structural analysis of the sequence coding for an inducible 26-kDa protein in human fibroblasts, Eur. J. Biochem. 159 (1986) 625–632.
[10] K. Yasukawa, T. Hirano, Y. Watanabe, K. Muratani, T. Matsuda, S. Nakai, T. Kishimoto, Structure and expression of human B cell stimulatory factor-2 (BSF-2/IL-6) gene, EMBO J. 6 (1987) 2939–2945.
[11] D.E. Cressman, L.E. Greenbaum, R.A. DeAngelis, G. Ciliberto, E.E. Furth, V. Poli, R. Taub, Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice, Science 274 (1996) 1379–1383.
[12] E. Galun, E. Zeira, O. Pappo, M. Peters, S. Rose-John, Liver regeneration induced by a designer human IL-6/sIL-6R fusion protein reverses severe hepatocellular injury, FASEB J. 14 (2000) 1979–1987.
[13] S. Grivennikov, E. Karin, J. Terzic, D. Mucida, G.Y. Yu, S. Vallabhapurapu, J. Scheller, S. Rose-John, H. Cheroutre, L. Eckmann, M. Karin, IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer, Cancer Cell 15 (2009) 103–113.
[14] S. Matsumoto, T. Hara, K. Mitsuyama, M. Yamamoto, O. Tsuruta, M. Sata, J. Scheller, S. Rose-John, S. Kado, T. Takada, Essential roles of IL-6 trans-signaling in colonic epithelial cells, induced by the IL-6/soluble-IL-6 receptor derived from lamina propria macrophages, on the development of colitis-associated premalignant cancer in a murine model, J. Immunol. 184 (2010) 1543–1551.
[15] C. Becker, M.C. Fantini, C. Schramm, H.A. Lehr, S. Wirtz, A. Nikolaev, J. Burg, S. Strand, R. Kiesslich, S. Huber, H. Ito, N. Nishimoto, K. Yoshizaki, T. Kishimoto, P.R. Galle, M. Blessing, S. Rose-John, M.F. Neurath, TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling, Immunity 21 (2004) 491–501.
[16] B. Rabe, A. Chalaris, U. May, G.H. Waetzig, D. Seegert, A.S. Williams, S.A. Jones, S. Rose-John, J. Scheller, Transgenic blockade of interleukin 6 transsignaling abrogates inflammation, Blood 111 (2008) 1021–1028.
[17] E. Fattori, M. Cappelletti, P. Costa, C. Sellitto, L. Cantoni, M. Carelli, R. Faggioni, G. Fantuzzi, P. Ghezzi, V. Poli, Defective inflammatory response in interleukin 6-deficient mice, J. Exp. Med. 180 (1994) 1243–1250.
[18] J. Hoge, I. Yan, N. Janner, V. Schumacher, A. Chalaris, O.M. Steinmetz, D.R. Engel, J. Scheller, S. Rose-John, H.W. Mittrucker, IL-6 controls the innate immune response against Listeria monocytogenes via classical IL-6 signaling, J. Immunol. 190 (2013) 703–711.
[19] T. Alonzi, E. Fattori, D. Lazzaro, P. Costa, L. Probert, G. Kollias, F. De Benedetti, V. Poli, G. Ciliberto, Interleukin 6 is required for the development of collagen-induced arthritis, J. Exp. Med. 187 (1998) 461–468.
[20] M. Sasai, Y. Saeki, S. Ohshima, K. Nishioka, T. Mima, T. Tanaka, Y. Katada, K. Yoshizaki, M. Suemura, T. Kishimoto, Delayed onset and reduced severity of collagen-induced arthritis in interleukin-6-deficient mice, Arthritis Rheum. 42 (1999) 1635–1643.
[21] R. Atreya, J. Mudter, S. Finotto, J. Mullberg, T. Jostock, S. Wirtz, M. Schutz, B. Bartsch, M. Holtmann, C. Becker, D. Strand, J. Czaja, J.F. Schlaak, H.A. Lehr, F. Autschbach, G. Schurmann, N. Nishimoto, K. Yoshizaki, H. Ito, T. Kishimoto, P.R. Galle, S. Rose-John, M.F. Neurath, Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn disease and experimental colitis in vivo, Nat. Med. 6 (2000) 583–588.
[22] K.M. Andrejko, N.R. Raj, P.K. Kim, M. Cereda, C.S. Deutschman, IL-6 modulates sepsis-induced decreases in transcription of hepatic organic anion and bile acid transporters, Shock 29 (2008) 490–496.
[23] S.A. Jones, J. Scheller, S. Rose-John, Therapeutic strategies for the clinical blockade of IL-6/gp130 signaling, J. Clin. Invest. 121 (2011) 3375–3383.
[24] X. Wang, P. Lupardus, S.L. Laporte, K.C. Garcia, Structural biology of shared cytokine receptors, Annu. Rev. Immunol. 27 (2009) 29–60.
[25] J.F. Bazan, Haemopoietic receptors and helical cytokines, Immunol. Today 11 (1990) 350–354.
[26] T. Taga, T. Kishimoto, Cytokine receptors and signal transduction, FASEB J. 6 (1992) 3387–3396.
[27] P.C. Heinrich, I. Behrmann, S. Haan, H.M. Hermanns, G. Muller-Newen, F. Schaper, Principles of interleukin (IL)-6-type cytokine signalling and its regulation, Biochem. J. 374 (2003) 1–20.

[28] S. Bauer, B.J. Kerr, P.H. Patterson, The neuropoietic cytokine family in development, plasticity, disease and injury, Nat. Rev. Neurosci. 8 (2007) 221–232.
[29] T. Taga, T. Kishimoto, Gp130 and the interleukin-6 family of cytokines, Annu. Rev. Immunol. 15 (1997) 797–819.
[30] C. Garbers, H.M. Hermanns, F. Schaper, G. Muller-Newen, J. Grotzinger, S. Rose-John, J. Scheller, Plasticity and cross-talk of interleukin 6-type cytokines, Cytokine Growth Factor Rev. 23 (2012) 85–97.
[31] C.R. Gomez, J. Goral, L. Ramirez, M. Kopf, E.J. Kovacs, Aberrant acute-phase response in aged interleukin-6 knockout mice, Shock 25 (2006) 581–585.
[32] T. Kishimoto, S. Akira, M. Narazaki, T. Taga, Interleukin-6 family of cytokines and gp130, Blood 86 (1995) 1243–1254.
[33] M.A. Klein, J.C. Moller, L.L. Jones, H. Bluethmann, G.W. Kreutzberg, G. Raivich, Impaired neuroglial activation in interleukin-6 deficient mice, Glia 19 (1997) 227–233.
[34] J.D. Morrow, M.R. Opp, Sleep–wake behavior and responses of interleukin-6-deficient mice to sleep deprivation, Brain Behav. Immun. 19 (2005) 28–39.
[35] M. Penkowa, T. Moos, J. Carrasco, H. Hadberg, A. Molinero, H. Bluethmann, J. Hidalgo, Strongly compromised inflammatory response to brain injury in interleukin-6-deficient mice, Glia 25 (1999) 343–357.
[36] E. Fattori, D. Lazzaro, P. Musiani, A. Modesti, T. Alonzi, G. Ciliberto, IL-6 expression in neurons of transgenic mice causes reactive astrocytosis and increase in ramified microglial cells but no neuronal damage, Eur. J. Neurosci. 7 (1995) 2441–2449.
[37] I.L. Campbell, C.R. Abraham, E. Masliah, P. Kemper, J.D. Inglis, M.B. Oldstone, L. Mucke, Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 10061–10065.
[38] T. Li, S. He, Induction of IL-6 release from human T cells by PAR-1 and PAR-2 agonists, Immunol. Cell Biol. 84 (2006) 461–466.
[39] Y.B. Lee, A. Nagai, S.U. Kim, Cytokines, chemokines, and cytokine receptors in human microglia, J. Neurosci. Res. 69 (2002) 94–103.
[40] S. Akira, T. Hirano, T. Taga, T. Kishimoto, Biology of multifunctional cytokines: IL 6 and related molecules (IL 1 and TNF), FASEB J. 4 (1990) 2860–2867.
[41] M.V. Hobbs, R.J. McEvilly, R.J. Koch, G.J. Cardenas, D.J. Noonan, Interleukin-6 production by murine B cells and B cell lines, Cell. Immunol. 132 (1991) 442–450.
[42] P. März, J.G. Cheng, R.A. Gadient, P.H. Patterson, T. Stoyan, U. Otten, S. Rose-John, Sympathetic neurons can produce and respond to interleukin 6, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 3251–3256.
[43] B.K. Pedersen, M.A. Febbraio, Muscle as an endocrine organ: focus on muscle-derived interleukin-6, Physiol. Rev. 88 (2008) 1379–1406.
[44] T. Skurk, C. Alberti-Huber, C. Herder, H. Hauner, Relationship between adipocyte size and adipokine expression and secretion, J. Clin. Endocrinol. Metab. 92 (2007) 1023–1033.
[45] L.T. May, G. Torcia, F. Cozzolino, A. Ray, S.B. Tatter, U. Santhanam, P.B. Sehgal, D. Stern, Interleukin-6 gene expression in human endothelial cells: RNA start sites, multiple IL-6 proteins and inhibition of proliferation, Biochem. Biophys. Res. Commun. 159 (1989) 991–998.
[46] J.V. Castell, T. Geiger, V. Gross, T. Andus, E. Walter, T. Hirano, T. Kishimoto, P.C. Heinrich, Plasma clearance, organ distribution and target cells of interleukin-6/hepatocyte-stimulating factor in the rat, Eur. J. Biochem. 177 (1988) 357–361.
[47] H.H. Oberg, D. Wesch, S. Grussel, S. Rose-John, D. Kabelitz, Differential expression of CD126 and CD130 mediates different STAT-3 phosphorylation in CD4+CD25- and CD25high regulatory T cells, Int. Immunol. 18 (2006) 555–563.
[48] M.P. Hsu, R. Frausto, S. Rose-John, I.L. Campbell, Analysis of IL-6/gp130 family receptor expression reveals that in contrast to astroglia, microglia lack the oncostatin M receptor and functional responses to oncostatin M, Glia 63 (2015) 132–141.
[49] H.W. Lin, S.W. Levison, Context-dependent IL-6 potentiation of interferon-gamma-induced IL-12 secretion and CD40 expression in murine microglia, J. Neurochem. 111 (2009) 808–818.
[50] M. Sawada, Y. Itoh, A. Suzumura, T. Marunouchi, Expression of cytokine receptors in cultured neuronal and glial cells, Neurosci. Lett. 160 (1993) 131–134.
[51] J.A. Lust, K.A. Donovan, M.P. Kline, P.R. Greipp, R.A. Kyle, N.J. Maihle, Isolation of an mRNA encoding a soluble form of the human interleukin-6 receptor, Cytokine 4 (1992) 96–100.
[52] S. Horiuchi, Y. Koyanagi, Y. Zhou, H. Miyamoto, Y. Tanaka, M. Waki, A. Matsumoto, M. Yamamoto, N. Yamamoto, Soluble interleukin-6 receptors released from T cell or granulocyte/macrophage cell lines and human peripheral blood mononuclear cells are generated through an alternative splicing mechanism, Eur. J. Immunol. 24 (1994) 1945–1948.
[53] J. Müllberg, H. Schooltink, T. Stoyan, M. Gunther, L. Graeve, G. Buse, A. Mackiewicz, P.C. Heinrich, S. Rose-John, The soluble interleukin-6 receptor is generated by shedding, Eur. J. Immunol. 23 (1993) 473–480.
[54] J. Müllberg, F.H. Durie, C. Otten-Evans, M.R. Alderson, S. Rose-John, D. Cosman, R.A. Black, K.M. Mohler, A metalloprotease inhibitor blocks shedding of the IL-6 receptor and the p60 TNF receptor, J. Immunol. 155 (1995) 5198–5205.
[55] V. Matthews, B. Schuster, S. Schutze, I. Bussmeyer, A. Ludwig, C. Hundhausen, T. Sadowski, P. Saftig, D. Hartmann, K.J. Kallen, S. Rose-John, Cellular cholesterol depletion triggers shedding of the human interleukin-6 receptor by ADAM10 and ADAM17 (TACE), J. Biol. Chem. 278 (2003) 38829–38839.
[56] K. Althoff, P. Reddy, N. Voltz, S. Rose-John, J. Mullberg, Shedding of interleukin-6 receptor and tumor necrosis factor alpha. Contribution of the stalk sequence to the cleavage pattern of transmembrane proteins, Eur. J. Biochem. 267 (2000) 2624–2631.
[57] T. Taga, T. Kishimoto, Signaling mechanisms through cytokine receptors that share signal transducing receptor components, Curr. Opin. Immunol. 7 (1995) 17–23.
[58] T. Taga, M. Hibi, Y. Hirata, K. Yamasaki, K. Yasukawa, T. Matsuda, T. Hirano, T. Kishimoto, Interleukin-6 triggers the association of its receptor with a possible signal transducer, gp130, Cell 58 (1989) 573–581.
[59] M. Hibi, M. Murakami, M. Saito, T. Hirano, T. Taga, T. Kishimoto, Molecular cloning and expression of an IL-6 signal transducer, gp130, Cell 63 (1990) 1149–1157.
[60] S. Rose-John, P.C. Heinrich, Soluble receptors for cytokines and growth factors: generation and biological function, Biochem. J. 300 (Pt 2) (1994) 281–290.
[61] M. Saito, K. Yoshida, M. Hibi, T. Taga, T. Kishimoto, Molecular cloning of a murine IL-6 receptor-associated signal transducer, gp130, and its regulated expression in vivo, J. Immunol. 148 (1992) 4066–4071.
[62] P. März, K. Heese, B. Dimitriades-Schmutz, S. Rose-John, U. Otten, Role of interleukin-6 and soluble IL-6 receptor in region-specific induction of astrocytic differentiation and neurotrophin expression, Glia 26 (1999) 191–200.
[63] M. Peters, P. Schirmacher, J. Goldschmitt, M. Odenthal, C. Peschel, E. Fattori, G. Ciliberto, H.P. Dienes, K.H. Meyer zum Buschenfelde, S. Rose-John, Extramedullary expansion of hematopoietic progenitor cells in interleukin (IL)-6-sIL-6R double transgenic mice, J. Exp. Med. 185 (1997) 755–766.
[64] C. Drucker, B. Rabe, A. Chalaris, E. Schulz, J. Scheller, S. Rose-John, Interleukin-6 trans-signaling regulates glycogen consumption after D-galactosamine-induced liver damage, J. Interf. Cytokine Res. 29 (2009) 711–718.
[65] I.L. Campbell, M. Erta, S.L. Lim, R. Frausto, U. May, S. Rose-John, J. Scheller, J. Hidalgo, Trans-signaling is a dominant mechanism for the pathogenic actions of interleukin-6 in the brain, J. Neurosci. 34 (2014) 2503–2513.
[66] M.A. Nowell, P.J. Richards, S. Horiuchi, N. Yamamoto, S. Rose-John, N. Topley, A.S. Williams, S.A. Jones, Soluble IL-6 receptor governs IL-6 activity in experimental arthritis: blockade of arthritis severity by soluble glycoprotein 130, J. Immunol. 171 (2003) 3202–3209.
[67] P.J. Richards, M.A. Nowell, S. Horiuchi, R.M. McLoughlin, C.A. Fielding, S. Grau, N. Yamamoto, M. Ehrmann, S. Rose-John, A.S. Williams, N. Topley, S.A. Jones, Functional characterization of a soluble gp130 isoform and its therapeutic capacity in an experimental model of inflammatory arthritis, Arthritis Rheum. 54 (2006) 1662–1672.
[68] K. Mitsuyama, S. Matsumoto, S. Rose-John, A. Suzuki, T. Hara, N. Tomiyasu, K. Handa, O. Tsuruta, H. Funabashi, J. Scheller, A. Toyonaga, M. Sata, STAT3 activation via interleukin 6 trans-signalling contributes to ileitis in SAMP1/Yit mice, Gut 55 (2006) 1263–1269.
[69] M. Narazaki, K. Yasukawa, T. Saito, Y. Ohsugi, H. Fukui, Y. Koishihara, G.D. Yancopoulos, T. Taga, T. Kishimoto, Soluble forms of the interleukin-6 signal-transducing receptor component gp130 in human serum possessing a potential to inhibit signals through membrane-anchored gp130, Blood 82 (1993) 1120–1126.
[70] T. Jostock, J. Müllberg, S. Ozbek, R. Atreya, G. Blinn, N. Voltz, M. Fischer, M.F. Neurath, S. Rose-John, Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses, Eur. J. Biochem. 268 (2001) 160–167.
[71] E.N. Benveniste, Cytokine actions in the central nervous system, Cytokine Growth Factor Rev. 9 (1998) 259–275.
[72] A. Lilja, C. Nordborg, A. Brun, L.G. Salford, P. Aman, Expression of the IL-6 family cytokines in human brain tumors, Int. J. Oncol. 19 (2001) 495–499.
[73] K. Frei, S. Fredrikson, A. Fontana, H. Link, Interleukin-6 is elevated in plasma in multiple sclerosis, J. Neuroimmunol. 31 (1991) 147–153.
[74] D. Maimone, G.C. Guazzi, P. Annunziata, IL-6 detection in multiple sclerosis brain, J. Neurol. Sci. 146 (1997) 59–65.
[75] C. Ali, O. Nicole, F. Docagne, S. Lesne, E.T. MacKenzie, A. Nouvelot, A. Buisson, D. Vivien, Ischemia-induced interleukin-6 as a potential endogenous neuroprotective cytokine against NMDA receptor-mediated excitotoxicity in the brain, J. Cereb. Blood Flow Metab. 20 (2000) 956–966.
[76] J.A. Wagner, Is IL-6 both a cytokine and a neurotrophic factor? J. Exp. Med. 183 (1996) 2417–2419.
[77] A. Bonni, Y. Sun, M. Nadal-Vicens, A. Bhatt, D.A. Frank, I. Rozovsky, N. Stahl, G.D. Yancopoulos, M.E. Greenberg, Regulation of gliogenesis in the central nervous system by the JAK–STAT signaling pathway, Science 278 (1997) 477–483.
[78] D.L. Gruol, T.E. Nelson, Physiological and pathological roles of interleukin-6 in the central nervous system, Mol. Neurobiol. 15 (1997) 307–339.
[79] Y. Akaneya, M. Takahashi, H. Hatanaka, Interleukin-1 beta enhances survival and interleukin-6 protects against MPP+ neurotoxicity in cultures of fetal rat dopaminergic neurons, Exp. Neurol. 136 (1995) 44–52.
[80] S. Toulmond, X. Vige, D. Fage, J. Benavides, Local infusion of interleukin-6 attenuates the neurotoxic effects of NMDA on rat striatal cholinergic neurons, Neurosci. Lett. 144 (1992) 49–52.
[81] Y. Kushima, H. Hatanaka, Interleukin-6 and leukemia inhibitory factor promote the survival of acetylcholinesterase-positive neurons in culture from embryonic rat spinal cord, Neurosci. Lett. 143 (1992) 110–114.
[82] Y. Kushima, T. Hama, H. Hatanaka, Interleukin-6 as a neurotrophic factor for promoting the survival of cultured catecholaminergic neurons in a chemically defined medium from fetal and postnatal rat midbrains, Neurosci. Res. 13 (1992) 267–280.
[83] H. Hirota, H. Kiyama, T. Kishimoto, T. Taga, Accelerated nerve regeneration in mice by upregulated expression of interleukin (IL) 6 and IL-6 receptor after trauma, J. Exp. Med. 183 (1996) 2627–2634.
[84] P. Marz, K. Heese, C. Hock, S. Golombowski, F. Muller-Spahn, S. Rose-John, U. Otten, Interleukin-6 (IL-6) and soluble forms of IL-6 receptors are not altered in cerebrospinal fluid of Alzheimer's disease patients, Neurosci. Lett. 239 (1997) 29–32.
[85] M. Fischer, J. Goldschmitt, C. Peschel, J.P. Brakenhoff, K.J. Kallen, A. Wollmer, J. Grotzinger, S. Rose-John, I. A bioactive designer cytokine for human hematopoietic progenitor cell expansion, Nat. Biotechnol. 15 (1997) 142–145.
[86] A.J. Chucair-Elliott, C. Conrady, M. Zheng, C.M. Kroll, T.E. Lane, D.J. Carr, Microglia-induced IL-6 protects against neuronal loss following HSV-1 infection of neural progenitor cells, Glia 62 (2014) 1418–1434.

[87] P. Yang, H. Wen, S. Ou, J. Cui, D. Fan, IL-6 promotes regeneration and functional recovery after cortical spinal tract injury by reactivating intrinsic growth program of neurons and enhancing synapse formation, Exp. Neurol. 236 (2012) 19–27.
[88] M. Mogi, M. Harada, T. Kondo, P. Riederer, H. Inagaki, M. Minami, T. Nagatsu, Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients, Neurosci. Lett. 180 (1994) 147–150.
[89] M. Sawada, K. Imamura, T. Nagatsu, Role of cytokines in inflammatory process in Parkinson's disease, J. Neural Transm. Suppl. (2006) 373–381.
[90] J. Bauer, S. Strauss, U. Schreiter-Gasser, U. Ganter, P. Schlegel, I. Witt, B. Yolk, M. Berger, Interleukin-6 and alpha-2-macroglobulin indicate an acute-phase state in Alzheimer's disease cortices, FEBS Lett. 285 (1991) 111–114.
[91] J.A. Wood, P.L. Wood, R. Ryan, N.R. Graff-Radford, C. Pilapil, Y. Robitaille, R. Quirion, Cytokine indices in Alzheimer's temporal cortex: no changes in mature IL-1 beta or IL-1RA but increases in the associated acute phase proteins IL-6, alpha 2-macroglobulin and C-reactive protein, Brain Res. 629 (1993) 245–252.
[92] M. Hull, M. Berger, B. Volk, J. Bauer, Occurrence of interleukin-6 in cortical plaques of Alzheimer's disease patients may precede transformation of diffuse into neuritic plaques, Ann. N. Y. Acad. Sci. 777 (1996) 205–212.
[93] M. Periquet, T. Fulga, L. Myllykangas, M.G. Schlossmacher, M.B. Feany, Aggregated alpha-synuclein mediates dopaminergic neurotoxicity in vivo, J. Neurosci. 27 (2007) 3338–3346.
[94] M. Ahmed, J. Davis, D. Aucoin, T. Sato, S. Ahuja, S. Aimoto, J.I. Elliott, W.E. Van Nostrand, S.O. Smith, Structural conversion of neurotoxic amyloid-beta(1-42) oligomers to fibrils, Nat. Struct. Mol. Biol. 17 (2010) 561–567.
[95] I. Grundke-Iqbal, K. Iqbal, Y.C. Tung, M. Quinlan, H.M. Wisniewski, L.I. Binder, Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology, Proc. Natl. Acad. Sci. U. S. A. 83 (1986) 4913–4917.
[96] C. Van Cauwenberghe, C. Van Broeckhoven, K. Sleegers, The genetic landscape of Alzheimer disease: clinical implications and perspectives, Genet. Med. (2015).
[97] M. Chin-Chan, J. Navarro-Yepes, B. Quintanilla-Vega, Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases, Front. Cell. Neurosci. 9 (2015) 124.
[98] G. Forloni, F. Mangiarotti, N. Angeretti, E. Lucca, M.G. De Simoni, Beta-amyloid fragment potentiates IL-6 and TNF-alpha secretion by LPS in astrocytes but not in microglia, Cytokine 9 (1997) 759–762.
[99] C.M. Sondag, G. Dhawan, C.K. Combs, Beta amyloid oligomers and fibrils stimulate differential activation of primary microglia, J. Neuroinflammation 6 (2009) 1.
[100] D.K. Song, Y.B. Im, J.S. Jung, J. Cho, H.W. Suh, Y.H. Kim, Central beta-amyloid peptide-induced peripheral interleukin-6 responses in mice, J. Neurochem. 76 (2001) 1326–1335.
[101] G.E. Ringheim, A.M. Szczepanik, W. Petko, K.L. Burgher, S.Z. Zhu, C.C. Chao, Enhancement of beta-amyloid precursor protein transcription and expression by the soluble interleukin-6 receptor/interleukin-6 complex, Brain Res. Mol. Brain Res. 55 (1998) 35–44.
[102] Z. Qiu, D.L. Gruol, Interleukin-6, beta-amyloid peptide and NMDA interactions in rat cortical neurons, J. Neuroimmunol. 139 (2003) 51–57.
[103] P. Chakrabarty, K. Jansen-West, A. Beccard, C. Ceballos-Diaz, Y. Levites, C. Verbeeck, A.C. Zubair, D. Dickson, T.E. Golde, P. Das, Massive gliosis induced by interleukin-6 suppresses Abeta deposition in vivo: evidence against inflammation as a driving force for amyloid deposition, FASEB J. 24 (2010) 548–559.
[104] T. Hama, Y. Kushima, M. Miyamoto, M. Kubota, N. Takei, H. Hatanaka, Interleukin-6 improves the survival of mesencephalic catecholaminergic and septal cholinergic neurons from postnatal, two-week-old rats in cultures, Neuroscience 40 (1991) 445–452.
[105] C.A. Davie, A review of Parkinson's disease, Br. Med. Bull. 86 (2008) 109–127.
[106] L.M. Bolin, I. Strycharska-Orczyk, R. Murray, J.W. Langston, D. Di Monte, Increased vulnerability of dopaminergic neurons in MPTP-lesioned interleukin-6 deficient mice, J. Neurochem. 83 (2002) 167–175.
[107] K.A. McKay, H. Tremlett, The systematic search for risk factors in multiple sclerosis, Lancet Neurol. 14 (2015) 237–238.
[108] J.F. Kurtzke, Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS), Neurology 33 (1983) 1444–1452.
[109] E.B. Samoilova, J.L. Horton, B. Hilliard, T.S. Liu, Y. Chen, IL-6-deficient mice are resistant to experimental autoimmune encephalomyelitis: roles of IL-6 in the activation and differentiation of autoreactive T cells, J. Immunol. 161 (1998) 6480–6486.
[110] Y. Okuda, S. Sakoda, C.C. Bernard, H. Fujimura, Y. Saeki, T. Kishimoto, T. Yanagihara, IL-6-deficient mice are resistant to the induction of experimental autoimmune encephalomyelitis provoked by myelin oligodendrocyte glycoprotein, Int. Immunol. 10 (1998) 703–708.
[111] H.P. Eugster, K. Frei, M. Kopf, H. Lassmann, A. Fontana, IL-6-deficient mice resist myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis, Eur. J. Immunol. 28 (1998) 2178–2187.
[112] A.A. Kruglov, V. Lampropoulou, S. Fillatreau, S.A. Nedospasov, Pathogenic and protective functions of TNF in neuroinflammation are defined by its expression in T lymphocytes and myeloid cells, J. Immunol. 187 (2011) 5660–5670.
[113] C. Wu, N. Yosef, T. Thalhamer, C. Zhu, S. Xiao, Y. Kishi, A. Regev, V.K. Kuchroo, Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1, Nature 496 (2013) 513–517.
[114] J.B. Hernandez, C. Chang, M. LeBlanc, D. Grimm, J. Le Lay, K.H. Kaestner, Y. Zheng, M. Montminy, The CREB/CRTC2 pathway modulates autoimmune disease by promoting Th17 differentiation, Nat. Commun. 6 (2015) 7216.
[115] G. Murugaiyan, A.P. da Cunha, A.K. Ajay, N. Joller, L.P. Garo, S. Kumaradevan, N. Yosef, V.S. Vaidya, H.L. Weiner, MicroRNA-21 promotes Th17 differentiation and mediates experimental autoimmune encephalomyelitis, J. Clin. Invest. 125 (2015) 1069–1080.
[116] T. Korn, E. Bettelli, W. Gao, A. Awasthi, A. Jager, T.B. Strom, M. Oukka, V.K. Kuchroo, IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells, Nature 448 (2007) 484–487.
[117] Y. Naito, T. Takagi, K. Uchiyama, M. Kuroda, S. Kokura, H. Ichikawa, R. Yanagisawa, K. Inoue, H. Takano, M. Satoh, N. Yoshida, T. Okanoue, T. Yoshikawa, Reduced intestinal inflammation induced by dextran sodium sulfate in interleukin-6-deficient mice, Int. J. Mol. Med. 14 (2004) 191–196.
[118] A. Quintana, M. Müller, R.F. Frausto, R. Ramos, D.R. Getts, E. Sanz, M.J. Hofer, M. Krauthausen, N.J. King, J. Hidalgo, I.L. Campbell, Site-specific production of IL-6 in the central nervous system retargets and enhances the inflammatory response in experimental autoimmune encephalomyelitis, J. Immunol. 183 (2009) 2079–2088.
[119] M. Giralt, R. Ramos, A. Quintana, B. Ferrer, M. Erta, M. Castro-Freire, G. Comes, E. Sanz, M. Unzeta, P. Pifarre, A. Garcia, I.L. Campbell, J. Hidalgo, Induction of atypical EAE mediated by transgenic production of IL-6 in astrocytes in the absence of systemic IL-6, Glia 61 (2013) 587–600.
[120] E. Bettelli, Y. Carrier, W. Gao, T. Korn, T.B. Strom, M. Oukka, H.L. Weiner, V.K. Kuchroo, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature 441 (2006) 235–238.
[121] S. Dominitzki, M.C. Fantini, C. Neufert, A. Nikolaev, P.R. Galle, J. Scheller, G. Monteleone, S. Rose-John, M.F. Neurath, C. Becker, Cutting edge: trans-signaling via the soluble IL-6R abrogates the induction of FoxP3 in naive CD4 + CD25 T cells, J. Immunol. 179 (2007) 2041–2045.
[122] S. Serada, M. Fujimoto, M. Mihara, N. Koike, Y. Ohsugi, S. Nomura, H. Yoshida, T. Nishikawa, F. Terabe, T. Ohkawara, T. Takahashi, B. Ripley, A. Kimura, T. Kishimoto, T. Naka, IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 9041–9046.
[123] R.A. Linker, F. Luhder, K.J. Kallen, D.H. Lee, B. Engelhardt, S. Rose-John, R. Gold, IL-6 transsignalling modulates the early effector phase of EAE and targets the blood–brain barrier, J. Neuroimmunol. 205 (2008) 64–72.
[124] E.M. Briso, O. Dienz, M. Rincon, Cutting edge: soluble IL-6R is produced by IL-6R ectodomain shedding in activated CD4 T cells, J. Immunol. 180 (2008) 7102–7106.
[125] M.D. Burton, J.L. Rytych, G.G. Freund, R.W. Johnson, Central inhibition of interleukin-6 trans-signaling during peripheral infection reduced neuroinflammation and sickness in aged mice, Brain Behav. Immun. 30 (2013) 66–72.
[126] X. Ma, S.L. Reynolds, B.J. Baker, X. Li, E.N. Benveniste, H. Qin, IL-17 enhancement of the IL-6 signaling cascade in astrocytes, J. Immunol. 184 (2010) 4898–4906.
[127] H. Ogura, M. Murakami, Y. Okuyama, M. Tsuruoka, C. Kitabayashi, M. Kanamoto, M. Nishihara, Y. Iwakura, T. Hirano, Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction, Immunity 29 (2008) 628–636.
[128] P. Marz, K. Heese, B. Dimitriades-Schmutz, S. Rose-John, U. Otten, Role of interleukin-6 and soluble IL-6 receptor in region-specific induction of astrocytic differentiation and neurotrophin expression, Glia 26 (1999) 191–200.
[129] N.J. Van Wagoner, J.W. Oh, P. Repovic, E.N. Benveniste, Interleukin-6 (IL-6) production by astrocytes: autocrine regulation by IL-6 and the soluble IL-6 receptor, J. Neurosci. 19 (1999) 5236–5244.
[130] S. Pawate, Q. Shen, F. Fan, N.R. Bhat, Redox regulation of glial inflammatory response to lipopolysaccharide and interferongamma, J. Neurosci. Res. 77 (2004) 540–551.
[131] M.C. Lavigne, H.L. Malech, S.M. Holland, T.L. Leto, Genetic requirement of p47phox for superoxide production by murine microglia, FASEB J. 15 (2001) 285–287.
[132] L. Haider, M.T. Fischer, J.M. Frischer, J. Bauer, R. Hoftberger, G. Botond, H. Esterbauer, C.J. Binder, J.L. Witztum, H. Lassmann, Oxidative damage in multiple sclerosis lesions, Brain 134 (2011) 1914–1924.
[133] J.D. Haines, M. Inglese, P. Casaccia, Axonal damage in multiple sclerosis, Mt Sinai J. Med. 78 (2011) 231–243.
[134] S. Love, Demyelinating diseases, J. Clin. Pathol. 59 (2006) 1151–1159.
[135] L. Imeri, M.R. Opp, How (and why) the immune system makes us sleep, Nat. Rev. Neurosci. 10 (2009) 199–210.
[136] L. Besedovsky, T. Lange, J. Born, Sleep and immune function, Pflugers Arch. 463 (2012) 121–137.
[137] T. Lange, S. Dimitrov, T. Bollinger, S. Diekelmann, J. Born, Sleep after vaccination boosts immunological memory, J. Immunol. 187 (2011) 283–290.
[138] S. Dimitrov, T. Lange, C. Benedict, M.A. Nowell, S.A. Jones, J. Scheller, S. Rose-John, J. Born, Sleep enhances IL-6 trans-signaling in humans, FASEB J. 20 (2006) 2174–2176.
[139] M. Keller, J. Mazuch, U. Abraham, G.D. Eom, E.D. Herzog, H.D. Volk, A. Kramer, B. Maier, A circadian clock in macrophages controls inflammatory immune responses, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 21407–21412.
[140] D. Hogan, J.D. Morrow, E.M. Smith, M.R. Opp, Interleukin-6 alters sleep of rats, J. Neuroimmunol. 137 (2003) 59–66.
[141] J.H. Benington, H.C. Heller, Restoration of brain energy metabolism as the function of sleep, Prog. Neurobiol. 45 (1995) 347–360.
[142] J. Horne, Human slow wave sleep: a review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness, Experientia 48 (1992) 941–954.
[143] C. Benedict, J. Scheller, S. Rose-John, J. Born, L. Marshall, Enhancing influence of intranasal interleukin-6 on slow-wave activity and memory consolidation during sleep, FASEB J. 23 (2009) 3629–3636.
[144] A.N. Vgontzas, M. Zoumakis, E.O. Bixler, H.M. Lin, P. Prolo, A. Vela-Bueno, A. Kales, G.P. Chrousos, Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications, J. Clin. Endocrinol. Metab. 88 (2003) 2087–2095.

[145] I. Burgos, L. Richter, T. Klein, B. Fiebich, B. Feige, K. Lieb, U. Voderholzer, D. Riemann, Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study, Brain Behav. Immun. 20 (2006) 246–253.
[146] A.N. Vgontzas, M. Zoumakis, D.A. Papanicolaou, E.O. Bixler, P. Prolo, H.M. Lin, A. Vela-Bueno, A. Kales, G.P. Chrousos, Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime, Metabolism 51 (2002) 887–892.
[147] R.E. Brown, R. Basheer, J.T. McKenna, R.E. Strecker, R.W. McCarley, Control of sleep and wakefulness, Physiol. Rev. 92 (2012) 1087–1187.
[148] U. May, T. Schiffelholz, P.C. Baier, J.M. Krueger, S. Rose-John, J. Scheller, IL-6-trans-signalling increases rapid-eye-movement sleep in rats, Eur. J. Pharmacol. 613 (2009) 141–145.
[149] C.N. Oyanedel, E. Kelemen, J. Scheller, J. Born, S. Rose-John, Peripheral and central blockade of interleukin-6 trans-signaling differentially affects sleep architecture, Brain Behav. Immun. (2015).
[150] B. Klein, J. Wijdenes, X.G. Zhang, M. Jourdan, J.M. Boiron, J. Brochier, J. Liautard, M. Merlin, C. Clement, B. Morel-Fournier, et al., Murine anti-interleukin-6 monoclonal antibody therapy for a patient with plasma cell leukemia, Blood 78 (1991) 1198–1204.
[151] Z.Y. Lu, J. Brochier, J. Wijdenes, H. Brailly, R. Bataille, B. Klein, High amounts of circulating interleukin (IL)-6 in the form of monomeric immune complexes during anti-IL-6 therapy. Towards a new methodology for measuring overall cytokine production in human in vivo, Eur. J. Immunol. 22 (1992) 2819–2824.
[152] N. Nishimoto, T. Kishimoto, Humanized antihuman IL-6 receptor antibody, tocilizumab, Handb. Exp. Pharmacol. (2008) 151–160.
[153] H.I. Brunner, N. Ruperto, Z. Zuber, C. Keane, O. Harari, A. Kenwright, P. Lu, R. Cuttica, V. Keltsev, R.M. Xavier, I. Calvo, I. Nikishina, N. Rubio-Perez, E. Alexeeva, V. Chasnyk, G. Horneff, V. Opoka-Winiarska, P. Quartier, C.A. Silva, E. Silverman, A. Spindler, E. Baildam, M.L. Gamir, A. Martin, C. Rietschel, D. Siri, E. Smolewska, D. Lovell, A. Martini, F. De Benedetti, P. Paediatric rheumatology international trials organisation, G. Pediatric rheumatology collaborative study, efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial, Ann. Rheum. Dis. 74 (2015) 1110–1117.
[154] F. De Benedetti, H.I. Brunner, N. Ruperto, A. Kenwright, S. Wright, I. Calvo, R. Cuttica, A. Ravelli, R. Schneider, P. Woo, C. Wouters, R. Xavier, L. Zemel, E. Baildam, R. Burgos-Vargas, P. Dolezalova, S.M. Garay, R. Merino, R. Joos, A. Grom, N. Wulffraat, Z. Zuber, F. Zulian, D. Lovell, A. Martini, Printo, Prcsg, Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis, N. Engl. J. Med. 367 (2012) 2385–2395.
[155] F. Garcia-Oscos, H. Salgado, S. Hall, F. Thomas, G.E. Farmer, J. Bermeo, L.C. Galindo, R.D. Ramirez, S. D'Mello, S. Rose-John, M. Atzori, The stress-induced cytokine interleukin-6 decreases the inhibition/excitation ratio in the rat temporal cortex via trans-signaling, Biol. Psychiatry 71 (2012) 574–582.
[156] F. Garcia-Oscos, D. Pena, M. Housini, D. Cheng, D. Lopez, M.S. Borland, R. Salgado-Delgado, H. Salgado, S. D'Mello, M.P. Kilgard, S. Rose-John, M. Atzori, Vagal nerve stimulation blocks interleukin 6-dependent synaptic hyperexcitability induced by lipopolysaccharide-induced acute stress in the rodent prefrontal cortex, Brain Behav. Immun. 43 (2015) 149–158.
[157] L.H. Calabrese, S. Rose-John, IL-6 biology: implications for clinical targeting in rheumatic disease, Nat. Rev. Rheumatol. 10 (2014) 720–727.
[158] F. Schaper, S. Rose-John, Interleukin-6: biology, signaling and strategies of blockade, Cytokine Growth Factor Rev. 26 (2015) 475–487.
[159] L.L. Rubin, J.M. Staddon, The cell biology of the blood–brain barrier, Annu. Rev. Neurosci. 22 (1999) 11–28.
[160] W.M. Pardridge, R.J. Boado, Reengineering biopharmaceuticals for targeted delivery across the blood–brain barrier, Methods Enzymol. 503 (2012) 269–292.
[161] N. Bien-Ly, Y.J. Yu, D. Bumbaca, J. Elstrott, C.A. Boswell, Y. Zhang, W. Luk, Y. Lu, M.S. Dennis, R.M. Weimer, I. Chung, R.J. Watts, Transferrin receptor (TfR) trafficking determines brain uptake of TfR antibody affinity variants, J. Exp. Med. 211 (2014) 233–244.
[162] R.J. Boado, Y. Zhang, Y. Wang, W.M. Pardridge, Engineering and expression of a chimeric transferrin receptor monoclonal antibody for blood–brain barrier delivery in the mouse, Biotechnol. Bioeng. 102 (2009) 1251–1258.
[163] R.J. Boado, Y. Zhang, Y. Zhang, W.M. Pardridge, Humanization of anti-human insulin receptor antibody for drug targeting across the human blood–brain barrier, Biotechnol. Bioeng. 96 (2007) 381–391.
[164] R.J. Boado, J.Z. Lu, E.K. Hui, W.M. Pardridge, Insulin receptor antibody-sulfamidase fusion protein penetrates the primate blood–brain barrier and reduces glycosoaminoglycans in Sanfilippo type A cells, Mol. Pharm. 11 (2014) 2928–2934.
[165] R.J. Boado, Y. Zhang, Y. Zhang, C.F. Xia, Y. Wang, W.M. Pardridge, Genetic engineering, expression, and activity of a chimeric monoclonal antibody-avidin fusion protein for receptor-mediated delivery of biotinylated drugs in humans, Bioconjug. Chem. 19 (2008) 731–739.
[166] Q.H. Zhou, J.Z. Lu, E.K. Hui, R.J. Boado, W.M. Pardridge, Delivery of a peptide radiopharmaceutical to brain with an IgG-avidin fusion protein, Bioconjug. Chem. 22 (2011) 1611–1618.
[167] T. Müller, D. Blum-Degen, H. Przuntek, W. Kuhn, Interleukin-6 levels in cerebrospinal fluid inversely correlate to severity of Parkinson's disease, Acta Neurol. Scand. 98 (1998) 142–144.