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Review

Interleukin-6, a Major Cytokine in the Central Nervous System

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Abstract

Interleukin-6 (IL-6) is a cytokine originally identified almost 30 years ago as a B-cell differentiation factor, capable of inducing the maturation of B cells into antibody-producing cells. As with many other cytokines, it was soon realized that IL-6 was not a factor only involved in the immune response, but with many critical roles in major physiological systems including the nervous system. IL-6 is now known to participate in neurogenesis (influencing both neurons and glial cells), and in the response of mature neurons and glial cells in normal conditions and following a wide arrange of injury models. In many respects, IL-6 behaves in a neurotrophin-like fashion, and seemingly makes understandable why the cytokine family that it belongs to is known as neuropoietins. Its expression is affected in several of the main brain diseases, and animal models strongly suggest that IL-6 could have a role in the observed neuropathology and that therefore it is a clear target of strategic therapies.

Key words: Neuropoietin, Neuroinflammation, Neurogenesis, Gliogenesis, Alzheimer's disease, Multiple Sclerosis, Stroke, Trauma.

Interleukin-6, the founding member of the neuropoietins

Cytokines are small proteins initially thought to be components of the immune system, but have since been found to play a much broader role in physiology. Interleukin-6 (IL-6) is a cytokine originally identified as a B-cell differentiation factor (BSF-2) in 1985 [1], as a factor that induced the maturation of B cells into antibody-producing cells. Human IL-6 [2] and IL-6 receptor [3] were cloned soon thereafter. As with many other cytokines, it was soon realized that IL-6 was not a factor only involved in the immune response. In early 1990s it was clear that besides controlling other immune cells such as T cells, IL-6 was also important in the regulation of hepatocytes, hematopoietic progenitor cells, the skeleton, the cardiovascular system, the placenta and the nervous and endocrine systems [4].

The number of cytokines known nowadays is enormous. Structural analysis has allowed the grouping of these proteins into different structural classes such as the helical cytokines, the trimeric tumor necrosis factor (TNF) family, the cysteine knot growth factors and the β-trefoil growth factors [5]. Cytokines can also be grouped according to the type of receptor they bind, which comprise six major families: class I cytokine receptors (the largest family), class II cytokine receptors, TNF receptors, tyrosine kinase receptors, and chemokine receptors [5]. Cytokine families may be named differently according to other aspects such as the sharing of a receptor subunit (i.e. the gp130 family) or its physiological roles (i.e.

neuropoietic family, for its effects on hematopoietic and nervous system).

IL-6 is a prototypical four-helix bundle cytokine that is the founder member of the neuropoietins, a group of cytokines structurally related, that include IL-6, IL-11, IL-27, IL-31, leukemia inhibitory factor, oncostatin M, cardiotrophin-1, neuropoietin and cytokine cardiotrophin-like (also known as new neurotrophin 1 and B cell stimulatory factor-3), and two viral analogs of IL-6 [5-10]. These cytokines bind to class I cytokine receptors, membrane proteins with a characteristic modular architecture that do not have intrinsic enzymatic activity, and that for signaling often need to recruit additional receptor proteins shared by different cytokines: gp130, βc or γc. The IL-6 family of cytokines recruits gp130 for signaling (Figure 1). Thus, the family is also known as the gp130 family of cytokines. This protein has also a modular architecture, part of which has features typical of the cytokine receptors (two fibronectin type III modules containing conserved cysteine residues and a WSXWS motif) [4]. For IL-6 specifically, a hexamer forms (two IL-6, two IL-6R and two gp130) that can activate intracellular tyrosin-kinases such as Janus kinase (JAK) and, to a lesser extent, TYK, which, in turn, activate a number of proteins including the STAT (signal transducer and activator of transcription) family of transcription factors, or the RAS-RAF-MAPK pathway, PI3 (phosphatidyl inositol-3) kinase, or IRS (insulin receptor substrate) [11]. The sharing of gp130 explains at least in part the redundancy of the actions of these cytokines.

It was soon established that the expression of IL-6R is restricted to some tissues, while that of gp130 is ubiquitous, and that IL-6 may upregulate gp130 expression [12]. The same study already provided evidence that extracellular, soluble IL-6R (sIL-6R) in the presence of IL-6 could activate cells expressing gp130, and stated that naturally occurring sIL-6R could be found in the murine serum. It is now widely accepted that sIL-6R is formed physiologically, either by limited proteolysis of the extracellular domain of membrane IL-6R (mIL-6R) by metalloproteases such as ADAM10 and ADAM17, or by alternative splicing of IL-6R mRNA, and that sIL-6R can bind both IL-6 and gp130 and signal in cells with or without endogenous IL-6R expression, a mechanism known as trans-signaling [13]. To complicate things further, it is also known that a soluble form of gp130 (sgp130) is also formed [14], in this case only by alternative splicing of gp130 mRNA; sgp130 can inhibit trans-signaling but does not affect normal signaling by mIL-6R (Figure 1).

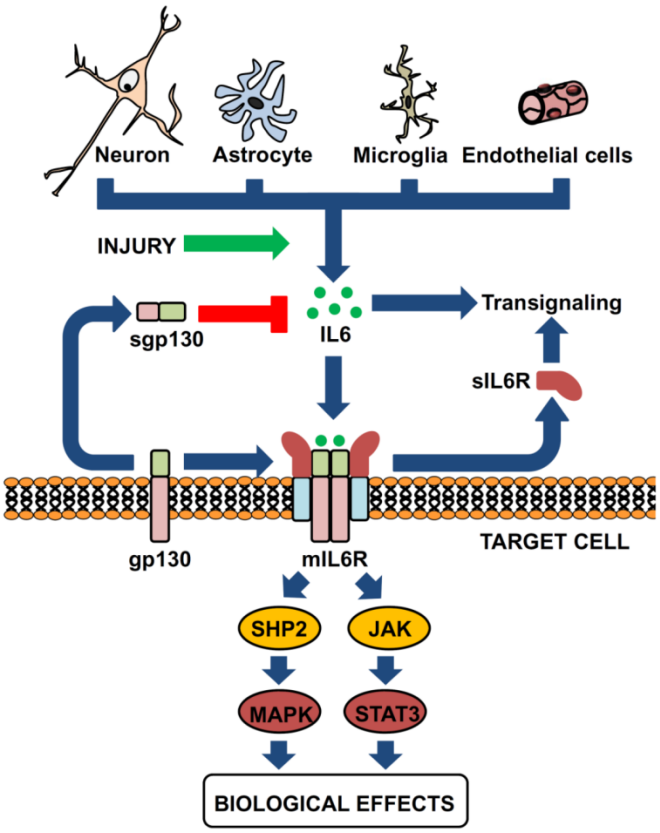

Figure 1. IL-6 is produced by different brain cells and may signal in a complex manner. Neurons, astrocytes, microglia and endothelial cells the essential sources of IL-6 in the CNS. All of them may produce some amounts of IL-6, but upon proper stimuli such as injury copious amounts of IL-6 will be secreted. IL-6 can bind to the membrane-bound IL-6 receptor (mIL-6R, expressed in limited cells) or to the soluble form of the receptor (sIL-6R), which is known as trans-signaling; both of them can properly signal upon interaction with the sgp130 protein (expressed ubiquitously). A releasable form of gp130 can also be found in biological fluids, which will exert inhibitory actions on trans-signaling.

Interleukin-6 expression in the central nervous system

Soon after its discovery, it was demonstrated that some astrocytoma and glioma lines expressed IL-6 when stimulated with IL-1β, which prompted speculation that IL-6 could have a role in the CNS [2]. The same group demonstrated that IL-6 indeed was capable of inducing the neuronal differentiation of the rat pheochromocytoma PC12 cell line, to some extent similarly to the prototypical neurotrophin NGF [15, 16]. It was therefore not surprising the finding that both glial and neuronal cells expressed IL-6 and IL-6R to various degrees throughout the brain [17-24]. In vitro, microglia, astrocytes and the neuronal line N18, but not oligodendrocytes, expressed IL-6R [25]; in vivo, nevertheless, oligodendrocytes may express IL-6 and IL-6R [26]. Also, IL-6 and IL-6R were expressed in sympathetic and sensory ganglia, predominantly in neurons [27], as well as in adrenal chromaffin cells

[28], of adult rats. In line with these results, in vitro studies demonstrated that dissociated sympathetic neurons and PC12 cells expressed IL-6 and the two receptors, IL-6R and gp130 [29, 30]. Besides neurons and glial cells, endothelial cells produce copious amounts of IL-6, which can act on surrounding cells but also in an autocrine manner regulating a number of adhesion proteins but also IL-6 synthesis, particularly in the presence of sIL-6R [31-33]. Thus, both the central and the peripheral nervous system appear to express IL-6 and the corresponding receptors (Figure 1).

Many cytokines and inflammatory factors as well as neurotranmitters and neuropeptides have been shown to affect IL-6 regulation in brain cells; we will comment here some of them studied in in vitro assays. Both virus-infected microglial cells and astrocytes secreted IL-6 [34, 35]. IL-1β and TNFα induced IL-6 in cultured cortical neurons [36] and astrocytes [37, 38], in the latter involving NFκB [39] and the PKC pathway [40]. The AMPc-PKA pathway may also induce astrocytic IL-6 [40-42]. It is likely that membrane depolarization is one of the main mechanisms for neuronal upregulation of IL-6, where Ca^{2+} currents (such as those elicited by the glutamate agonist NMDA) and Ca^{2+}/calmodulin-dependent kinases are critical factors [43, 44]. The major bacterial pathogen, LPS, normally induces IL-6 in both astrocytes and microglia [45-47], but TNF-α induces IL-6 in astrocytes but not microglia [45]. There may be species-specific effects since in human cells in vitro LPS mostly affect microglia rather than astrocytes (obtained from brains at second trimester of gestation) regarding TNFα, IL-1β and IL-6 production, although IL-1β is a potent stimulator of IL-6 production in astrocytes (in microglia the 3 cytokines are upregulated) [46, 48]. GM-CSF stimulates microglial IL-6 but not that of astrocyte [49], whereas IFN-γ induces IL-6 (and NO) in the murine microglial cell line 6-3 [50]; this cytokine does not induce IL-6 in astrocytes unless it is coincubated with IL-1β [37]. Interestingly, adult human astrocyte cultures subjected to mechanical injury upregulated IL-6 [51]. IL-6 production by astrocytes is subjected to autocrine regulation by IL-6, and the addition of sIL-6R synergizes dramatically with IL-1β and TNFα to induce IL-6 [52]. Oncostatin M (OSM) induced IL-6 alone and synergized with TNFα to induce IL-6 [52]. IL-17 functioned in a synergistic manner with IL-6 (+ sIL-6R) to induce IL-6 expression in astrocytes [53].

Norepinephrine, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP38) stimulate IL-6 in astrocytes, and may synergize with IL-1β and TNFα [54-56]; in contrast any of these factors have a major effect in microglia [54]. VIP may induce IL-6 through the PKA pathway and independently of prostaglandins [57, 58]. Prostaglandin E1 (PGE1) and PGE2, but not PGD2 and PGF2 alphaE2, induce IL-6 in human astrocytoma cells; PGE2 potentiates IL-1β induction of IL-6 [59, 60]. The synthetic ceramides C2- and C6-ceramide as well as the enzyme sphingomyelinase were able to induce IL-6 in astrocytes [61]. IL-1β, substance P and histamine induced IL-6 expression in human astrocytoma cells [41, 62], through NF-κB for IL-1β and through NF-IL-6 for SP and histamine [63]. Bradykinin stimulates IL-6 expression through activation of NF-κB in murine astrocytes [64]. Serotonin and adenosine agonists were also effective inducers in human astrocytoma cells [65] [66]; in mouse astrocytes, adenosine induces IL-6 through activation of PKA and NF-IL-6 [67]. TGF-β inhibits microglia proliferation and activation, including IL-6 production [68]; in contrast, it stimulates IL-6 production in astrocytes [69].

Role of interleukin-6 in development and normal physiology

IL-6 may affect neuronal functionality, for instance it induces the cholinergic phenotype of sympathetic neurons [30, 70, 71]. Sensory neurons are particularly affected by IL-6 deficiency, since in normal conditions IL-6 KO mice show a 60% reduction of the compound action potential of the sensory branch of the sciatic nerve and a dramatic decrease of temperature sensitivity in the frontpaw withdrawal time in the hot-plate assay [72]; these neurons are also highly dependent on IL-6 for functional recovery following injury [72, 73]. Results with IL-6 KO mice imply a role for IL-6 on sympathetic sprouting induced by nerve injury [74, 75]. It also promotes sprouting and functional recovery of organotypical cultures of hippocampus [76], and causes a dose-dependent decrease of post-tetanic potentiation (PTP) and long-term potentiation (LTP) in the CA1 region of rat hippocampus [77].

IL-6 also has a notorious role in adult neurogenesis [10, 78], the process of creating new neurons and glial cells from neural stem cells (NSCs) discovered almost 50 years ago [79], which is now known to be dramatically affected by a myriad of factors such as exercise, environmental enrichment, stress, or aging. Not surprisingly, neurogenesis is also altered in many neuropathological situations like stroke, status epilepticus, mechanical damage, and Alzheimer, Parkinson and Huntington diseases; in all these cases a detrimental role of inflammation has usually been suggested [80, 81], and, as stated above, IL-6 will be upregulated and could have a role on neurogenesis.

GFAP-IL6 mice, indeed, show a diminished hippocampal neurogenesis [82], and moreover, in vitro IL-6 clearly decreases the differentiation of neural stem/progenitor cells into neurons [83, 84]. In contrast, IL-6 is involved in oligodendrogliogenesis [85, 86] and astrogliogenesis [84]. Yet, other studies claimed that IL-6 promotes both gliogenesis (through the STAT-3 pathway) and neurogenesis (MAPK/CREB pathway) [87, 88].

Besides effects on neurons, IL-6 also displays a number of effects in glial and endothelial cells. Early in vitro assays showed that both virus-infected microglia and astrocytes secreted IL6, and that IL-6 induced the secretion of the major neurotrophin NGF by the latter [34]. In vitro there is some conflicting results whether or not IL-6 does have proliferative effects on astrocytes [89, 90], probably it does but synergizing with other factors [91]. Microglia in culture consistently proliferate when stimulated with IL-6 [92]IL-6-IL-6/sIL-6R may alter the factors produced by astrocytes: for instance it induces specific patterns of neurotrophins [93], inhibits TNFα [94], and together with sIL-6R and IL-17, it may shift chemokine production to that favoring T cell recruitment to the CNS [95]. Differences in the pattern of cytokines secreted by astrocytes of IL-6 KO mice are readily noticeable in vitro [96]. In vivo experiments demonstrate that IL-6 exerts profound effects on their differentiation, which is dependent on the brain area from which they are isolated [93]. Transgenic mice overexpressing IL-6 show prominent astrogliosis and microgliosis [97-100], whereas the opposite is usually observed in IL-6 KO mice in different models of injury [101-105]. IL-6 alone does not affect intercellular adhesion molecule-1 (ICAM-1) gene expression, but dramatically inhibits the activating effect of IFN-γ, IL-1β and TNFα in rat astrocytes, and that of IFN-γ in microglia, very much alike IL-10 [106]. In human astrocytes, IL-6, sIL-6R or both do not affect VCAM-1 or ICAM-1, but IL-6/sIL-6R complex (and H-IL-6) inhibits TNF-α-induced VCAM-1 gene expression; sIL-6R upregulates endogenous IL-6 production [107]. This inhibitory effect of IL-6 in astrocytes is in sharp contrast with the stimulatory effect it has on endothelial cells, where again sIL-6R greatly affects the activation of endothelial cells, not only upregulating the adhesion proteins E-selectin, ICAM-1 and VCAM-1 but also IL-6, IL-8 and monocyte chemotactic protein 1 (MCP-1); this constitutes a model where neutrophils may retrogradely signal inflammation to endothelial cells by shedding sIL-6R, which can then recruit leukocytes and contribute to their extravasation [32, 108]. Regarding oligodendrocytes, in addition to promoting oligondendrogenesis IL-6 promotes survival and myelin production of oligodendrocytes [85, 86, 109, 110].

Although IL-6 is often related to inflammatory and pathological situations, it is a factor that contributes decisively in the normal function of the brain. Thus, IL-6 is involved in the control of body weight, food intake and energy expenditure [111-115], stimulates the pituitary-adrenal axis [116] [117], induces fever [111, 118, 119] and is for instance very important in the control of body temperature following recovery from stroke [120]. Results with IL-6 KO mice imply a facilitatory role for IL-6 in pain [74, 75], effects on sleep-wake beavior [121], emotional reactivity [122, 123], sickness behaviour [124] and learning and memory [125-127].

Dual role of interleukin-6 in injury/disease

As stated above, soon after its discovery IL-6 was shown to induce the neuronal differentiation of PC12 cells [15, 16]. After these initial studies, a flurry of papers demonstrated that IL-6 affected in many different ways neurons and glial cells. Thus, it was shown to promote the survival of cultured basal forebrain and septal cholinergic neurons and mesencephalic catecholaminergic neurons [128, 129], retinal ganglion cells [130], sympathetic neurons and dorsal root ganglia (DRG), particularly if sIL-6R was added to the culture [30, 131]. It has been suggested that a survival mechanism could be the inhibition of neuronal activity and release of glutamate [132].

In vivo, the role of IL-6 on survival depends on the type of neuron. IL-6 increases with development in DRG, but levels are low in adults; however, following sciatic nerve transection its expression increases dramatically, not only in the DRG but also in many neurons in the corresponding motor nucleus or sympathetic ganglion [133]. Studies in a drop weight model of cortex lesion (closed skull) also indicate that IL-6 expression increases following axonal damage, mainly in neurons [134], thus probably neuronal induction of IL-6 in response to injury is a general response. In the sciatic model, IL-6 expression increases potently within large and medium-sized axotomized neurons [133], whose survival is decreased by 50% in IL-6 KO mice [135]. IL-6 probably promotes survival through inducing BDNF, and indeed in vivo IL-6 KO mice do not upregulate this neurotrophin in DRG following nerve injury [136]. Experiments after injury of the hypoglossal nerve in mice also demonstrated a nerve regenerating role of IL-6 [137]. In contrast, in the facial nerve axotomy model no difference in neuronal survival was observed [104], whereas IL-6 was shown to be detrimental in a model of optic nerve injury [138].

CNS IL-6 is upregulated whenever neuroinflammation is expected, such as following CNS infection or injury or in a number of CNS diseases (Figures 2 and 3). Early studies demonstrated that IL-6 was expressed and produced in CNS during viral meningitis, in encephalitis mouse models, and in CSF of patients with acute viral infections [139]. IL-6 was also found to be upregulated in mouse experimental cerebral malaria (ECM) [140]. Moreover, IL-6 was highly found in CSF of patients with systemic lupus erithematosus (SLE) with CNS involvement [141] or in those in advanced stages of patients with human immunodeficiency virus [142] infections [143]. IL-6 levels in CSF were also significantly higher than plasma levels in patients who had suffered traumatic brain injury [144], and recently an IL-6 polymorphism (-174C/G) has been associated with fatal outcome in patients with severe traumatic brain injury [145]. As expected, IL-6 is upregulated in several animal models of brain injury and shows a myriad of actions as suggested by studies in IL-6 KO mice which show a compromised inflammatory response, increased oxidative stress, impaired neuroglial activation, decreased lymphocyte recruitment and a slower rate of recovery and healing [47, 101, 102, 104, 134, 146-148]. Of note, IL-6 is a critical cytokine controlling the transition from innate to acquired immunity, which is imperative for dealing properly with injured (and infected) CNS tissue, and where IL-6 trans-signalling is dramatically important [149]. In line with the results with IL-6 KO mice, GFAP-IL-6 mice (which overexpress IL-6 in the CNS) showed more rapid healing and recovery after traumatic brain injury because of extensive revascularization [148, 150]. The transcriptomic analysis of IL-6KO mice versus WT mice [151] and that of GFAP-IL-6 mice [152] in a model of brain cortex cryoinjury revealed that IL-6 modulates the expression of many genes involved in inflammation, apoptosis and oxidative stress among others.

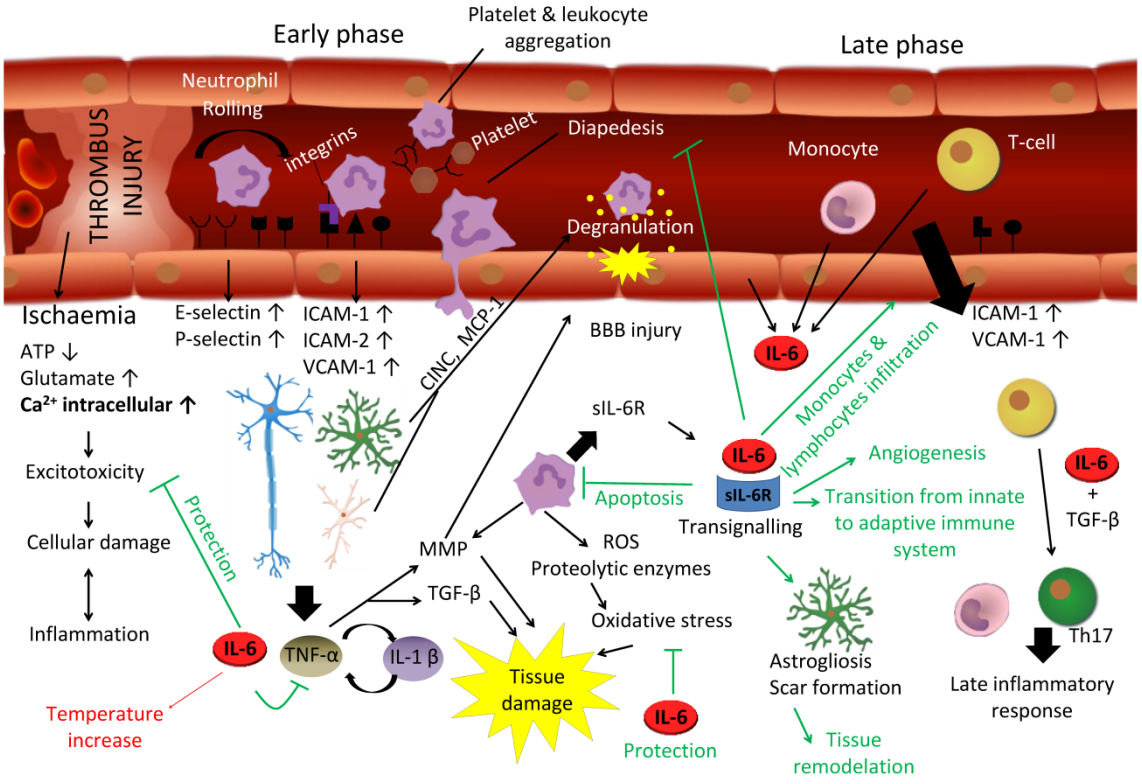

Figure 2. IL-6 has a major role in the response of the brain to injury. To some extent the response of the brain to trauma and stroke is similar. Stroke may be caused by an embolus/thrombus occlusion, an hemorrhage or a vasospasm, resulting in ischemia. Hypoxia initiates a biochemical cascade leading towards cell death, involving excitotoxicity, oxidative stress and apoptosis in which IL-6 has a protective effect. In the early response, neutrophils extravasate to nervous parenchyma involving a process of rolling, activation and transmigration due to an upregulation of P and E-selectin, followed then by an upregulation of ICAM and VCAM. Neutrophils are a rich source of sIL-6R, and damaged resident cells produce IL-6, TNF-α, IL-1β and chemokines, enhancing leukocyte migration toward parenchyma. TNF-α and IL-1β lead to neutrophil degranulation and tissue destruction by means of metalloproteinase (MMP) and TGF-β, while IL-6 inhibits TNF-α and neutrophils' diapedesis. Moreover, it induces apoptosis in neutrophils in a negative feedback loop. In the late phase of this response, IL-6 orchestrates the transition between innate and adaptive immune response, not only inhibiting neutrophils but recruiting monocytes and T-cells for a late inflammatory response. Besides, it induces astrogliosis and angiogenesis needed for the tissue remodelation and recovering. On the other hand, IL-6 exhibits a detrimental effect for instance in relation with body temperature increase, critical in the patient outcome. If deregulated, chronic IL-6 may cause significant brain damage.

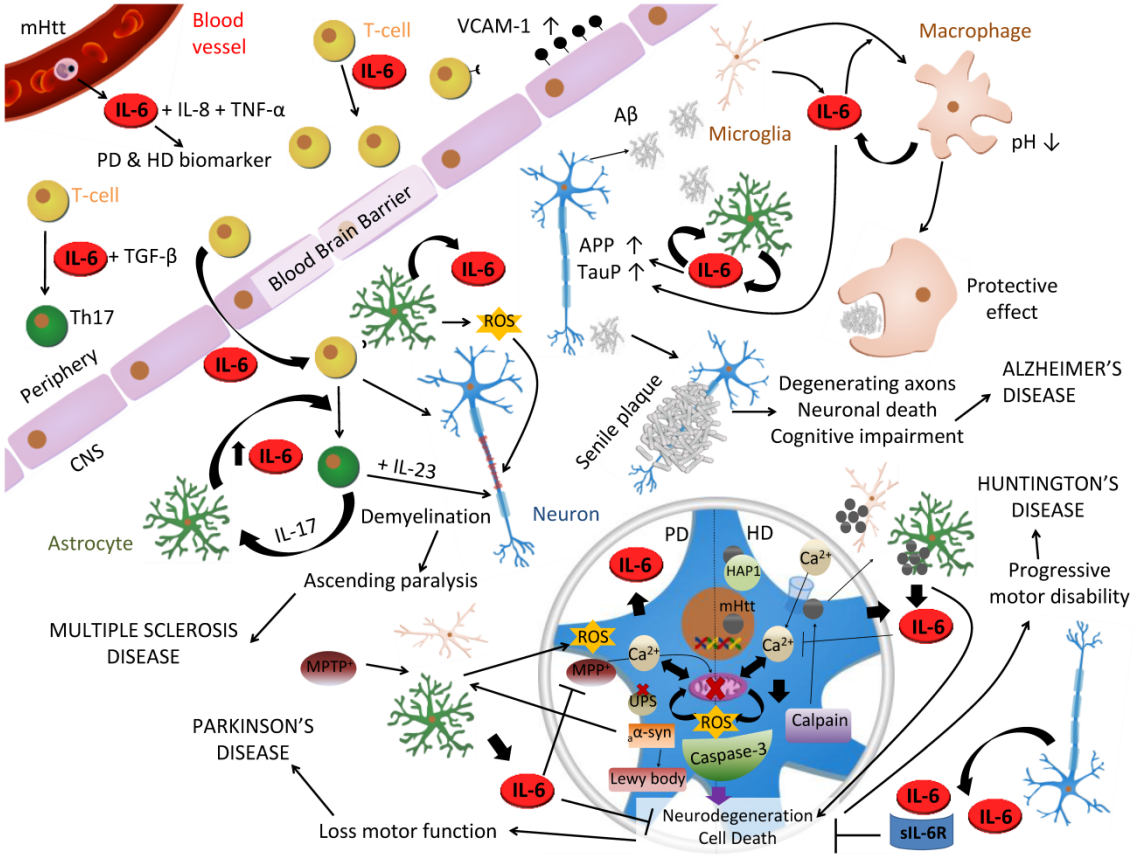

Figure 3. Role of IL-6 in CNS diseases. IL-6 has been related to many brain diseases. In Multiple Sclerosis (MS) IL-6 influences T-cell function inducing its proliferation and infiltration into CNS by upregulation of VCAM-1 on the vascular endothelial cells. In the presence of TGF-β, it also induces T-cells differentiation into Th17 cells, which secrete IL-17 that stimulates IL-6 production in astrocytes in a positive feedback loop. Besides, T-cell direct contact induces production of IL-6, reactive oxygen species (ROS) and nitric oxide (NO) in astrocytes, which contribute to damaging myelin sheath and neurons that will led to ascending paralysis and, as long as IL-23 is present, the fully development of MS. In Alzheimer's disease, Amyloid-β peptide (Aβ) produced by cleavage of amyloid precursor protein (APP), induces microgliosis, astrogliosis and triggers IL-6 production in both types of cells which upregulates APP and hyperphosphorylates tau in neurons. Aβ is accumulated in the extracellular space forming senile plaques and inducing neuronal death. However, IL-6 can play a protective role differentiating microglia into phagocytic macrophages capable of degrading Aβ. Mutant Huntingtin (mHtt), associated with Huntington's disease [208], is a CAG expansion translated into intracellular polyglutamine inclusions which are toxic for the cell due to different pathways: increase in intracellular Ca^{2+} due to NMDA receptor binding, increase mitochondrial dysfunction with ROS production, and axonal transport disruption due to mHtt/HAP1 complexes. Elevated intracellular Ca^{2+} activates caspases and calpains, which cleave mHtt into toxic N-terminal fragments triggering apoptosis in a positive feed-back loop. Furthermore, calpain causes autophagy inhibition resulting in high levels of mHtt in another positive feed-back loop. Moreover, microglia cells expressing mHtt also contribute to neuronal cells degeneration. Parkinson's disease (PD) is considered a synucleinopathy due to an abnormal intracellular accumulation of insoluble alpha-synuclein aggregations ($_a$α-syn) in the form of Lewy bodies in dopaminergic (DA) neurons due to a mutation, a toxic or an idiopathic form. Its etiopathogenesis remains unclear but, like HD, neuronal death is thought to be as a result of mitochondrial dysfunction with ROS production, an intracellular increase of Ca^{2+}, oxidative stress and alterations in the ubiquitinproteasomal system (UPS) that become incapable to degrade $_a$α-syn, which triggers microglia to produce ROS. All together produce neurodegeneration and PD symptomatology. MPTP is metabolized into MPP+ by glial cells and primarily kills DA neurons, by interfering with mitochondrial metabolism, producing PD symptoms and being able to model a toxic PD in animals. In both diseases, IL-6 protects against Ca^{2+} and ROS excitotoxicity decreasing neuronal death.

Stroke patients also show significant elevations of CSF and serum IL-6 shortly after the ischemic event that correlate with brain infarct volume, and IL-6 haplotype affects both infarct size and IL-6 levels [153-157]. Ischemic brain injury involves inflammation, excitotoxicity, oxidative damage and apoptosis, and thus to some extent it is a similar scenario as that following traumatic brain injury. It is therefore not surprising that IL-6 may be an important factor orchestrating the responses elicited by stroke. In animal models of cerebral ischemia it has been a consistent finding an upregulation of IL-6, mostly in neurons but also in glial cells and vascular endothelium [158-161]. In line with the in vitro studies detailed above, neuronal IL-6 upregulation following cerebral ischemia is likely mediated by glutamate-induced neuronal depolarization [44, 162, 163]. Several of these studies clearly demonstrated a neuroprotective role of exogenously administered IL-6, as did experiments injecting anti-mouse IL-6 receptor monoclonal antibody [164] and with IL-6 KO mice provided body temperature is controlled [120, 165]. Controlling oxidative

stress [166] and angiogenesis [165] are among the attributed functions of IL-6 during stroke. Epileptic seizures often involve excitotoxicity, and thus it was expected to find that patients suffering of epilepsy show increased CSF levels of IL-6 after seizures [167], and that well-known animal models of epilepsy such as the glutamate analog kainic acid (KA) upregulate CNS IL-6 [162]. IL-6 KO mice are more susceptible to various convulsant stimuli including several glutamate analogs and show clear signs of increased hippocampal damage [168-170]. Yet, this is a complex system, since intranasal administration of IL-6 to rats [171] and transgenic IL-6 expression in the brain [172] are proconvulsive. Also, some authors also claim a damaging role of IL-6 on neuron development in culture and on the response to NMDA [173] [174]. The reasons for such dual effects of IL-6 remain uncertain, but probably reflect that the context has a dramatic effect as often is the case with growth factors.

As a prototypical cytokine with roles in the control of inflammation, IL-6 is altered in CNS diseases where neuroinflammation may have a role. It is therefore not surprising that IL-6 expression is altered in the brains of Alzheimer's disease (AD) patients, being increased around amyloid plaques and in cerebrospinal fluid [175-179]. IL-6 stimulated the synthesis of the AD beta-amyloid precursor protein [180, 181], and, conversely, IL-6 is upregulated in cultured glial cells upon stimulation with the carboxy-terminal 105 amino acids of APP [182]. Moreover, IL-6 also enhances neuronal damage induced by beta-amyloid peptide in cultured rat cortical neurons [174]. Despite this detrimental role of IL-6 seen in vitro, in vivo studies with AD transgenic mouse models rather show a beneficial role of IL-6, in principle due to a massive gliosis which attenuated beta-amyloid peptide deposition and enhanced plaque clearance [183]. This is not unexpected as activated microglia can efficiently phagocytize beta-amyloid peptide and delay pathology course in transgenic models [184-186]. Astrocytes also may be involved in the clearance of beta-amyloid peptide [187], also by regulating microglial phagocytosis [188]. In humans, attempts to find important interactions between polymorphisms in specific alleles, such as the IL-6-174 G/C promoter allele, and genotype frequencies, are not conclusive [189-191]. The -572C/G polymorphism of IL-6 gene promoter region is another polymorphism that might be associated with AD [192].

Multiple sclerosis (MS) is an inflammatory demyelinating autoimmune disease of CNS mediated by CD4+T cells and soluble inflammatory mediators, in which IL-6 has an important role. While there is significant controversy on whether or not MS is correlated with either plasma or CSF IL-6, sIL6R and sgp130 levels [193-196], it has been demonstrated the presence of IL-6 in acute and chronic active plaques of MS patients, mainly associated with astrocytes rather than macrophages or mononuclear infiltrating cells [197]. Yet, the association of MS with IL-6 polymorphisms is again not conclusive [198, 199]. One of the most common animal model of MS is Experimental Autoimmune Encephalomyelitis (EAE) [200]. IL-6 is upregulated in CNS during EAE [201], and different approaches have demonstrated a major role of this cytokine. Thus, it was soon established that neutralization of IL-6 with antibodies led to a reduced disease [202], which later on was seen to be due to the suppression of the MOG-induced differentiation of naive T cells into Th17 and Th1 cells [203]. A seminal series of early studies demonstrated that IL-6 deficient mice were resistant to EAE [204-207], highlighting the essential role of this cytokine. Absence of infiltrating cells in the CNS, reduction of lymphocyte proliferation, change of the cytokine profile and failure to stimulate endothelial VCAM-1 were some of the reasons suggested to be responsible for resistance to EAE at the time. Trans-signaling is also crucial for EAE induction as its blockade with gp130-Fc fusion protein delayed the onset of adoptively transferred EAE compared to controls due to a reduction in VCAM-1 expression on spinal cord microvessels [208]. Since the discovery of two novel subsets of T helper cells, named Treg and Th17 cells, and its importance in MS, it has been shown that IL-6 has a major role in Th17 cell differentiation from naive $CD4^+$ T cells, particularly in the EAE model [203, 209, 210]. Th17 cells produce IL-17 (among other cytokines) which enhances IL-6 production by astrocytes, which in turn induces differentiation of Th17 cells in a positive feedback loop between IL-17 and IL-6 [53, 211]. Although EAE is considered a disease mostly induced peripherally, the fact is that the CNS local milieu may have dramatic effects. Thus, the GFAP-IL6 mouse model of chronic transgenic IL-6 expression [97] presents an atypical EAE due to a retargeting of the immune attack, with no signs of spinal cord damage while showing a prominent cerebellar damage [212]. The mechanisms responsible for these responses to IL-6 in the cerebellum are complex and likely to include an increased vascular activation, loss of integrity of the BBB and the induction of specific cytokines and chemokines.

Parkinson's disease (PD) is a degenerative disorder of the CNS with severe motor impairment, like shaking or rigidity among many others, due to the death of dopaminergic neurons in the substantia nigra. IL-6 is upregulated in PD [213, 214], and IL-6

levels in the CSF of PD patients are elevated [215], although an inverse correlation between severity of PD and IL-6 levels is observed [216]. IL-6 KO mice show increased vulnerability to the MPTP, a molecule that is metabolized into the complex I inhibitor MPP+ by astrocytes and is a selective dopaminergic toxin [217], whereas IL-6 is capable of protecting rat dopaminergic neurons from the neurotoxicity of MPP^+ [218]. Altogether, the results with these animal models of PD suggest that IL-6 could be exerting a neuroprotective role during PD.

Huntington's disease [208] is an inherited neurodegenerative disorder with both neurological and systemic abnormalities, characterized by abnormalities in the huntingtin gene. IL-6 expression is dramatically elevated in the striatum of HD patients, and in general these patients show clear signs of abnormal immune activation, IL-6 being one of the cytokines affected and monocytes, macrophages and microglia (from both HD and mouse HD models) being overactive upon stimulation [219]. IL-6 is suggested to be neuroprotective as concluded from results with the quinolonic acid rat model of HD [220].

IL-6 has also been related to some psychiatric disorders. IL-6 is significantly elevated and highly correlated with major depression [221, 222]. Some studies have pointed out that IL-6 levels in CSF but not in plasma were increased in combat veterans with posttraumatic stress disorder (PTSD) in comparison with those of controls [223], and that IL-6 and/or sIL-6R levels in plasma but not sgp130 were significantly higher in PTSD patients respect to controls, and higher in PTSD patients with concurrent major depression than in PTSD patients or controls [224]. IL-6 has also been related with schizophrenia (SZ), a complex neurological disorder characterized by a breakdown of thought processes and by poor emotional responsiveness, commonly manifested with hallucinations, delusions, paranoid and mental deterioration [225, 226]. Thus, a single maternal injection of IL-6 during pregnancy causes schizophrenia-like behavioral abnormalities in WT mice but not in IL-6 KO mice [227]. Finally, IL-6 has been found to be increased in the cerebellum of autistic brain [228] and has been suggested to mediate autism-like behaviors [229].

Perspectives

IL-6 is a major cytokine in the central nervous system. Many of its effects are caused by trans-signaling, while others are mediated by the membrane receptor; both can be essentially considered an integrated, unique system. The relevance of trans-signaling in vivo in a number of peripheral and CNS diseases is widely recognized [111, 149, 230-234], and not surprisingly therapeutic approaches aiming to counteract IL-6 effects not only focus in IL-6 membrane receptor [235-238] but also in IL-6/sIL-6R complex [13, 239-241]. Likewise, sgp130 is also of an invaluable utility to specifically block diseases states in which trans-signaling responses exist [232, 234, 241], to the extent that the molecule has recently been structurally-optimized to better antagonize trans-signaling pathologic effects [242]. Still, we must keep in mind that IL-6 has a role in the normal brain, and interfering with them may be a significant source of concern. Finally, we need to understand in vivo what the role(s) of IL-6 are to be due to specific cellular production of and response to IL-6; hopefully the production of floxed mice for IL-6 will help to answer these questions.

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Competing Interests

The authors declare that no competing interest exists.

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