Role of Interleukin-10 in Acute Brain Injuries

Joshua M. Garcia1†, Stephanie A. Stillings1†, Jenna L. Leclerc2,3†, Harrison Phillips4, Nancy J. Edwards5,6, Steven A. Robicsek4,7,8, Brian L. Hoh7, Spiros Blackburn9 and Sylvain Doré2,3,10,11,12,13*

1 College of Medicine, University of Florida, Gainesville, FL, United States, 2 Department of Anesthesiology, College of Medicine, Center for Translational Research in Neurodegenerative Disease, University of Florida, Gainesville, FL, United States, 3 Department of Neurosurgery, University of Florida, Gainesville, FL, United States, 4 Department of Anesthesiology, University of Florida, Gainesville, FL, United States, 5 Department of Neurology, University of California, San Francisco, CA, United States, 6 Department of Neurosurgery, University of California, San Francisco, CA, United States, 7 Department of Neurosurgery, University of Florida, Gainesville, FL, United States, 8 Department of Neurology, University of Texas, Houston, TX, United States, 9 Department of Neurosurgery, Center for Translational Research in Neurodegenerative Disease, McKnight Brain Institute, University of Florida, Gainesville, FL, United States, 10 Department of Psychology, Center for Translational Research in Neurodegenerative Disease, McKnight Brain Institute, University of Florida, Gainesville, FL, United States, 11 Department of Psychiatry, Center for Translational Research in Neurodegenerative Disease, McKnight Brain Institute, University of Florida, Gainesville, FL, United States, 12 Department of Pharmaceutics, Center for Translational Research in Neurodegenerative Disease, McKnight Brain Institute, University of Florida, Gainesville, FL, United States

Interleukin-10 (IL-10) is an important anti-inflammatory cytokine expressed in response to brain injury, where it facilitates the resolution of inflammatory cascades, which if prolonged causes secondary brain damage. Here, we comprehensively review the current knowledge regarding the role of IL-10 in modulating outcomes following acute brain injury, including traumatic brain injury (TBI) and the various stroke subtypes. The vascular endothelium is closely tied to the pathophysiology of these neurological disorders and research has demonstrated clear vascular endothelial protective properties for IL-10. In vitro and in vivo models of ischemic stroke have convincingly directly and indirectly shown IL-10-mediated neuroprotection; although clinically, the role of IL-10 in predicting risk and outcomes is less clear. Comparatively, conclusive studies investigating the contribution of IL-10 in subarachnoid hemorrhage are lacking. Weak indirect evidence supporting the protective role of IL-10 in preclinical models of intracerebral hemorrhage exists; however, in the limited number of clinical studies, higher IL-10 levels seen post-ictus have been associated with worse outcomes. Similarly, preclinical TBI models have suggested a neuroprotective role for IL-10; although, controversy exists among the several clinical studies. In summary, while IL-10 is consistently elevated following acute brain injury, the effect of IL-10 appears to be pathology dependent, and preclinical and clinical studies often paradoxically yield opposite results. The pronounced and potent effects of IL-10 in the resolution of inflammation and inconsistency in the literature regarding the contribution of IL-10 in the setting of acute brain injury warrant further rigorously controlled and targeted investigation.

Keywords: concussion, endothelium, intracerebral hemorrhage, ischemia, stroke, subarachnoid hemorrhage, traumatic brain injury, vasculature
INTRODUCTION

Stroke and traumatic brain injury (TBI) are devastating acute neurological disorders that can result in high mortality rates or long-lasting disability. Approximately 87% of strokes are ischemic and 13% are hemorrhagic, with 10 and 3% of the latter representing intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), respectively (1). Stroke is the fourth most common cause of death in the United States, and ischemic stroke (IS) in particular is the seventh most frequent emergency department presentation (2, 3). TBI and concussions have over twice the incidence of all strokes combined (4), with more than three million people in the United States alone living with long-term disability as a result of TBI (5). Collectively, stroke and TBI have very few treatments, and despite advances in clinical management of these disorders, they are still associated with significant disability and mortality (6, 7).

Inflammation plays a central role in the pathophysiology of stroke and TBI and can have both protective and harmful effects on brain tissue (8–15). Although there are some distinct differences in the inflammatory cascades following the various types of acute brain injury, there are also numerous commonalities. Acute neuroinflammation is characterized by the activation of resident central nervous system (CNS) immune surveillance glial cells that release cytokines, chemokines, and other immunologic mediators, which facilitate the recruitment of peripheral cells such as monocytes, neutrophils, and lymphocytes (8, 9, 12, 15). Collectively, this initial response is helpful in the clearance of toxic entities and the restoration and repair of damaged tissue. However, during the resolution phase, with an uncontrolled and prolonged inflammatory response, secondary damage results from overactivation of this inflammatory surge and release of additional factors that lead to breakdown of the blood–brain barrier (BBB), cerebral edema, cerebral hypertension, and ischemia.

Interleukin-10 (IL-10) is generally known as an anti-inflammatory cytokine that exerts a plethora of immunomodulatory functions during an inflammatory response and is particularly important during the resolution phase. Expression of IL-10 in the brain increases with CNS pathology, promoting neuronal and glial cell survival, and dampening of inflammatory responses via a number of signaling pathways (16). IL-10 was originally described as cytokine synthesis inhibitory factor and in addition to attenuating the synthesis of proinflammatory cytokines, IL-10 also limits inflammation by reducing cytokine receptor expression and inhibiting receptor activation (16). Furthermore, IL-10 has potent and diverse effects on essentially all hematopoetic cells that infiltrate the brain following injury. For example, IL-10 reduces the activation and effector functions of T cells, monocytes, and macrophages, ultimately ending the inflammatory response to injury (17). The structure, function, and regulation of IL-10 have been extensively reviewed elsewhere, including a review of IL-10 in the brain (16–20), although not in the context of the various forms of acute brain injury. Please refer to the aforementioned reviews for additional details, including the potential cellular sources, target cells, signal transduction, and mode of action of IL-10.

Given the intriguing multifactorial role of IL-10 in the resolution of inflammatory cascades that are important for promoting neurologic recovery from acute brain injury, here we present a comprehensive literature review of preclinical and clinical studies in this area. We focus on the contribution of IL-10 in modulating various important parameters and pathophysiologic processes important for IS, SAH, ICH, and TBI outcomes, and whether IL-10 has therapeutic or biomarker potential. A better understanding of the many functions of IL-10 in the brain after injury, particularly in the resolution phase of inflammatory processes, will promote our knowledge of the pathophysiology of these debilitating disorders and guide future development of novel therapeutic approaches.

VASCULAR ENDOTHELIUM, REMODELING, AND DYSFUNCTION

The neurovascular unit, including the vascular endothelium, has become a therapeutic target of interest in the various types of acute brain injury (14, 21–24). IL-10 has an assortment of functions acting at the vascular and endothelial level, such as modulating vascular remodeling, reducing leukocyte adhesion and extravasation, mitigating leukocyte–endothelial interactions that facilitate coagulation, promoting vasodilatation via increased production of nitric oxide, and direct protection of the endothelium from oxidative stress via the downregulation of harmful reactive oxygen species (ROS)-producing enzymes, and/or the upregulation of antioxidant pathways.

IL-10 in Preclinical Studies

Interleukin-10 deficiency results in a spectrum of problems with the vasculature, including everything from vascular and endothelial damage from increased oxidative stress and inflammation to deleterious remodeling and an inability of the vasculature to respond to physiological demands such as the requirement for vasodilation. IL-10 inhibits Nox1, a subunit of NADPH oxidase, which plays a role in degenerative vascular remodeling by generating ROS, causing oxidative stress (25). IL-10 knockout (IL-10−/−) mice have higher levels of Nox1, Nox2, and p22phox (two additional NADPH oxidase components) and superoxide production and display decreased aortic medial thickness, a loss of smooth muscle cells, and increased vascular collagen deposition, indicating harmful vascular remodeling with IL-10 deficiency (25, 26). Administration of a superoxide scavenger in IL-10−/− mice prevented vascular remodeling, suggesting the oxidative stress-dependent mechanism (ROS formation by NADPH oxidase) of injurious vascular remodeling with IL-10 deficiency (26). Additionally, IL-10 deficiency led to increased levels of matrix metalloproteinase-9 (MMP-9) in aortic smooth muscle cells, IL-6 in aortas, and the vasoconstrictor endothelin-1 in plasma (25).

Interleukin-10 attenuates endothelial dysfunction and vasconstriction mediated by ROS, endothelin-1 (27), angiotensin II (28), and by ischemia-reperfusion injury (29), among other mediators, and these protective mechanisms may become more important with age. Old, but not young, IL-10−/− mice have diminished vasodilatory responses to acetylcholine, while the
nitroprusside response is intact, suggesting endothelial rather than vascular smooth muscle dysfunction (26). Additionally, viral transduction of canine basilar arteries with IL-10 increases vasodilatory responses and reduces levels of ICAM-1 and VCAM-1, further supporting the protective role of IL-10 on the endothelium (29). IL-10 has also been shown to act via the AKT pathway to decrease TNF-α-directed ceramide synthesis, resulting in lower levels of ROS and ICAM-1 (30). In aortic rings from IL-10−/− mice, TNF-α reduces endothelial nitric oxide synthase expression and vasodilatory ability, and IL-10 administration restores function, providing a protective effect (31). A similar experiment showed that murine aortic rings treated with angiotensin II showed impaired relaxation that was reversible with IL-10 administration (32). High cyclooxygenase-2 activity also plays a role in these stiffer vessels seen in IL-10−/− mice, ultimately resulting in decreased vascular relaxation, impaired cardiac function, and a larger heart size (33).

The source of endothelial protective IL-10 may come from CD4+CD25+ regulatory T cells (Tregs) (34), as well as the various other types of IL-10-producing cells, including B cells (see the “IS” section below). For example, hypertensive IL-10−/− mice transduced with hypertensive wildtype (WT) Tregs have a better vasodilatory response to acetylcholine and lower levels of NADPH oxidase, whereas hypertensive IL-10−/− Tregs does not confer protection on hypertensive WT mice (34). In middle-aged spontaneously hypertensive rats that display features similar to early-stage human cerebral small vessel disease, there is a decreased level of IL-10 in the cerebrospinal fluid and other immune changes (35).

Of interest, inflammation mediated by toxic bacterial agents, such as lipopolysaccharide (LPS), is more severe in IL-10−/− mice (36). Surprisingly, cerebral bacteremia may result in so much endothelial damage in the absence of IL-10 as to cause ICH and death shortly following peak bacterial loads (37). These findings are associated with increases in the FAS/FAS-ligand apoptotic pathway, which IL-10 reverses (37). However, the effects of IL-10 seem to be specific to the noxious stimuli generating its production. For example, IL-10 produced in response to both LPS and Borrelia burgdorferi reduces lymphocyte endothelial migration and blunts endothelial production of chemokines; however, IL-10 produced in response to IL-1β and TNFα does not show such effects (38).

Summary of Evidence Describing the Role of IL-10 in Protecting the Vasculature

Given the intimate tie between the vascular endothelium and pathophysiology of all forms of acute brain injury, it is important to consider the effects of IL-10 on the vasculature. The above studies have shown that following injury, the inflammatory system works on many different levels to cause endothelial cell damage and vascular dysfunction. IL-10 appears to play a central and multifaceted role in attenuating these effects and facilitating the resolution phase of the inflammatory system. In contrast, low or absent IL-10 leads to several changes in gene expression that ultimately results in deleterious vascular remodeling and impaired vascular relaxation in response to physiologic mediators (Figure 1), outcomes that would exacerbate secondary brain damage following acute injury. In summary, IL-10 plays a crucial role in restoring vascular function following injury to the vasculature, similar to that which occurs after IS, SAH, ICH, and TBI.

ISCHEMIC STROKE

Ischemic stroke occurs when a local thrombus or embolus occludes in a cerebral vessel and obstructs blood flow to the brain. Approximately 800,000 people per year in the United States experience a new or recurrent stroke (1) and approximately 33% of these patients will die within 1 year post-stroke (39). Consequently, IS is a significant cause of morbidity, particularly in the elderly, where approximately half of these patients will have

![Low IL-10 Levels Lead to Impaired Vascular Relaxation](https://example.com/figure1.png)

**FIGURE 1 |** Role of interleukin-10 (IL-10) in vascular remodeling and dysfunction. Low or absent IL-10 results in numerous changes to the vasculature leading to harmful vascular remodeling and impaired vascular relaxation in response to important physiologic mediators.
enduring moderate-to-severe neurologic deficits (40). Tables 1–3 provide a summary of the IL-10 preclinical and clinical IS studies described below.

**IL-10 in In Vitro Models**

Cortical neuron cultures from IL-10−/− mice are more susceptible to neurotoxicity following excitotoxicity and combined oxygen–glucose deprivation, and administration of exogenous IL-10 provides neuroprotection to cultures from both WT and knockout strains (42). This IL-10-mediated protection was later separately shown to be via the IL-10 receptor on cortical neurons and PI3K/AKT and STAT3 signal transduction pathways (87). The transcription factor Nrf2 is expressed widely throughout the body and upregulates the expression of numerous antioxidant genes in response to oxidative stress (88, 89). In astroglia preconditioned to oxidative stress, neuroprotection from oxidative stress–glucose deprivation was reported to be via an Nrf2/IL-10-dependent mechanism (90). Lipocalin-2 is significantly increased in neurons following stroke and is proposed to signal stress from injured neurons to supporting glia (91). Lipocalin-2 treatment of microglia results in glial activation, IL-10 release, and enhanced phagocytosis, and conditioned media from these microglia protect neurons from oxygen–glucose deprivation (91).

**IL-10 in Preclinical Models**

In a permanent middle cerebral artery occlusion (MCAO) model, IL-10−/− C57BL/6 mice have 30% larger infarct volumes compared with WT mice 24 h post-stroke (42). In this model, WT and IL-10−/− mice display similar degrees of proinflammatory molecules within the first 6 h. However, after 4 days, the

### TABLE 1 | Summary of IL-10 ischemic stroke preclinical studies.

| Experimental paradigm | Model | Outcomes | Animals | Reference |
|-----------------------|-------|----------|---------|-----------|
| –                     | pMCAO | IL-10 is upregulated in neurons after stroke | Wistar | (41)      |
| –                     | tMCAO | Hypertension blunts neuronal upregulation of IL-10 | Wistar, spontaneously hypertensive rats | (41)      |
| IL-10−/−              | pMCAO | Larger infarct 24 h post-stroke in IL-10-deficient mice | C57BL/6 | (42)      |
| IL-10−/−              | pMCAO | Larger infarct and increased neurologic deficits in IL-10-deficient mice | C57BL/10J | (43)     |
| IL-10−/−, MOG35-55    | tMCAO | CD4+ T cells reduce infarct through IL-10 secretion | C57BL/6 | (44)      |
| IL-10−/−, MOG35-55    | tMCAO | Smaller infarct in WT mice treated with MOG35-55, benefit not seen in IL-10-deficient mice | C57BL/6 | (45)      |
| IV IL-10              | pMCAO | IL-10 significantly reduces infarct volume | Spontaneously hypertensive rats | (46)      |
| ICV IL-10             | pMCAO | IL-10 significantly reduces infarct volume | Spontaneously hypertensive rats | (46)      |
| ICV IL-10             | pMCAO | IL-10 downregulates proinflammatory molecules and reduces infarct volume | C57BL/6J | (47)      |
| Transgenic IL-10      | pMCAO | Transgenics have smaller infarcts and reduced proinflammatory cytokines | C57BL/6J | (48)      |
| Carotid AAV IL-10     | tMCAO | Smaller infarct and less neuronal injury and neurological deficit scores with AAV treatment | Wistar | (49)      |
| IM AAV IL-10          | –     | Reduced stroke incidence, prolonged survival with AAV treatment | Spontaneously hypertensive rats | (50)      |
| H2S donor             | tMCAO | H2S donors at reperfusion lead to increased IL-10 levels and BBB integrity | ICR | (51)      |
| Transgenic IL-32α      | tMCAO | IL-10 and STAT3 upregulation observed in mice with better outcomes | C57BL/6 | (52)      |
| Histone deacetylase inhibition | pMCAO | Treg activation is neuroprotective through IL-10 secretion | C57BL/6J | (53)      |
| IP CD28SA             | pMCAO | Treg amplification reduces infarct through increasing IL-10 levels | C57BL/6J | (54)      |
| SQ G-CSF and SCF      | pMCAO | Early and late treatment improves motor and cognitive function and promotes neurogenesis | C57BL/6, GFP-transgenic mice | (55)      |
| SQ G-CSF and SCF      | pMCAO | Early and late treatment increases IL-10 mRNA and reduces activated macrophages and microglia | C57BL/6 | (56)      |
| IV B-cells-expressing IL-10 | tMCAO | Smaller infarct, less T-cell proliferation | C57BL/6J | (57)      |
| µMT−/−, IV B-cells-expressing IL-10 | tMCAO | IL-10-secreting B-cell replenishment in B-cell-deficient mice reduces infarct volumes | C57BL/6J | (58)      |
| ICV Treg              | tMCAO | Tregs act via IL-10 to promote neural stem cell proliferation | C57BL/6 | (59)      |
| ICV MSC               | pMCAO | Increased IL-10 mRNA and protein levels, smaller infarct, decreased TNFα | Sprague-Dawley | (60)      |
| ICV, IA, IV ADSC      | tMCAO | Smaller infarct, improved neurological function, decreased TNFα | Sprague-Dawley | (61, 62) |

AAV, adeno-associated virus; ADSC, adipose-derived stem cells; CD288SA, CD28 superagonist antibody; G-CSF, granulocyte colony-stimulating factor; IA, intra-arterial; ICV, intracerebroventricular; IM, intramuscular; IL-10, interleukin-10; IP, intraperitoneal; IV, intravenous; MSC, mesenchymal stem cells; SCF, stem cell factor; SQ, subcutaneous; Treg, regulatory T cell; µMT−/−, B-cell-deficient mice.
IL-10<sup>−/−</sup> mice have higher levels of proinflammatory molecules that persist through the end of the first week after stroke (43).

Both systemic intravenous (IV) and central intracerebroventricular (ICV) exogenous administration of IL-10 reduces infarct volumes following permanent MCAO (46). Similarly, in a transgenic C57BL/6J mouse model overexpressing IL-10 (56% increase in the brain and 200% increase in the plasma), infarct volumes were reduced by 40% 4 days following permanent MCAO (48). In the same study, these findings were associated with upregulation of free radical scavengers such as glutathione and manganese superoxide dismutase, reduced activity of the proapoptotic protein caspase 3, and downregulation of NFκB (92). Administration of IL-10<sub>−/−</sub> mice have higher levels of proinflammatory molecules that persist through the end of the first week after stroke (43).

Both systemic intravenous (IV) and central intracerebroventricular (ICV) exogenous administration of IL-10 reduces infarct volumes following permanent MCAO (46). Similarly, in a transgenic C57BL/6J mouse model overexpressing IL-10 (56% increase in the brain and 200% increase in the plasma), infarct volumes were reduced by 40% 4 days following permanent MCAO (48). In the same study, these findings were associated with upregulation of free radical scavengers such as glutathione and manganese superoxide dismutase, reduced activity of the proapoptotic protein caspase 3, and downregulation of NFκB (92). Administration of
were transplanted into the lateral ventricle of Sprague-Dawley study where bone marrow-derived mesenchymal stem cells inflammatory cytokine expression in C57BL/6J mice (56). Another MCAO markedly elevates IL-10 mRNA levels, reduces the levels with these cytokines early (1–10 days) and later (11–20 days) after initial signals to produce IL-10 in the setting of IS (56). Treatment neurogenesis (55) and also may be responsible for providing the such as GCSF and stem cell factor have been shown to promote neural stem cell proliferation (59). Hematopoietic cytokines neuroprotective feedback loop between B cells and Tregs, both of which are B cell-sufficient mice (57). Notably, IL-10-producing B cells also milieu (58). A follow-up to this study showed similar results in the brain parenchyma, and the peripheral proinflammatory MCAO reduced infarct size, the amount of T cells and monocytes IL-10-producing B cells into B cell-deficient mice 24 h after attributing to an increased amount of IL-10 (54). Transferring superagonist monoclonal antibody at onset of reperfusion Treg cell population in the CNS beyond the BBB integrity after ischemia/reperfusion and is accompanied by enhanced IL-10 expression, reduced NFκB nuclear translocation, and MMP-9 and NOX4 activity (51). Moreover, upregulation of IL-10 and the STAT3 pathway and downregulation of NFκB have been proposed as the mechanisms for improved outcomes following cerebral ischemia in mice that overexpress IL-32 (52). A recent whole genome array in C57BL/6 mice showed that stroke upregulated 347 genes 24 h after reperfusion. In this study, ICV injection of IL-10 5 min after occlusion downregulated 341 of these genes (47).

Immune cells, including T and B cells, are important in attenuating neuroinflammation via the modulation of various cytokines and chemokines, with IL-10 playing a central immunomodulatory role (53, 58). Tolerizing mice to oligodendrocyte glycoprotein prior to MCAO reduces infarct size by 70% at 24 h and by 50% at 72 h, but this effect was not seen in IL-10−/− mice (45). This protection is specifically mediated by IL-10 secreted from CD4+ T cells, which were able to protect mice from stroke only when originating from WT mice (44). Elevated levels of IL-10 also reduce the number of CD11b+ cells that may contribute to secondary infarct expansion via nitric oxide pathways (45). Histone deacetylase plays a role in activating the expression of Foxp3 on Tregs, which secrete IL-10, and IL-10 was suggested as the main mediator of attenuated infarct volume and behavioral deficits, reduced levels of proinflammatory cytokines, and increased number of Tregs in the brain of MCAO mice with histone deacetylase inhibition (53). Similarly, expansion of the Treg cell population in the CNS via administration of a CD28 superagonist monoclonal antibody at onset of reperfusion reduced infarct size 7 days following MCAO, and its effect was attributed to an increased amount of IL-10 (54). Transferring IL-10-producing B cells into B cell-deficient mice 24 h after MCAO reduced infarct size, the amount of T cells and monocytes in the brain parenchyma, and the peripheral proinflammatory milieu (58). A follow-up to this study showed similar results in B cell-sufficient mice (57). Notably, IL-10-producing B cells also upregulated the number of Tregs (58), perhaps indicating a positive feedback loop between B cells and Tregs, both of which are neuroprotective via IL-10 production.

Neurogenesis is a highly debated topic for potentially enhancing neural recovery following IS. Injection of activated Tregs into the lateral ventricle of C57BL/6 mice after 60 min of transient MCAO promotes neural stem cell proliferation in the subventricular zone in ischemic and normal mouse brains. However, this effect was eliminated by blocking IL-10 with a neutralizing antibody, indicating that activated Tregs act via IL-10 to promote neural stem cell proliferation (59). Hematopoietic cytokines such as GCSF and stem cell factor have been shown to promote neurogenesis (55) and also may be responsible for providing the initial signals to produce IL-10 in the setting of IS (56). Treatment with these cytokines early (1–10 days) and later (11–20 days) after MCAO markedly elevates IL-10 mRNA levels, reduces the levels of activated microglia/macrophages, and does not change proinflammatory cytokine expression in C57BL/6 mice (56). Another study where bone marrow-derived mesenchymal stem cells were transplanted into the lateral ventricle of Sprague-Dawley rats before permanent MCAO afforded similar results, where IL-10 mRNA and protein levels are increased for up to 4 days post-stroke, TNFx is decreased, infarct volumes are smaller, and neurologic function is preserved (60). Adipose tissue-derived stem cells trigger similar effects as mesenchymal stem cells (61) and are most effective when delivered intravenously at 24 h after MCAO (62). Thus, either administration of stem cells themselves or hematopoietic cytokines seem to improve outcomes following IS in part through increasing IL-10 levels.

IL-10 in Clinical Studies

Several epidemiologic studies have analyzed the genetic contribution of IL-10 to IS risk and outcome. A study in a Chinese population showed that lower basal serum levels of IL-10, an IL-10 promoter single nucleotide polymorphism (SNP) rs1800872 (AA vs. AC + CC), and IL-10 intron SNPs rs1554286 (TT vs. CT + CC) and rs3021094 (CC/CA vs. AA) are all associated with higher risk for IS (70). Similarly, subjects with low IL-10 production in response to LPS stimulation have a higher risk for fatal stroke (74). A study in a South Indian population showed an increased risk of IS with the A allele of the IL-10 promoter SNP rs1800896 (A vs. G), which is associated with low IL-10 production (63). In agreement, a recent meta-analysis showed that the IL-10 1082G/A SNP (rs1800896) is associated with increased risk of IS, but not the 819 C/T SNP (rs1800871) (64, 65). Several other studies further revealed that the IL-10 1082G/A SNP is associated with susceptibility for an IS (66, 67, 93, 94). However, in a different study, the IL-10 1082G/A SNP was not associated with the occurrence of an IS, but the GG genotype predicted early stroke progression and functional dependency independent of other standard risk factors (68). Similarly, another study showed that the IL-10 1082G/A SNP was significantly associated with the risk for specific subtypes of IS, but no significant association was found with the overall risk for an IS (69). A study in a Korean population showed that rs1518111 and rs1554286 are not associated with IS per se, but are associated with hypertension in the risk of IS (71). Similar results were seen in a Russian population, where the IL-10 627*C/*C genotype is protective against hypertension in male patients with stroke (72). One other study in an Eastern Finland population showed that IL-10 plasma concentration independently correlates with cardioembolic high-risk sources, suggesting its usefulness in improving diagnosis of stroke etiology (81). Lastly, in Caucasian patients with peripheral artery disease receiving elective revascularization, the IL-10ATA haplotypes that are associated with lower serum IL-10 levels correlate with a high risk for postoperative cardiovascular events (73).

The relative levels of IL-10 at various times following IS differ from controls and appear to have important implications on IS patient outcomes. For example, at 48 h after IS, mean serum IL-10 is significantly higher than in healthy or at-risk controls, and high IL-10 sera levels independently correlate with severe neurologic deficits (NIHSS ≥12) at 48 h post-stroke and predict major adverse clinical outcomes (recurrent IS, any cause of death, NIHSS ≥12) at 90 days (85). However, in another study, IL-10 levels within the first 72 h after IS were lower than in controls and no significant correlation with NIHSS at admission was observed (78). As compared to those who die, IS patients who improve have been
shown to have lower IL-10 at 24 h, but increased levels at 72 h and 144 h (79). In other studies, low IL-10 levels are associated with acute neurologic decline post-stroke (76, 77). Yet another small study found no correlation with IL-10 and other cytokines and IS patient prognosis (86). IS patients with low levels of IL-10 had a higher incidence of hemorrhagic transformation (75), perhaps providing a link between IL-10 and endothelial integrity. At 7 and 28 days, IS patients appear to have lower number of Tregs and IL-1 and higher relative levels of proinflammatory cytokines such as IL-6 and IL-1β (80). In the Leiden 85- plus study, patients with a history of stroke displayed lower IL-10 production in response to LPS stimulation than subjects without stroke (74). No correlation between IL-10 levels and infarct volume has been found (81, 86). Considerable variation exists among the aforementioned studies and is likely due to the different study populations, relatively small cohort sizes, differences in study methodology, and the consistency or lack thereof for identifying and correcting for covariates. Additional large and controlled prospective studies are needed to establish the link between IL-10 and IS severity, recovery, and outcomes.

Ischemic stroke may induce a functional immunosuppressive state that may persist for several weeks, wherein patients may be more susceptible to infection, and infection is a leading cause of the high mortality rates seen long after stroke (82, 95). The temporal IL-10 profile appears to be different between those that develop stroke-associated infection (82, 83). Two studies have shown that high IL-10 levels at admission or 6 h following ischemia is an independent predictor of infection (82, 83). In one of those studies, TNFα and the TNFα/IL-10 ratio was decreased (82). Another study found that the levels of IL-10-secreting mononuclear cells (MNCs) were highly elevated in IS patients compared with healthy individuals (84). Thus, the immunomodulatory role of IL-10 may be an important consideration in understanding infectious processes and mortality after IS.

**Summary and Comparison of the Role of IL-10 in Preclinical and Clinical IS Studies**

Ischemic stroke invokes a robust local inflammatory response in the brain that significantly contributes to secondary brain damage and poor outcomes. With IL-10 representing a canonical anti-inflammatory cytokine that intriguingly has a special role in the resolution of inflammation, it is not surprising that many studies investigating the role of IL-10 in IS have been performed. In *vitro* models have provided evidence for a neuroprotective function of IL-10 under hypoxic and excitotoxic conditions. In IS preclinical models, IL-10 reduces infarct volume *via* its protective effects on the vascular endothelium and attenuation of inflammatory cascades. Multiple epidemiologic genetic studies have in general shown that polymorphisms in the IL-10 gene that lower IL-10 levels increase the risk of IS. However, clinical studies measuring IL-10 levels after IS are more varied with regard to the role of IL-10 in predicting neurologic outcomes and complications. Even with all of the studies described here, it is clear that additional work is needed to clarify the role of IL-10 in predicting the risk for IS, modulating IS outcomes, and whether IL-10 has biomarker and/or therapeutic potential after IS.

**SUBARACHNOID HEMORRHAGE**

Subarachnoid hemorrhage affects an estimated 7.2–9.0 per 100,000 people/year in the United States (96), and most cases are due to the rupture of a cerebral aneurysm resulting in bleeding within the subarachnoid space (97). Although approximately 15% of people die within a few hours from the bleed and a proportion will never make it to a hospital (98), even those who initially survive the bleed can have significant morbidity and mortality. In addition to early brain injury that occurs at the time of SAH, patients can also develop neurological deficits or die from delayed cerebral ischemia (DCI), which is often secondary to cerebral vasospasm (CV) (99, 100). Among the possible mechanisms for CV and DCI (13, 100–110), inflammation is a common element. IL-10 has not been extensively studied in the context of SAH, despite its proposed pleiotropic immunomodulatory effects relevant to SAH pathophysiology. Tables 4 and 5 provide a summary of the IL-10 preclinical and clinical SAH studies described below.

**TABLE 4 | Summary of IL-10 subarachnoid hemorrhage preclinical studies.**

| Experimental paradigm | Model | Outcomes | Animals | Reference |
|-----------------------|-------|----------|---------|-----------|
| –                     | Cisternal Autologous Blood | Non-significant change in IL-10 mRNA levels in the basilar artery | Mongrel Canines | (111) |
| IGV ACh               | Cisternal Autologous Blood | Non-significant change in CSF IL-10 levels; ACh had no effect on IL-10 level | Sprague-Dawley | (112) |
| –                     | Endovascular Perforation | Non-significant change in IL-10 mRNA levels in the cortex | Wistar | (113) |

ACh, acetylcholine; IGV, intracerebroventricular; IL-10, interleukin-10.

**TABLE 5 | Summary of IL-10 subarachnoid hemorrhage clinical studies.**

| Study modality | Population | Outcomes | Reference |
|----------------|------------|----------|-----------|
| –              | Austrian   | Mean blood IL-10 levels low throughout ICU stay | (114) |
| ELISA          | Swedish    | Microdialysate IL-10 present at low levels and remained constant through 7 days post-bleed | (115) |
| ELISA          | British    | Plasma and CSF IL-10 levels constant through 10 days post-bleed, plasma and CSF levels equal | (116) |
| PCR            | American   | IL-10 mRNA not found in aneurysm walls, but was present in temporal artery controls | (117) |
| TaqMan Allelic Assay | Indian | IL-10 SNPs rs1800871 and 1800872 associated with intracranial aneurysm incidence, no correlation with rupture | (118) |

ICU, intensive care unit; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; IL-10, interleukin-10.
IL-10 in Preclinical Models

Temporal changes in IL-10 are seen following experimental SAH, although these are not statistically significant (111–113). After autologous blood infusion into the cisterna magna of canines, IL-10 mRNA expression in the basilar artery tends to be increased for up to 14 days post-ictus (111). Similarly, IL-10 tends to be increased in the CSF at 6 h and then declines, but remains elevated through 48 h after autologous blood injection into the cisterna magna of male adult Sprague-Dawley rats (112). Interestingly, although acetylcholine was able to attenuate CV in this model, it had no effect on IL-10 levels (112). Last in an endovascular perforation model of SAH in Wistar rats, trends toward higher IL-10 mRNA in the cortex are seen at 48 h (113). In contrast to the less impressive changes in IL-10, these studies have shown highly increased levels of proinflammatory cytokines such as IL-1α (111), IL-1β (113), IL-6 (111, 112), IL-8 (111), and TNFα (111) at 48 h following experimental SAH. Indeed, Aihara and colleagues postulated that the anti-inflammatory effects of IL-10 were overwhelmed by these proinflammatory cytokines such that IL-10 was unable to counteract the deleterious inflammatory processes involved in CV pathophysiology and thereby improve SAH outcomes (111).

IL-10 in Clinical Studies

Studies in humans have also not shown significant changes in IL-10 after SAH (114–117). One study reported that IL-10 mRNA expression was virtually non-existent in aneurysm walls, although it was present in the walls of temporal artery controls (117). In microdialysate, when detectable, IL-10 was present in extremely small concentrations and remained at relatively constant levels through 7 days post-bleed (115). Similarly, IL-10 levels were constant through at least 10 days post-bleed in paired plasma and CSF samples, and the levels were not significantly different between the CSF and plasma (means were below 10 pg/ml) (116). In another study, mean IL-10 blood levels throughout the intensive care unit stay were also quite low (mean ≈11 pg/ml) (114). However, a study in an Indian population showed that IL-10 SNPs rs1800871 and rs1800872 are significantly associated with the incidence of intracranial aneurysms, independent of epidemiological factors, although it is unclear whether this increases the risk for aneurysm rupture and thus the incidence of SAH (118). Additional larger controlled studies are necessary to clarify the association of IL-10 with aneurysm formation and rupture and the role of IL-10 after SAH, including its prognostic and diagnostic predictive potential for SAH outcomes.

Summary and Comparison of the Role of IL-10 in Preclinical and Clinical SAH Studies

In comparison with the other forms of acute brain injury described herein, substantially fewer studies have explored the contribution of IL-10 in the setting of SAH. Preclinical studies have shown non-significant increases in IL-10 after SAH, accompanied by robust changes in proinflammatory cytokines, suggesting an imbalance in the inflammatory milieu that could possibly contribute to prolonged disease course and worse SAH outcomes. In addition, clinical studies have not shown significant changes in IL-10 after SAH, but no studies have investigated whether IL-10 affects clinical outcomes or complications such as CV and/or DCI, or whether IL-10 has therapeutic or biomarker potential. It is clear that additional work is needed to understand how IL-10 changes in the various biocompartments (serum, CSF, brain) after SAH and the resulting implications on SAH pathophysiology.

INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage is characterized by bleeding within the brain parenchyma and can result from various etiologies such as trauma, vascular malformations, medical therapies such as anticoagulants, amyloid angiopathy, and most commonly, hypertension. ICH has a poor prognosis, and there are currently no therapies to decrease the 30-day mortality rate of 35–50% (119). At present, the only available interventions include supportive care, and in some select cases, invasive surgery to evacuate hematomas (120), yet, it is well established that inflammation is a key player in the overall brain damage and edema after ICH that results in enduring neurological deficits. Tables 6 and 7 provide a summary of the IL-10 preclinical and clinical ICH studies described below.

IL-10 in Preclinical Models

Microglia, a primary player in immune surveillance and the initiation of inflammation in the CNS (127), become activated shortly after ICH (12) and secrete proinflammatory cytokines such as TNFα, IL-6, and IL-1β (127). These microglia also secrete IL-10, which acts on astrocytes in the brain to redirect their focus from the production of a proinflammatory cytokine profile toward the production of TGFβ (127). TGFβ then feeds back to act on the microglia and attenuate their proinflammatory response. IL-10 can also increase CD36 expression and thereby enhance the erythrophagocytic ability of microglia, and with CD36 deficiency, mRNA levels of TNFα and IL-1β are higher and IL-10 levels are significantly lower in the perihematomal tissues (123). Additionally, IL-10 levels are significantly increased at 6 h and 7 days after ICH with respect to sham, suggesting that IL-10 may have early and late influences on ICH outcomes (121).

TABLE 6 | Summary of IL-10 intracerebral hemorrhage preclinical studies.

| Experimental paradigm | Model Outcomes | Animals | Reference |
|-----------------------|----------------|---------|-----------|
| −                     | Collagenase IL-10 increased at 6 h and 7 days | Sprague-Dawley | (121) |
| Atorvastatin         | Collagenase Atorvastatin treatment leads to both dose-dependent increases in IL-10 and decreases in TNFα | Sprague-Dawley | (122) |
| CD36−−                | Autologous CD36 deficiency leads to decreased perihematomal IL-10 levels | C57BL/6 | (123) |

LPS, lipopolysaccharide; TGFβ, transforming growth factor-β; TNFα, tumor necrosis factor alpha; IL-10, interleukin-10.
### IL-10 in Clinical Studies

Only a couple of studies have looked at IL-10 genetic polymorphisms and the risk for developing ICH. The IL-10 1082G/A SNP has been identified as a risk factor for ICH in a North Indian population (132). This SNP was not associated with the risk for hemorrhagic presentation of brain arteriovenous malformations (133).

Interleukin-10 and the amount of IL-10-secreting MNCs are elevated in peripheral blood 2 days following ICH (84, 125). Another study found that systemic IL-10 release was significantly higher in ICH patients with left hemisphere hemorrhage compared with those with right hemisphere hemorrhage at 2 days, whereas no such correlation was found for IL-6 (126). Because dysfunction of the autonomic nervous system is a common ICH complication (134), the autonomic nervous system can be regulated asymmetrically, and the sympathetic nervous system can induce a notable increase in systemic IL-10 release, this study posits autonomic dysfunction as a potential mechanism for asymmetrical regulation of IL-10 after ICH (126).

At admission, IL-10 levels are negatively correlated with the Glasgow Coma Scale (GCS), although a stronger negative correlation was found for IL-6 and GCS (125). At 2 days post-bleed, IL-10 levels correlate with IL-6 levels, and IL-6 levels correlate with hematoma volume and mass effect, but IL-10 does not (125).

Hematoma expansion is a major cause of morbidity and mortality after ICH, and inflammation may be associated with its pathogenesis (119). In spontaneous ICH, higher plasma IL-10 levels on admission are associated with hematoma expansion and worse 30-day outcomes (119). Another study also found that plasma IL-10 levels were higher in ICH patients with poor outcome (modified Rankin Scores of 3–6) at 1 month (124), although this study did not utilize a multivariate model.

### Summary and Comparison of the Role of IL-10 in Preclinical and Clinical ICH Studies

Similar to IL-10 and SAH, few studies have explored the contribution of IL-10 in the setting of ICH, although IL-10 appears to be elevated following experimental and clinical ICH. In preclinical models, IL-10 exerts a protective effect against spontaneous cerebral hemorrhage by downregulating TNFα, a key proinflammatory cytokine, and some weak evidence exists suggesting that IL-10 is neuroprotective after ICH. Clinically, very little is evident regarding the contribution of IL-10 polymorphisms. However, other studies generally have found that IL-10 levels correlate with the extent of initial brain injury and have prognostic value, suggesting both diagnostic and prognostic biomarker potential for IL-10 after ICH.

### TRAUMATIC BRAIN INJURY

Traumatic brain injury can result from a direct force like a concussion, an indirect force from a blast injury, or a penetrating injury. TBI is a prevalent clinical problem (9), with an estimated two million people in the United States sustaining a TBI each year (135, 136), leading to an astounding estimated 30.5% of injury-related deaths (137). TBI has substantial long-term effects on patients (137, 138) and imposes a significant financial burden (9, 135, 136, 138). The outcome for a TBI patient is determined by the severity of the initial injury, which is related to the mechanism of primary injury and degree of physical force, and secondary injury, linked to neuroinflammation (8, 9, 139). It is proposed that the majority of damage from TBI is the product of secondary damage, which is closely associated with the production and recruitment of proinflammatory cytokines and other inflammatory mediators (8, 140). Tables 8 and 9 provide a summary of the IL-10 preclinical and clinical TBI studies described below.

### IL-10 in Preclinical Models

Understanding the temporal relationship between the injury and elaboration of IL-10 provides insight into its immunomodulatory role after TBI. A study in adult male Sprague-Dawley rats found that brain IL-10 mRNA expression increases immediately following TBI, whereas IL-10 protein levels are stable initially, and only begin to rise rapidly after 2 h (135). These findings suggest that the surge in IL-10 levels is due to an increase in local IL-10 synthesis rather than systemic IL-10 entering through a leaky BBB. IL-10 protein levels continue to rise through 24 h, although at a slower rate (135). No change in plasma IL-10 levels is seen throughout this timeframe (135). Following repetitive mild TBI,
TABLE 8 | Summary of IL-10 traumatic brain injury preclinical studies.

| Experimental paradigm | Model | Outcomes | Animals Reference |
|-----------------------|-------|----------|-------------------|
| –                     | Weight Drop | IL-10 mRNA increases immediately post-injury, IL-10 protein elevated at 2 h | Sprague-Dawley (135) |
| IL-10 Gelfoam | Corticectomy | Local IL-10 administration reduces reactive astrocytes and TNFα at 4 days | CD1 (141) |
| IL10−/− and SQ IL-10 | CCI | IL-10 treatment at 1 h reduces lesion volume, edema, and improves motor and cognitive function at 5d | C57BL/6 (142) |
| IP IL-10 | CCI | IL-10 treatment reduces inflammation at 5 h, but does not affect cognitive or motor function | Sprague-Dawley (143) |
| IP Triptolide | CCI | Triptolide treatment increases brain IL-10 levels at 1d and improves anatomical and neurobehavioral outcomes | Sprague-Dawley (144) |
| – | Repetitive mTBI | IL-10 lower at days 1, 3, 7, 14, and 30 compared to single mTBI | Sprague-Dawley (145) |
| IL10−/− and HBOT | CCI | HBOT increases serum and ipsilateral cortex IL-10 levels, reduced lesion volume, and improved outcome in WT mice | C57BL/6 (142) |
| HBOT | Fluid Percussion | HBOT increases IL-10 level at 4 days and stimulates angiogenesis and neurogenesis | Sprague-Dawley (146) |
| IV, SQ, SCV | IL-10 | Fluid Percussion | IL-10 treatment (5 µg) improves neurological recovery | Sprague-Dawley (147) |

CCI, controlled cortical impact; HBOT, hyperbaric oxygen therapy; ICV, intracerebroventricular; IP, intraperitoneal; IV, intravenous; mTBI, mild traumatic brain injury; SQ, subcutaneous; TNFα, tumor necrosis factor alpha; IL-10, interleukin-10.

TNFα and IL-6 are higher, and the expression of IL-10 is lower when compared to a single TBI group on days 1, 3, 7, 14, and 30 post-injury (145).

Studies with IL-10−/− mice have suggested that IL-10 is beneficial after TBI, although IL-10 administered after TBI as a therapeutic agent has provided mixed results depending on the experimental paradigm and administration route. At 4 weeks after TBI, 8-week-old IL-10−/− C57BL/6 female mice have larger lesion volumes, increased edema and inflammation, worse motor and cognitive function, and higher levels of BBB dysfunction and apoptosis after controlled cortical impact-induced TBI (142). Additionally, using the lateral fluid percussion TBI model, SQ IL-10 (100 µg) administered 1 h after TBI results in a significant reduction in lesion volume and edema at 5 days, as well as improved recovery of motor and cognitive function (142). In another study using the lateral fluid percussion model and adult male Sprague-Dawley rats, both SQ and IV IL-10 (100 µg) improved neurological recovery, but ICV dosing (1 or 6 µg) did not (147). Although not statistically significant, survival rates in the SQ and IV groups were higher than in the controls, and the ICV group had dose-dependent lower survival rates (147). IV administration also reduced TNFα and IL-1B expression in the injured cortex and hippocampus (147). Although these studies have shown that systemic IL-10 treatment reduces neuroinflammation and improves neurological recovery (142, 147), a different study found that while systemically administered IL-10 (5 µg) does reduce inflammation (75% reduction in neutrophil accumulation) at 5 h, there is no improvement in motor or cognitive recovery (143). Last, central IL-10 administration following corticectomy in adult female CD1 mice results in a reduction in the number of reactive astrocytes and TNFα levels at 4 days (141), corroborating previous studies showing a reduction in neuroinflammation with IL-10 treatment.

A couple of studies with drugs or therapeutic regimens have demonstrated improved TBI outcomes through increased IL-10 protein levels and IL-10-dependent mechanisms. TBI has a significant ischemic injury component associated with poor cerebral blood flow (157). Hyperbaric oxygen (HBO) therapy has been suggested to provide some therapeutic benefit in conditions where poor blood flow and hypoxia lead to secondary tissue injury, and HBO therapy following TBI improves outcomes (142, 158). HBO therapy increases IL-10 at 4 days in adult Sprague-Dawley rats and mice above the levels induced by TBI alone in both the lateral fluid percussion (146) and the controlled cortical impact (142) models. The reported beneficial effects of HBO therapy after TBI are thought to be through an IL-10-dependent mechanism, as the smaller lesion volumes, less edema, improved motor and cognitive recovery, decreased inflammation, reduced apoptosis and BBB dysfunction 4 weeks after TBI with HBO therapy are only seen in WT mice and not in IL-10−/− mice. Triptolide, an anti-inflammatory molecule, given immediately after TBI significantly increases IL-10 levels in the brain after 1 day and attenuates increases in proinflammatory cytokines; improves neurobehavioral outcomes; and reduces edema, contusion volume, and apoptosis (144).

IL-10 in Clinical Studies

The temporal profile of IL-10 in clinical TBI studies is not conclusive. Early reports found that plasma IL-10 levels peak within the first 3 h (151, 152), while a later study showed the peak is between 5 and 6 days post-injury (148). IL-10 levels may remain elevated for up to 22 days (131, 139) or even up to 6 months (137), and in some cases, there is a second peak in concentration (131, 152). In contrast to this general pattern of a rise in IL-10 levels followed by a gradual decline in the CSF and plasma (153), others have been unable to identify any pattern of IL-10 levels in microdialysate (115). Another study in patients with a severely disrupted BBB found high initial CSF IL-10 levels that decreased over time and serum IL-10 levels that increased over time (156), supporting a
heightened intrathecal IL-10 synthesis after TBI with overflow of the cytokine into the systemic circulation (137), augmenting baseline systemic IL-10 levels. However, there is inconsistency in the literature as to whether IL-10 levels are more dramatically increased in the CSF or serum following TBI (131, 139), rendering it difficult to determine the source of increased IL-10 levels. This discrepancy likely relates to isolated head injury versus multiple injuries, as one study found that serum levels were higher than CSF levels in patients with additional injuries; however, in patients with isolated TBI, CSF concentrations were greater than or equal to the corresponding serum levels (155). Isolated head injuries have also been shown to result in either no difference in serum IL-10 levels (129) or lower IL-10 levels than that seen with multiple injuries (151, 152). Moreover, serum levels of IL-10 are elevated in trauma patients with and without brain injury (150, 159). Thus, the heterogeneous nature of clinical TBI patients may be in part responsible for the inconclusive patterns and biocompartmental distribution of IL-10 following TBI.

Similarly, it seems that clinical severity measures and TBI complications such as GCS, various Injury Scores/Scales, and BBB dysfunction/disruption have not been definitively correlated with IL-10 levels. Although most studies found no correlation with GCS (129, 130, 153–155) or Injury Severity Score (129, 155) and IL-10 levels, a minority endorse a significant association (149, 151). Blood–brain barrier BBB dysfunction/disruption is one component of secondary brain damage after TBI (8, 135, 139, 147, 160), and although more severe BBB dysfunction is evident in non-survivors of TBI (156), no significant correlation can be made between IL-10 levels in either the serum or CSF and the degree of BBB disruption (131, 139, 156). Disruption to BBB integrity often contributes to elevated intracranial pressure (ICP), another common complication of TBI (140, 161) that is associated with poor outcomes (136, 140). Although high ICP coupled with sympathetic activation has been shown to increase systemic IL-10 levels (162), and some studies have demonstrated higher IL-10 levels in patients with both high ICP and unfavorable outcomes (155, 156), not all studies have found such an association between ICP and IL-10 levels (131, 150). Although some interleukins exhibit a stronger and more prolonged response in females (115), no studies have found a clear association between IL-10 levels and gender (115, 136). One study has shown that increased IL-10 levels after TBI are associated with age, such that increased levels after TBI are found with ages less than 4 years (154).

Interleukin-10 is elevated after TBI and exhibits a more prolonged response when compared to other cytokines (115), and although many have attempted to correlate IL-10 levels with outcomes, this effort has not been reliably successful (129, 130, 136, 139, 150, 153, 163–166). However, a few studies did find that elevated IL-10 concentrations are associated with unfavorable outcomes (137, 149, 154–156). Higher CSF IL-10 in pediatric patients (154) and elevated serum and CSF IL-10 levels in adult patients were significantly associated with mortality (156). Non-survivors demonstrate higher serum IL-10 levels at admission that continued to rise over the next 24 h, whereas survivors have lower IL-10 serum levels at admission that subsequently decrease (156). Additionally, non-survivors have higher CSF IL-10 levels at admission; however, both the non-survivors and survivors demonstrate decreasing CSF IL-10 levels over time (156). In another study, elevated IL-10 levels at 10 or 30 h after TBI were 6 and 5 times more frequently associated with hospital mortality, independent of GCS, age, and systemic trauma (149). It appears that early IL-10 correlates best with outcome, as both admission CSF and serum IL-10 levels within the first 30 h correlate with mortality, whereas later time points do not (149, 156). Increased CSF and serum levels correlate with a GCS score less than 4 (137, 155). Additionally, in a multivariate analysis, one study found that a higher IL-6/IL-10 ratio from 2 weeks to 3 months was significantly associated with a GCS score less than 4 at 6 months (78). Hypothermia is known to attenuate the proinflammatory response following TBI147; however, monitoring of IL-10 levels in severe TBI patients divided into hypothermia and normothermia treatment groups revealed no significant differences in CSF or serum IL-10 levels, nor outcomes in pediatric or adult patients (130, 153, 167).

It is well documented that IL-10 levels in humans and experimental models increase in both the serum and CSF shortly after TBI (8, 129, 135, 151, 152, 168) and remain elevated for many days (131, 152) followed by a slow decline. However, due to

---

**TABLE 9 | Summary of IL-10 traumatic brain injury clinical studies.**

| Study modality | Population | Outcomes | Reference |
|---------------|------------|----------|-----------|
| Multi-analyte assay | British | Plasma IL-10 levels peak between days 5 and 6 | (148) |
| Multiplex bead array assay | American | IL-10 elevated compared to controls, no correlation with initial GCS, age, gender, or outcome | (130) |
| Multiplex bead array assay | Brazilian | Elevated serum IL-10 levels correlates with GCS and hospital mortality in severe TBI patients | (149) |
| Multiplex bead array assay | American | IL-10 elevated at 6 months old and correlate with GOS at 6 and 12 months old | (157) |
| Multiplex bead array assay | American | Serum IL-10 levels elevated in trauma patient with and without TBI | (150) |
| ELISA | German | Plasma IL-10 levels peak within 3 h | (151) |
| ELISA | German | Plasma IL-10 levels elevated within 3 h | (152) |
| ELISA | Swiss | IL-10 levels elevated up to 22 days post-injury and second peak in concentration seen | (131) |
| ELISA | Japanese | CSF IL-10 elevated for 24 h post-injury before declining | (153) |
| ELISA | American | IL-10 elevated in pediatric TBI relative to controls at days 1–3 and predicts mortality, no correlation with GCS | (154) |
| ELISA | Swedish | Temporal IL-10 pattern has no initial peak and no gradual decrease from 2 to 7 days | (155) |
| ELISA | Japanese | CSF IL-10 is better predictor of outcomes after TBI with extracranial injuries compared to serum IL-10 levels | (155) |
| ELISA | Polish | Isolated head injury vs. those with accompanying injury results in no difference in serum IL-10 level | (129) |
| ELISA | German | No correlation between BBB disruption in TBI and serum or CSF IL-10 level | (139) |
| Immulite | German | High initial CSF IL-10 that decreases over time and serum IL-10 that increases over time predicts mortality | (156) |

GCS, Glasgow Coma Scale; GCS, Glasgow Outcome Scale; ELISA, enzyme-linked immunosorbent assay; IL-10, interleukin-10; TBI, traumatic brain injury; BBB, blood–brain barrier.
methodological variations in studies, the prognostic and diagnostic value of this cytokine remains unclear.

Summary and Comparison of the Role of IL-10 in Preclinical and Clinical TBI Studies

Traumatic brain injury is a heterogenous type of acute brain injury that involves a complex interplay of both direct primary injury and secondary injury, the latter of which is closely linked to neuroinflammatory processes. Preclinical studies have shown that IL-10 reduces neuroinflammation following brain trauma and, in general, IL-10 treatment improves neurological outcomes after TBI. Clinically, several studies have shown that IL-10 levels increase after TBI, although the temporal profile of IL-10 levels and whether IL-10 correlates with initial injury severity is less clear. Regarding the prognostic potential, it appears that IL-10 has the most utility in predicting mortality after TBI, although given the controversy in the literature, future work is necessary to further define the role of IL-10 in predicting other outcomes.

CONCLUSION

Interleukin-10 is significantly elevated following brain injury and appears to play a variety of roles depending on the type of acute neurologic insult, where it interacts with each condition's overlapping, yet distinct, pathophysiology and secondary complications. High IL-10 levels tend to predict worse outcomes after hemorrhagic brain injury, whereas the converse is true for brain ischemia, low IL-10 levels resulting from SNPs increase the risk for IS and low levels after IS predict worse outcome. While IL-10 appears to have prognostic value, comparatively far fewer studies report on diagnostic potential. In the limited work in the literature, significant controversy exists where some report no correlation with measures of initial brain injury severity and others report significant correlations. From a therapeutic perspective, preclinical models have shown that IL-10 administration after IS and TBI lend better outcomes, although no work has been done in this area for SAH or ICH. Intertwined with all these acute pathologic processes are the effects of IL-10 on the vasculature, where it is crucial for protection. Finally, the varied effects and roles of IL-10 after IS, SAH, ICH, and TBI likely stems from pathology-dependent differences in the temporal balance of pro- and anti-inflammatory mediators. The latter point is particularly important in the context of IL-10, given its pleiotropic immunomodulatory functions that polarize the inflammatory system to an anti-inflammatory phenotype, aiding in the resolution of the neuroinflammation. It is likely that the ability of IL-10 to overcome the proinflammatory milieu is temporally different between the various forms of acute brain injury, with delays resulting in prolonged inflammation that exacerbates secondary brain damage, leading to worse outcomes. Novel therapies targeted to control inflammation will hinge on an understanding of the complex balance of the pro- and anti-inflammatory mediators, of which IL-10 plays a central overarching role. This represents an exciting avenue of research that will hopefully usher unique immunomodulatory therapies, changing the management of patients with acute neurologic injury from supportive measures to active therapeutic care to improve patient outcomes.

AUTHOR CONTRIBUTIONS

JG and SS drafted the manuscript. JL and SD made substantial contributions to the conception and design of the work and wrote the manuscript. JL, HP, NE, SR, BH, SB, and SD revised the manuscript. All authors have approved the manuscript for publication.

ACKNOWLEDGMENTS

The authors wish to thank members of the Dorelab, the University of Florida Center for Translational Research in Neurodegenerative Disease, and the McKnight Brain Institute. We also thank Corey Astrom for her expert editorial assistance.

FUNDING

This work was supported by grants from the McKnight Brain Research Foundation, Brain and Spinal Cord Injury Research Trust Fund (SD), and National Institutes of Health T35HL007489 (JG and SS), F31NS086441 (JL), AHA33450010 (SD), R01NS046400 (SD), R01AT007429 (SD), and R21NS095166 (BH, SB, and SD).

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation (2014) 129(3):28–292. doi:10.1161/01 .cir.000041138.02102.80
2. Sauser K, Burke JF, Reeves MJ, Barsan WG, Levine DA. A systematic review and critical appraisal of quality measures for the emergency care of acute ischemic stroke. Ann Emerg Med (2014) 64(3):235–44.e5. doi:10.1016/j. annemergmed.2014.01.034
3. Centers for Disease C, Prevention. Prevalence of stroke – United States, 2006–2010. MMWR Morb Mortal Wkly Rep (2012) 61(20):379–82.
4. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. Arch Phys Med Rehabil (2014) 95(5):986–95.e1. doi:10.1016/j.apmr.2013.10.032
5. Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil (2008) 23(6):394–400. doi:10.1097/01.HTR.0000341435.52004.ac
6. Namjoshi DR, Good C, Cheng WH, Panenka W, Richards D, Cripton PA, et al. Towards clinical management of traumatic brain injury: a review of models and mechanisms from a biomechanical perspective. Dis Model Mech (2013) 6(6):1325–38. doi:10.1242/dmm.011320
7. Lee WI, Mitchell P, Dowling R, Yan B. Clinical factors are significant predictors of outcome post intra-arterial therapy for acute ischaemic stroke: a review. J Neurol Neurosurg Psychiatry (2013) 90(5):315–25. doi:10.1136/jnnp.2013.309002
8. Cederberg D, Siesjo B. What has inflammation to do with traumatic brain injury? Childs Nerv Syst (2010) 26(2):221–6. doi:10.1007/s00381-009-1029-x
9. Patterson ZR, Holahan MR. Understanding the neuroinflammatory response following concussion to develop treatment strategies. Front Cell Neurosci (2012) 6:58. doi:10.3389/fncel.2012.00058
10. Ziebell JM, Morganti-Kossmann MC. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurotherapeutics* (2010) 7(1):22–30. doi:10.1016/j.nurt.2009.10.016

11. Giunta B, Obregon D, Velissetty R, Sanberg PR, Borlongan CV. The immunology of traumatic brain injury: a prime target for Alzheimer's disease prevention. *J Neuroinflammation* (2012) 9:185. doi:10.1186/1742-9993-9-185

12. Wang J, Doré S. Inflammation after intracerebral hemorrhage. *J Cerebrovasc Brain Metab* (2007) 27(5):894–908. doi:10.1007/s10581-006-00403

13. Dumont AS, Dumont RJ, Chow MM, Lin CL, Calisanelter T, Ley KE, et al. Cerebral vasospasm after subarachnoid hemorrhage: putative role of inflammation. *Neurosurgery* (2003) 53(1):123–33; discussion 33–5. doi:10.1227/01.NEU.0000068863.3713.9E

14. Miller BA, Turan N, Chau M, Pradilla G. Inflammation, vasospasm, and brain injury after subarachnoid hemorrhage. *Biomed Res Int* (2014) 2014:384342. doi:10.1155/2014/384342

15. Iadeola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nat Med* (2011) 17(7):796–808. doi:10.1038/nm.2399

16. Strle K, Zhou JH, Shen WH, Boussad SR, Johnson RW, Freund GG, et al. Interleukin-10 in the brain. *Crit Rev Immunol* (2001) 21(5):427–49. doi:10.1615/CritRevImmunol.v21.i5.20

17. Moore KW, de Waal Malefyt R, Coffman RL, O’Garra A. Interleukin-10 and the interleukin-10 receptor. *Ann Rev Immunol* (2001) 19:683–765. doi:10.1146/annurev.immunol.19.1.683

18. MacKenzie KE, Pattison MJ, Arthur JS. Transcriptional regulation of IL-10 and its cell-specific role in vivo. *Crit Rev Immunol* (2014) 34(3):315–45. doi:10.1615/CritRevImmunol.2014010694

19. Saraiva M, O’Garra A. The regulation of IL-10 production by immune cells. *Nat Rev Immunol* (2010) 10(3):170–81. doi:10.1038/nri2711

20. Mosser DM, Zhang X. Interleukin-10: new perspectives on an old cytokine. *Immune Rev* (2008) 226:205–18. doi:10.1111/j.1600-065X.2008.00706.x

21. del Zoppo GJ, Hallenbeck JM. Advances in the vascular pathophysiology of ischemic stroke. *Thromb Res* (2000) 98(3):73–81. doi:10.1016/S0049-3848(00)00218-8

22. Sandovale KE, Witt KA. Blood-brain barrier tight junction permeability and ischemic stroke. *Neurobiol Dis* (2008) 32(2):200–19. doi:10.1016/j.nbd.2008.08.005

23. Alves JL. Blood-brain barrier and traumatic brain injury. *J Neurosci Res* (2014) 92(2):141–7. doi:10.1002/jnr.23300

24. Keep RF, Zhou N, Xiang J, Andjelkovic AV, Hua Y, Xi G. Vascular disruption and blood-brain barrier dysfunction in intracerebral hemorrhage. *Fluids Barriers CNS* (2014) 11:18. doi:10.1186/2045-8118-11-18

25. Dammanahalli JK, Wang X, Sun Z. Genetic interleukin-10 deficiency causes vascular remodeling via the upregulation of Nox1. *J Hypertens* (2011) 29(11):2161–25. doi:10.1097/HJH.0b013e32834e82a0

26. Kinzenbaw DA, Chu Y, Pena Silva RA, Didion SP, Faraci FM. Interleukin-10 protects against aging-induced endothelial dysfunction. *Physiol Rep* (2013) 1(6):e00149. doi:10.1212/PHY.0b013e282366a948

27. Zemse SM, Hilgers RH, Simkins GB, Rudic RD, Webb RC. Restoration of endothelin-1-induced impairment in endothelium-dependent relaxation by interleukin-10 in murine aortic rings. *Am J Physiol Heart Circ Physiol* (2007) 292(6):H3103–8. doi:10.1152/ajpheart.00456.2006

28. Sippka G, Miller KL, Steppan J, Pandey D, Jung SM, Fraser CD III, et al. Interleukin 10 knockout frail mice develop cardiac and vascular dysfunction with increased age. *Exp Gerontol* (2013) 48(2):128–35. doi:10.1016/j.exger.2012.11.001

29. Kassan M, Galan M, Partyka M, Trebak M, Matrougui K. Interleukin-10 released by CD4+(+)CD25(+). natural regulatory T cells improves microvascular endothelial function through inhibition of NADPH oxidase activity in hypertensive mice. *Arterioscler Thromb Vasc Biol* (2011) 31(11):2534–42. doi:10.1161/ATVBAHA.111.323562

30. Kaiser D, Weise G, Moller K, Scheibe J, Posel C, Baasch S, et al. Spontaneous white matter damage, cognitive decline and neuroinflammation in middle-aged hypertensive rats: an animal model of early-stage cerebral small vessel disease. *Acta Neuropathol Commun* (2014) 2:169. doi:10.1186/s40478-014-0169-8

31. Gunnett CA, Heistad DD, Berg DJ, Faraci FM. IL-10 deficiency increases superoxide and endothelial dysfunction during inflammation. *Am J Physiol Heart Circ Physiol* (2007) 297(4):H1555–62.

32. Londono D, Carvajal J, Strle K, Kim KS, Cadavid D. IL-10 Prevents apoptosis of brain endothelium during bacteremia. *J Immunol* (2011) 186(12):7176–86. doi:10.4049/jimmunol.1100060

33. Lissinski TJ, Furie MB. Interleukin-10 inhibits proinflammatory activation of endothelium in response to Borrelia burgdorferi or lipopolysaccharide but not interleukin-1beta or tumor necrosis factor alpha. *J Leukoc Biol* (2002) 72(3):503–11.

34. Appelros P, Nydevik I, Vitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. *Stroke* (2003) 34(1):122–6. doi:10.1161/01.STR.0000047852.05842.3C

35. Kelly-Hayes M, Beiser A, Kase CS, Scaramuzzi A, D’Agostino RB, Wolf PA. The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis* (2013) 12(3):119–26. doi:10.1016/j.scd.2013.01.065

36. Dias AM, Manto C, Maresca A, Taffoni M, Bellavista A. Anti-inflammatory IL-10 is upregulated in both hemispheres after experimental ischemic stroke: hypertension blunts the response. *Exp Trans Stroke Med* (2013) 5(1):12. doi:10.1080/20473557.2013.12

37. Spera PA, Ellison JA, Feuerstein GZ, Barone FC. IL-10 reduces rat brain injury following focal stroke. *Neurosci Lett* (1998) 251(3):189–92. doi:10.1016/S0304-3940(98)00337-0

38. Lantz A, Bauer A, Hoheisel JD, Veltkamp R. Intracerebral interleukin-10 injection modulates post-ischemic neuroinflammation: an experimental microaray study. *Neurourology* (2014) 37:19–23. doi:10.1016/j.neuro.2014.07.003

39. de Bilbao F, Arsenjevic D, Mall T, Garcia-Gabay I, Vallet P, Langhans W, et al. In vivo expression of interleukin-10 increases resistance to focal brain ischemia in mice. *J Neurochem* (2009) 110(1):12–22. doi:10.1111/j.1471-4159.2009.06098.x

40. Liang QJ, Jiang M, Wang XH, Le LL, Xiang M, Sun N, et al. Pre-existing interleukin 10 in cerebral arteries attenuates subsequent brain injury caused by ischemia/reperfusion. *J Intern Med* (2013) 273(3):124–35. doi:10.1111/j.1365-2958.2013.12429

41. Nonoto T, Okada T, Shimazaki K, Yoshitaka T, Nonaka-Sarukawa M, Ito T, et al. Systemic delivery of IL-10 by an AAV vector prevents vascular remodeling and end-organ damage in stroke-prone spontaneously hypertensive rat. *Gene Ther* (2009) 16(3):383–91. doi:10.1038/gt.2008.151
51. Wang Y, Jia J, Ao G, Hu L, Liu H, Xiao Y, et al. Hydrogen sulfide protects blood-brain barrier integrity following cerebral ischemia. J Neurochem (2014) 130(5):627–37.

52. Hwang CJ, Yun HM, Jung YY, Lee DH, Yoon NY, Seo HO, et al. Reducing effect of IL-32alpha in the development of stroke through blocking of NF-kappaB, but enhancement of STAT3 pathways. Mol Neurobiol (2015) 51(2):648–60. doi:10.1007/s12035-014-8739-0

53. Liesz A, Zhou W, Na SY, Hammerling GJ, Garbi N, Karcher S, et al. Boosting regulatory T cells limits neuroinflammation in permanent cortical stroke. J Neurosci (2013) 33(44):17350–62. doi:10.1523/JNEUROSCI.4901-12.2013

54. Na SY, Mracsko E, Liesz A, Hunig T, Veltkamp R. Amplification of regulatory T-cells limits neuroinflammation in the subacute phase after cerebral infarction is effective for functional recovery facilitating proliferation of intrinsic neural stem/progenitor cells and transition of bone marrow-derived neuronal cells. Circulation (2006) 113(5):701–10. doi:10.1161/CIRCULATIONAHA.105.563668

55. Kawada H, Takizawa S, Takanashi T, Morita Y, Fujita J, Fukuda K, et al. Administration of hematopoietic cytokines in the subacute phase after cerebral infarction is effective for functional recovery facilitating proliferation of intrinsic neural stem/progenitor cells and transition of bone marrow-derived neuronal cells. Circulation (2006) 113(5):701–10. doi:10.1161/CIRCULATIONAHA.105.563668

56. Morita Y, Takizawa S, Kamiguchi H, Uesugi T, Kawada H, Takagi S. Administration of hematopoietic cytokines increases the expression of anti-inflammatory cytokine (IL-10) mRNA in the subacute phase after stroke. Neurosci Res (2007) 58(4):356–60. doi:10.1016/j.neures.2007.04.006

57. Bodhankar S, Chen Y, Vandenbark AA, Murphy SJ, Offner H. IL-10-producing B-cells limit CNS inflammation and infarct volume in experimental stroke. Front Cell Neurosci (2015) 9:361. doi:10.3389/fncel.2015.00361

58. Bodhankar S, Chen Y, Vandenbark AA, Murphy SJ, Offner H. IL-10-producing B-cells limit CNS inflammation and infarct volume in experimental stroke. Metab Brain Dis (2014) 29(1):59–73. doi:10.1007/s11011-013-9474-3

59. Liu N, Chen R, Du H, Wang J, Zhang Y, Wen J. Expression of IL-10 and TNF-alpha in rats with cerebral infarction after transplantation with mesenchymal stem cells. Cell Mol Immunol (2009) 6(3):207–13. doi:10.1038/cmi.2009.28

60. Du HW, Liu N, Wang JH, Zhang YX, Chen RH, Xiao YC. [The effects of adipose-derived stem cell transplantation on the expression of IL-10 and TNF-alpha after cerebral ischemia in rats]. Xi Bao Yu Fen Zi Mian Yi Xue Xue Zhi (2009) 25(11):998–1001.

61. Du G, Liu Y, Dang M, Zhu G, Su R, Fan Y, et al. Comparison of administration routes for adipose-derived stem cells in the treatment of middle cerebral artery occlusion in rats. Acta Histochem (2014) 116(6):1075–84. doi:10.1016/j.acthis.2014.05.002

62. Munshi A, Rajeshwar K, Kaul S, Al-Hazzani A, Alshatwi AA, Sai Babu M, et al. Interleukin-10-1082 promoter polymorphism and ischemic stroke risk in a Chinese population. Acta Histochem (2010) 112(3):221–4. doi:10.1016/j.acthis.2010.03.012

63. Protti GG, Gagliardi RJ, Forte WC, Sprovieri MA. Interleukin-10-1082 promoter polymorphism and ischemic stroke risk in a Chinese population. Acta Histochem (2010) 112(3):221–4. doi:10.1016/j.acthis.2010.03.012

64. Yin GT, Ma YT, Zheng YY, Yang YN, Li XM, Fu ZY, et al. Polymorphisms of anti-inflammatory cytokines and neurological worsening in acute ischemic stroke. Stroke (2013) 44(1):67–71. doi:10.1016/j.stroke.2012.05.076

65. Timasheva YR, Nasibullin TR, Zakirova AN, Mustafina OE. Association of interleukin-6, interleukin-12, and interleukin-10 gene polymorphisms with the risk of ischemic stroke. Zh Nevrol Psikhiatr Im S S Korsakova (2014) 114(2):35–44. doi:10.1590/S0004-282X2014000200037

66. Na SY, Mracsko E, Liesz A, Hunig T, Veltkamp R. Amplification of regulatory T-cells limits neuroinflammation in permanent cortical stroke. J Neurosci (2013) 33(44):17350–62. doi:10.1523/JNEUROSCI.4901-12.2013

67. Vila N, Castillo J, Davalos A, Esteve A, Planas AM, Chamorro A. Levels of anti-inflammatory cytokines and neurological worsening in acute ischemic stroke. Stroke (2003) 34(3):671–7. doi:10.1016/S0023-2959(03)00057-9

68. Potti GG, Gagliardi RJ, Forte WC, Sprovieri MA. Interleukin-10-1082 promoter polymorphism and ischemic stroke risk in a Chinese population. Arq Neuropsiquiatr (2013) 71(11):846–51. doi:10.1590/S0001-10042013000100022

69. Nayak AR, Kashyap RS, Purohit HJ, Kabra D, Taori GM, Daginawala HJ. Evaluation of the inflammatory response in sera from acute ischemic stroke patients by measurement of IL-2 and IL-10. Inflamm Res (2009) 58(10):687–91. doi:10.1007/s00011-009-0036-4

70. Hyu Y, Zheng Y, Wu Y, Ni BI, Shi S. Imbalance between IL-17A-producing cells and regulatory T cells during ischemic stroke. Mediators Inflamm (2014) 2014:83045. doi:10.1155/2014/83045

71. Arponen O, Muuronen A, Taina M, Sapola P, Hedman M, Jakala P, et al. Acute phase IL-10 plasma concentration associates with the high risk sources of cardiac event. PLoS One (2015) 10(4):e0120910. doi:10.1371/journal.pone.0120910

72. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Torres F, et al. Interleukin-10, monocyes and increased risk of early infection in ischaemic stroke. J Neurol Neurosurg Psychiatry (2006) 77(11):1279–81. doi:10.1136/jnnp.2005.080080

73. Worthmann H, Tryc AB, Dirks M, Schuppner R, Brand K, Klavon F, et al. Lipopolysaccharide binding protein, interleukin-10, interleukin-6 and C-reactive protein blood levels in acute ischemic stroke patients with post-stroke infection. J Neuroinflammation (2015) 12:13. doi:10.1186/s12974-015-0231-2

74. Pelidou SH, Kostulas N, Matusevicius D, Kivisakk P, Kostulas V, Link H. High levels of IL-10 secreting cells are present in blood in cerebrovascular diseases. Eur J Neurol (1999) 6(4):437–42. doi:10.1046/j.1464-1331.1999.d437.x

75. Chang LT, Yuen CM, Liu CW, Lu CH, Chang WN, Youseff AA, et al. Link between interleukin-10 level and outcome after ischemic stroke. Neuroimmunomodulation (2010) 17(4):223–8. doi:10.1159/0001290038

76. Sahan M, Sebe A, Akcilan A, Akipinar O, Koc F, Ay MO, et al. Acute-phase reactants and cytokines in ischemic stroke: do they have any relationship with short-term mortality? Eur Rev Med Pharmacol Sci (2013) 17(20):2773–7.

77. Sharma S, Yang B, Xi X, Grotta JC, Aronowski J, Savitz SI. IL-10 directly protects cortical neurons by activating PI-3 kinase and STAT3 pathways. Brain Res (2011) 1375:189–94. doi:10.1016/j.brainres.2010.11.096

78. Zhu J, Wang H, Fan Y, Lin Y, Zhang L, Jin X, et al. Targeting the NF-E2-related factor 2 pathway: a novel strategy for glioblastoma (review). Oncol Rep (2014) 32(2):443–50. doi:10.3892/or.2014.3259
99. Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *Brain Res* (2013) 1467(1):143–53. doi:10.1016/j.brainres.2013.02.049
100. Zhang S, He WB, Chen NH. Causes of death among persons who survive aneurysmal subarachnoid hemorrhage. *J Neurosurg* (1995) 83(1):118–22. doi:10.3171/jns.1995.83.1.0118
101. Jin J, Li W, Peng L, Chen J, Li R, Wu P, et al. Relationship between interleukin-10 and Acute Brain Injury after aneurysmal subarachnoid hemorrhage in rats. *Neurosurgery* (2012) 70(4):954–61. doi:10.1227/01.NEU.0000419754.93925.07
102. Dziedzic T, Bartus S, Klimkowicz A, Motyl M, Slowik A, Szczudlik A. Influence of interleukin-1beta in early brain injury after subarachnoid hemorrhage. *Brain Res* (2005) 1089(1):1–11. doi:10.1016/j.brainres.2005.10.055
103. Schwartz AY, Sehba FA, Bederson JB. Decreased nitric oxide availability mediates astroglial neuroprotection in an IL-10-dependent manner. *Brain Behav Immun* (2011) 25(7):1197–204. doi:10.1016/j.bbi.2011.04.007
104. Assaf JK, Pluta RM, Boock RJ, Thompson BG, Oldfield EH. Effect of intracarotid nitric oxide on primate cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg* (1995) 83(1):118–22. doi:10.3171/jns.1995.83.1.0118
105. Schwetz BA, Seha FA, Bederson JB. Decreased nitric oxide availability mediates astroglial neuroprotection in an IL-10-dependent manner. *Brain Behav Immun* (2011) 25(7):1197–204. doi:10.1016/j.bbi.2011.04.007
Buttram SD, Wisniewski SR, Jackson EK, Adelson PD, Feldman K, Bayir H, Kumar RG, Boles JA, Wagner AK. Chronic inflammation after severe traumatic brain injury leads to severe neuropathological and neurobehavioral changes after repetitive mild traumatic brain injury. *Brain Res* (2017) 1657:1–8. doi:10.1016/j.brainsci.2016.11.028

Lin KC, Niu KC, Tsai KJ, Kuo JR, Wang LC, Chio CC, et al. Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. *J Trauma Acute Care Surg* (2012) 72(3):630–9. doi:10.1097/TA.0b013e31823c575f

Kobalch SM, Faden AF. Interleukin-10 improves outcome and alters proinflammatory cytokine expression after experimental traumatic brain injury. *Exp Neurol* (1998) 153(1):143–51. doi:10.1006/exnr.1998.6877

Helmy A, Antoniades CA, Guilfoyle MR, Carpenter KL, Hutchinson PJ. Principal component analysis of the cytokine and chemokine response to human traumatic brain injury. *PloS One* (2012) 7(6):e39677. doi:10.1371/journal.pone.0039677

Schneider Soares FM, Menezes de Souza N, Liborio Schwarzbold M, Paim Diaz A, Costa Nunes J, Hohl A, et al. Interleukin-10 is an independent biomarker of severe traumatic brain injury prognosis. *Neuroimmunomodulation* (2019) 26(6):377–85. doi:10.1159/000434244

Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Keledjian K, et al. Relationship of serum and cerebrospinal fluid biomarkers with intracranial hypertension and cerebral hypoperfusion after severe traumatic brain injury. *J Trauma* (2011) 70(5):1096–103. doi:10.1097/TA.0b013e3182e16930d

Hensler T, Sauerland S, Bouillon B, Raum M, Rixen D, Helling HJ, et al. Association between injury pattern of patients with multiple injuries and circulating levels of soluble tumor necrosis factor receptors, interleukin-6 and interleukin-10, and polymorphonuclear neutrophil elastase. *J Trauma* (2002) 52(5):962–70.

Hensler T, Sauerland S, Riess P, Hess S, Helling HJ, Anndermacher J, et al. The effect of additional brain injury on systemic interleukin (IL)-10 and IL-13 levels in trauma patients. *Inflamm Res* (2000) 49(10):524–8. doi:10.1007/s000110050626

Hayakata T, Shiozaki T, Tasaki O, Ikegawa H, Inoue Y, Toshiyuki F, et al. Changes in CSF S100B and cytokine concentrations in early-phase severe traumatic brain injury. *Shock* (2004) 22(2):102–7. doi:10.1097/01.shk.0000131193.80038.f1

Bell MJ, Koelner PK, Doughty LA, Carcillo JA, Adelson PD, Clark RS, et al. Interleukin-6 and interleukin-10 in cerebrospinal fluid after severe traumatic brain injury in children. *J Neurotrauma* (1997) 14(7):451–7.

Shiozaki T, Hayakata T, Tasaki O, Hosotsubo H, Fujitaka K, Mouri T, et al. Cerebrospinal fluid concentrations of anti-inflammatory mediators in early-phase severe traumatic brain injury. *Shock* (2003) 23(5):406–8. doi:10.1097/01.shk.0000102234.86381.7a

Kirchhoff C, Buhmann S, Bogner V, Stegmaier J, Leidel BA, Braunstein V, et al. Cerebrospinal IL-10 concentration is elevated in non-survivors as compared to survivors after severe traumatic brain injury. *Eur J Med Res* (2008) 13(10):464–8.

Mustafa AG, Ashboul OA. Pathophysiology of traumatic brain injury. *Neurosciences (Riyadh)* (2013) 18(3):222–34.

Prakash A, Pareidkan SV, Oake SN, Gupta RK, Sanghi BV, Bachani M, et al. Role of hyperbaric oxygen therapy in severe head injury in children. *Pediatr Neurosci* (2012) 38(1):1–8. doi:10.4103/1817-1475.97610

Neidhardt R, Keel M, Stockholzer U, Safret A, Ungethuem U, Trentz O, et al. Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. *J Trauma* (1997) 42(5):863–70; discussion 70–1

Morganti-Kossmann MC, Stagnaneseil L, Bye N, Kossmann T. Modulation of immune response by head injury. *Injury* (2007) 38(12):1392–400. doi:10.1016/j.injury.2007.10.005

Sellmann T, Miersch D, Kienbaum P, Flohe S, Schneppendahl J, Leiering R, et al. The impact of arterial hypertension on polytrauma and traumatic brain injury. *Disch Arztebl Int* (2012) 109(49):849–56. doi:10.3238/arztebl.2012.0849
162. Woiciechowsky C, Volk HD. Increased intracranial pressure induces a rapid systemic interleukin-10 release through activation of the sympathetic nervous system. *Acta Neurochir Suppl* (2005) 95:373–6. doi:10.1007/3-211-32318-X_76

163. Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platter C, Schoning B, et al. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. *Nat Med* (1998) 4(7):808–13. doi:10.1038/nm0798-808

164. Woiciechowsky C, Schoning B, Cobanov J, Lanksch WR, Volk HD, Docke WD. Early IL-6 plasma concentrations correlate with severity of brain injury and pneumonia in brain-injured patients. *J Trauma* (2002) 52(2):339–45.

165. Lo TY, Jones PA, Minns RA. Pediatric brain trauma outcome prediction using paired serum levels of inflammatory mediators and brain-specific proteins. *J Neurotrauma* (2009) 26(9):1479–87. doi:10.1089/neu.2008-0753

166. Lo TY, Jones PA, Minns RA. Combining coma score and serum biomarker levels to predict unfavorable outcome following childhood brain trauma. *J Neurotrauma* (2010) 27(12):2139–45. doi:10.1089/neu.2010.1387

167. Shiozaki T, Kato A, Taneda M, Hayakata T, Hashiguchi N, Tanaka H, et al. Little benefit from mild hypothermia therapy for severely head injured patients with low intracranial pressure. *J Neurosurg* (1999) 91(2):185–91. doi:10.3171/jns.1999.91.2.0185

168. Shimonkevitz R, Bar-Or D, Harris L, Dole K, McLaughlin L, Yukl R. Transient monocyte release of interleukin-10 in response to traumatic brain injury. *Shock* (1999) 12(1):10–6. doi:10.1097/00024382-199907000-00002

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Garcia, Stillings, Leclerc, Phillips, Edwards, Robicsek, Hoh, Blackburn and Doré. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.