HHS Public Access

Author manuscript

Prog Neurobiol. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Prog Neurobiol. 2017 May ; 152: 181–199. doi:10.1016/j.pneurobio.2016.04.004.

Help-Me Signaling: Non-Cell Autonomous Mechanisms of Neuroprotection and Neurorecovery

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Abstract

Self-preservation is required for life. At the cellular level, this fundamental principle is expressed in the form of molecular mechanisms for preconditioning and tolerance. When the cell is threatened, internal cascades of survival signaling become triggered to protect against cell death and defend against future insults. Recently, however, emerging findings suggest that this principle of self-preservation may involve not only intracellular signals; the release of extracellular signals may provide a way to recruit adjacent cells into an amplified protective program. In the central nervous system where multiple cell types co-exist, this mechanism would allow threatened neurons to “ask for help” from glial and vascular compartments. In this review, we describe this new concept of help-me signaling, wherein damaged or diseased neurons release signals that may shift glial and vascular cells into potentially beneficial phenotypes, and help remodel the neurovascular unit. Understanding and dissecting these non-cell autonomous mechanisms of self-preservation in the CNS may lead to novel opportunities for neuroprotection and neurorecovery.

1. Introduction

Cellular function requires the ability to respond to an existing stimulus and then adapt for future stimuli. Within this broad definition of homeostasis lies the concept of tolerance and preconditioning against injurious stimuli. Preconditioning is a well-defined phenomenon whereby a first sublethal dose of an otherwise harmful stimulus results in tolerance to a second injury stimulus (Stevens *et al.* 2014). A large amount of data from both experimental models as well as clinical conditions exists for cerebral ischemia. Therefore, this review is focused on signaling cascades for ischemic brain injury.

Ischemic preconditioning in the brain was described in 1990, wherein an initial sublethal ischemic stress induced tolerance in the hippocampal CA1 against subsequent lethal ischemic injury in gerbil models of transient global ischemia (Kitagawa *et al.* 1990). Then this phenomenon was confirmed for transient global ischemia in the rat brain (Nishi *et al.*

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1993) and other models of focal ischemia (Chen *et al.* 1996). Several retrospective studies have also suggested that transient ischemic attacks (TIAs) in humans are associated with improved clinical outcome after stroke, perhaps because TIAs are capable of inducing ischemic tolerance (Fu *et al.* 2008; Moncayo *et al.* 2000; Wegener *et al.* 2004; Weih *et al.* 1999). In the context of stroke, preconditioning induces a transient window of protection that requires gene activation and new protein synthesis (Dirnagl *et al.* 2009). This reprogrammed response forms the basis for endogenous neuroprotection and provides a conceptual framework for investigating the molecular mechanisms that protect the brain against ischemic injury (Chen *et al.* 1996; Kapinya *et al.* 2002; Koerner *et al.* 2007; Marsh *et al.* 2009; McCabe and Simon 1993; Stenzel-Poore *et al.* 2003; Stevens *et al.* 2011; Truettner *et al.* 2002; Zimmermann *et al.* 2001).

At a cellular level, the ability of preconditioning to trigger endogenous protective mechanisms can be viewed within a conceptually cell autonomous model **(Figure 1A)**. The initial sublethal insult induces intracellular signaling pathways that serve to block the second lethal insult. However, cells do not exist in isolation and beyond a theoretical single cell response, the release of extracellular signals may provide a way to recruit adjacent cells into an amplified protective program **(Figure 1B)**. The initial sublethal insult induces a cascade of intracellular signals that provoke the release of extracellular mediators that affect an adjacent cell. Then this second cell responds by releasing another set of extracellular signals that block a lethal insult against the original cell. This non-cell autonomous model thus sets the stage for the concept of help-me signaling, wherein multiple cells interact to assemble an integrated adaptive and protective response after injury and disease.

In the brain, these non-cell autonomous interactions should involve multiple cell types. The neurovascular unit is not only an anatomical construct but also serves as a functional unit for the interactions between neurons, glial cells and blood vessels under normal conditions and in response to injury. In this review, we will use the neurovascular unit as a basis to describe this new concept of help-me signaling, wherein damaged or diseased neurons release signals that may shift glial and vascular cells into potentially beneficial phenotypes **(Figure 2)**. Beyond neuronal help-me signals per se, we also discuss three representative classes of extracellular signals, i.e. cytokines, chemokines or growth factors, which are released after ischemia during the acute injury and delayed recovery stages after stroke. Finally, we explore the possibilities to develop potential therapeutic targets by finding new endogenous protective factors and help-me signals using transcriptome and secretome analyses.

2. Neuronal help-me signals and neuron-immune interactions

The brain is known as an “immune-privileged” organ. This does not imply the lack of an immune system in the brain, but means that brain immunity is kept under tight control to protect vulnerable nervous tissue from potential harmful immune reactions (Biber *et al.* 2007; Galea *et al.* 2007). Microglia play central roles to survey and regulate the microenvironment to support homeostasis during CNS development and under normal and diseased conditions (Prinz and Priller 2014). Microglia differ from macrophages that reside in other tissues based on their cell-specific gene expression signatures, distinct ontogeny and differential functions (Butovsky *et al.* 2012; Gautier *et al.* 2012; Ginhoux *et al.* 2010;

Kierdorf *et al.* 2013; Prinz and Priller 2014; Schulz *et al.* 2012). Microglial activation is restricted in the healthy brain, and shows a more quiescent immunological profile than other tissue macrophages. Once activated, microglial immune function is rapidly turned down to prevent the development of unwanted side effects, particularly secondary neuronal damage (Galea *et al.* 2007).

Traditionally, neurons are considered to be passive targets of activated microglia. However, accumulating evidence now suggest that neurons actively regulate microglia function and modulate immune pathways in the brain (Biber *et al.* 2007). Endangered or damaged neurons can release a repertoire of signaling molecules to attract surrounding cells including microglia, control microglial function and regulate microglia-mediated phagocytosis and neuroprotection (Biber *et al.* 2007). These molecules have traditionally been called “find-me” and “eat-me” signals (Chekeni *et al.* 2010; Grimsley and Ravichandran 2003; Lu *et al.* 2011; Napoli and Neumann 2009; Ravichandran 2010).

Emerging data now appears to recast some of these extracellular factors as neuronal “help-me” signals (Kyritsis *et al.* 2012; Mizuno *et al.* 2011; Noda *et al.* 2011; Noda *et al.* 2014; Xing *et al.* 2014). After brain injury, neurons can release unique “help-me” signals, including chemokines, cytokines, growth factors etc, which will interact with receptors expressed in microglia to guide microglial activation into a beneficial phenotype of neuroprotection and neurorecovery **(Figure 3)**. For example, in the regenerative process of adult zebrafish brain, injured neurons release cysteinyl leukotriene that stimulates resident immune cells (microglia, leukocytes, and other glia) to release beneficial signals that promote neurogenesis (Kyritsis *et al.* 2012). It has been showed that injury-induced inflammation is sufficient to enhance the neural progenitor proliferation and neurogenesis after traumatic brain injury (Kyritsis *et al.* 2012).

Mediators from the damage associated molecular pattern family (DAMPs) comprise a set of molecular determinants derived from cellular debris, intracellular proteins/enzymes or nuclear DNA/RNA that are released from injured cells (Seong and Matzinger 2004). Pattern recognition receptors are expressed on innate immune cells and bind DAMPs to initiate non-infectious immune responses in injured tissue. Several DAMPs, including high-mobility group box 1, ATP and S100 have been shown to be necessary for the initiation of immune responses following CNS injury (An *et al.* 2014). Although both help-me signals and DAMPs are released from injured neurons and may have functional overlap, the concept of help-me signals may fundamentally differ from DAMPs in terms of the balance between benefit versus harm. Damaged neurons can release many factors including DAMPs that activate glia into deleterious forms that worsen neuroinflammation. For example, damaged neurons release glutamate that activate metabotropic receptors on microglia and shift them into neurotoxic phenotypes (Taylor *et al.* 2005). In contrast, help-me signals released from distressed neurons are proposed to shift glial and vascular cells into potentially beneficial phenotypes. In this section, we briefly survey representative examples of help-me signals that have been described in recent literature.

2.1 CX3CL1/CX3CR1

Chemokines are small, secreted proteins and important inflammatory factors that regulate the attraction and migration of cells, especially immune cells (Conductier *et al.* 2010; Reaux-Le Goazigo *et al.* 2013). According to systematic nomenclature, chemokines are subdivided into four families, i.e. CXC, CC, CX3C and C. Chemokine receptors belong to the seven-transmembrane domain G protein coupled receptor superfamily. Neurons and glia constitutively express a wide spectrum of chemokines and their receptors. Thus, chemokines may play a dual role in the CNS, attracting and activating immune cells as well as modulating the survival and function of neurons (Conductier *et al.* 2010).

CX3CL1 is a transmembrane molecule that was cloned by two independent labs from neurons and endothelium (Bazan *et al.* 1997; Pan *et al.* 1997), and originally called neurotactin or fractalkine. When the extreme N-terminal chemokine domain is cleaved from the membrane domain, CX3CL1 can be released as a soluble form into extracellular space (Reaux-Le Goazigo *et al.* 2013). In the brain, neurons constitutively express high levels of CX3CL1, and its receptor, CX3CR1, is mostly expressed on microglia (Harrison *et al.* 1998; Nishiyori *et al.* 1998; Schwaeble *et al.* 1998). Besides this neuronal expression, CX3CL1 is also constitutively expressed by astrocytes at lower levels in adult mouse, rat and human brain (Hulshof *et al.* 2003; Sunnemark *et al.* 2005). Owing to expression patterns in the CNS, CX3CL1/CX3CR1 signaling may be an important pathway that allows neuronal cells to modify microglial functions during development and disease.

The effects of modifying CX3CL1/CX3CR1 pathways may be context dependent (Limatola and Ransohoff 2014). During inflammation post-injury, CX3CL1 may promote microglial activation, while under normal conditions, it may help maintain baseline microglia function (Sheridan and Murphy 2013). Despite controversial reports of benefit versus harm, many studies have provided evidence supporting the neuroprotective roles of CX3CL1. In stroke patients, higher plasma CX3CL1 level was associated with better outcome, and plasma CX3CL1 was inversely associated with systemic inflammatory markers, including white blood cell counts and high-sensitivity C-reactive protein (Donohue *et al.* 2012). The expression of CX3CL1 significantly increased in ischemic brain (Zhu *et al.* 2009). Compared to wild-type controls, knockout mice lacking CX3CL1 or CX3CR1 had smaller infarct volumes reduced blood-brain barrier (BBB) leakage, lower mortality and enhanced functional recovery after focal cerebral ischemia (Cipriani *et al.* 2011; Denes *et al.* 2008; Soriano *et al.* 2002). Intracerebroventricular administration of exogenous CX3CL1 to wild type rats subjected to permanent focal cerebral ischemia significantly reduced infarction and neurologic deficits. Correspondingly, exogenous CX3CL1 treatments in CX3CL1-deficient mice aggravated ischemic brain damage (Cipriani *et al.* 2011). Altogether, these studies suggest that the role of CX3CR1 receptors is dependent on constitutive baseline signaling. When normal CX3CR1-mediated signaling is present in microglia during development, exogenous CX3CL1 protects against cerebral ischemia; but when constitutive CX3CL1/CX3CR1 signaling is not present, further addition of CX3CL1 into the system significantly alters microglial response and exacerbates injury after brain ischemia (Cipriani *et al.* 2011).

The CX3CL1/CX3CR1 pathway is involved in multiple signaling cascades but its neuroprotective actions may primarily involve its ability to inhibit microglia by regulating

the release of proinflammatory substances. CX3CL1 significantly reduced neuronal death induced by lipopolysaccharide (LPS)- or interferon-gamma-activated microglia, and these mechanisms appear to involve the inhibition of nitric oxide (NO) production, tumor necrosis factor α (TNFα) and interleukin (IL)-6. Neutralizing antibodies against endogenous CX3CL1 abrogated this protective effect, suggesting that the function of CX3CL1 as an anti-inflammatory chemokine and an intrinsic inhibitor against neurotoxicity may depend on its ability to control the activation state of microglia (Mizuno *et al.* 2003; Zujovic *et al.* 2000). Compared to wild-type, LPS-treated neuron-glial co-cultures prepared from CX3CR −/− mice produced a reduced amount of TNFα, NO and superoxide; however, CX3CL1 treatment inhibited the release of pro-inflammatory factors in wild-type cultures (Mattison *et al.* 2013). In contrast, microglia from CX3CR1−/− mice produced higher IL-1β after LPS treatment, and was toxic when transplanted into wild-type brains (Cardona *et al.* 2006). CX3CL1-CX3CR1 signaling is multi-faceted, but clearly, it plays a key role in linking neuronal responses to microglial inflammation.

Normal neurons, not microglia, release CX3CL1, and mild to moderate excitotoxic neuronal damage amplifies CX3CL1 production, consistent with the putative role of CX3CL1 as a “help me” signal to modulate microglia phagocytosis (Noda *et al.* 2011). In neuron-microglia cocultures, CX3CL1 effectively decreased excitotoxic neuronal death by upregulating the expression of MFG-E8 that may enhance microglial phagocytosis and the clearance of damaged neurons (Fuller and Van Eldik 2008; Leonardi-Essmann *et al.* 2005; Noda *et al.* 2011). In addition, CX3CL1 upregulates microglial expression of the antioxidant enzyme heme oxygenase-1, but does not further elevate the production of neurotoxic glutamate, TNF or NO (Noda *et al.* 2011).

Beyond ischemia and excitotoxicity per se, beneficial effects of CX3CL1 have also been documented in other injury conditions such as 6-hydroxydopamine (6-OHDA) or MPTP models of Parkinson’s disease (Cardona *et al.* 2006; Pabon *et al.* 2011). Compared with wild-type mice, CX3CL1−/− or CX3CR1−/−mice displayed similar enhancement of dopaminergic neuronal loss induced by MPTP injection, indicating the perturbation of CX3CL1-mediated modulation of microglial activity worsens neuronal cell death (Cardona *et al.* 2006). Treatment with exogenous CX3CL1 reduced striatal injury and dopaminergic neuronal losses by suppressing microglia activation in 6-OHDA-damaged rats (Pabon *et al.* 2011).

The wide spectrum of studies in cell models, transgenic mice and in vivo models of CNS injury and disease, all suggest that CX3CL1 may be a key extracellular mediator that links neuronal perturbations to microglial response. Taken together, these phenomena enable neurons to modify the actions of microglial inflammation, thus allowing CX3CL1 to serve as a candidate help-me signal in the CNS.

2.2 IL-34/CSF1R

The cytokine interleukin-34 (IL-34) is a novel ligand of colony stimulating factor-1 receptor (CSF1R). CSF1R is a member of the platelet-derived growth factor family, and possesses a highly glycosylated extracellular region comprising five immunoglobulin domains, a transmembrane domain, and an intracellular tyrosine kinase domain (Stanley and Chitu

2014). IL-34 and colony-stimulating factor 1 (CSF1) lack sequence homology, but each is secreted as a dimeric glycoprotein and both bind similar regions of the CSF1R with similar affinities (Zelante and Ricciardi-Castagnoli 2012). IL-34 is broadly expressed in various organs including heart, brain, lung, liver, kidney, spleen, and colon (Lin *et al.* 2008). In the brain, IL-34 is mainly produced by neurons (Greter *et al.* 2012; Wang *et al.* 2012). Embryonic mRNA expression of IL-34 occurs before CSF1 expression in most brain regions (Wei *et al.* 2010), suggesting that IL-34 and CSF1 may play unique non-overlapping roles during development and adulthood (Hamilton and Achuthan 2013).

The major function of IL-34 is to stimulate the proliferation and differentiation of monocytes/macrophages through CSF1R, which is also shared by CSF1 (Mizuno *et al.* 2011). The development of microglia is independent of CSF but highly dependent on CSF1R signaling, and microglia are present in CSF1-deficient mice but absent from CSF1R-deficient mice (Greter *et al.* 2012; Wang *et al.* 2012). Notably, IL-34 but not CSF1, contributes to the development of microglia, and IL-34 deficient mice display a reduction of microglia, whereas monocytes/macrophages and dendritic cells are not affected (Greter *et al.* 2012; Wang *et al.* 2012).

IL-34 provides potent neuroprotection via microglia modulation. IL-34 protein in cell lysates was detected primarily in non-treated neurons but not in microglia and astrocytes, and CSF1R was only expressed in microglia, not neurons and astrocytes (Mizuno *et al.* 2011). The lack of IL-34 and consequent lower abundance of microglia impaired CNS defenses against virus infection (Wang *et al.* 2012). IL-34 promoted microglial proliferation, and IL-34-treated microglia increased the clearance of β amyloid (Aβ) 1-42 via upregulation of Aβ degrading enzyme insulin-degrading enzyme, and the production of antioxidant heme oxygenase-1 (Mizuno *et al.* 2011). IL-34-treated microglia could decrease Aβ neurotoxicity in neuron-microglia co-cultures but this protective effect was not observed in neuron cultures alone, which suggests that the protective effect of IL-34 might be indirect and mediated via microglia (Mizuno *et al.* 2011). In an APP/PS1 transgenic mouse model of Alzheimer's disease, administrating IL-34 intracerebroventricularly reduced Aβ levels and improved associative learning (Mizuno *et al.* 2011).

Recently, IL-34 was shown to protect against neurodegeneration, and this effect may be related to CSF1R signaling within the hippocampus and cortex. Neuronal expression of CSF1R is increased after kainic acid injections (Luo *et al.* 2013). Systemic administration of CSF1 and IL-34 reduced neuronal excitotoxicity and gliosis in wild-type mice, and selective cerebral deletion of CSF1R in mice exacerbated excitotoxic neurodegeneration (Luo *et al.* 2013). Endogenous CSF1 is upregulated in neurons after excitotoxic injury (Luo *et al.* 2013), but no studies have described changes of IL-34 in damaged neurons so far. Future studies to map neuronal IL-34 responses are warranted to determine whether these hypothesized mechanisms may be consistent with the role of CSF1R signaling as a help-me pathway in the brain.

2.3 Fibroblast growth factor 2

Fibroblast growth factors (FGFs) are a superfamily of proteins, most of which bind heparin and extracellular heparin sulfate proteoglycans and have a homologous central core of 140

amino acids (Burgess and Maciag 1989). FGF2 is expressed in different isoforms with distinct molecular weights (Forthmann *et al.* 2015). Signaling of FGF2 occurs through the high-affinity tyrosine kinase receptors FGFR1-4 (Jaye *et al.* 1992). FGF2 has pleiotropic effects in different tissues and organs, including potent angiogenic effects and an important role in differentiation and function in CNS (Woodbury and Ikezu 2014). In mammalian brain, FGF2 promotes neurogenesis by stimulating the proliferation and differentiation of neural stem cells (Mudo *et al.* 2009). Here, instead of discussing the well-known effects of FGF2 on neuroprotection, neurogenesis and angiogenesis, we will focus on the novel role of FGF2 as a candidate neuronal help-me signal. Basically, FGF2 can be released from damaged neurons, and mediates crosstalk between degenerating neurons and microglia (Figueiredo *et al.* 2008; Noda *et al.* 2014).

Intracerebroventricular administration of FGF2 in rats induced the appearance of reactive microglia with a multipolar and granular morphology, and doubled the number of microglia (Goddard *et al.* 2002). FGF2 plays a pivotal role in preventing quinolinic acid-induced neurotoxicity via the FGFR1 receptor after being released by neurons in the presence of microglia (Figueiredo *et al.* 2008). Cerebellar granule neurons became resistant to quinolinic acid-induced cell death when cultured with microglia or in the presence of mixed culture conditioned medium (Figueiredo *et al.* 2008). FGF2 was upregulated in neurons, not microglia and secreted and enriched in mixed culture conditioned medium, and the protective effect of mixed culture conditioned medium was lost when FGF receptor was impaired or when FGF2 was depleted from the conditioned medium of the mixed culture (Figueiredo *et al.* 2008).

In another study, damaged neurons rapidly released neuroprotective levels of FGF2 that also augmented microglial migration via FGFR3-Wnt-ERK signaling (Noda *et al.* 2014). Neurons comprise the major source of stimulated FGF2 release (Noda *et al.* 2014). In contrast, FGF2 secretion by astrocytes was not enhanced by various stimuli including glutamate, LPS, Aβ, and other proinflammatory cytokines. FGF2 significantly augmented microglial migration, and conditioned media from glutamate-treated neurons could attract microglia (Noda *et al.* 2014). FGF2 dose-dependently ameliorated neurotoxicity of glutamate in neuron-microglia co-cultures but not in neurons alone, while an anti-FGF2 antibody canceled the effect, suggesting that the neuroprotective affects of FGF2 involves its ability to suppress the production of neurotoxic molecules from activated microglia, such as glutamate and NO (Noda *et al.* 2014). Taken together, this collection of studies may be consistent with the role of FGF2 as a neuronal help-me signal.

2.4 Lipocalin-2

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin, siderocalin, uterocalin or 24p3, belongs to the lipocalin superfamily which includes a group of about 20 small secreted lipoproteins. Lipocalin superfamily acts as the transporters of small hydrophobic substances such as prostaglandins, retinoids, arachidonic acid, hormones and fatty acids (Bolignano *et al.* 2010; Flower 1996). LCN2 captures and transports iron particles to the inner cell by interacting with specific membrane receptors (24p3R or megalin) (Goetz *et al.* 2000). Although initially identified as an antibacterial factor released

from activated neutrophils (Flower 1996; Kjeldsen *et al.* 1993), LCN2 can be induced by many organs in response to injury and participates in inflammation and tissue remodeling. LCN2 is produced by renal tubular cells during kidney disease, and may be an early and specific biomarker of organ damage and prognosis (Bolignano *et al.* 2008). LCN2 is also increased after myocardial infarction, in both necrotic and surrounding healthy tissues (Hemdahl *et al.* 2006; Yndestad *et al.* 2009).

LCN2 may also be important in CNS disease. In human stroke, serum levels of LCN2 progressively increased following acute ischemia and transient ischemic attacks, and persisted for up to 1 year (Anwaar *et al.* 1998; Elneihoum *et al.* 1996). LCN2 levels in CSF were elevated in multiple sclerosis patients (Marques *et al.* 2012). LCN2 was increased in postmortem brain tissue of Alzheimer's disease patients (Naude *et al.* 2012). In rat brain, LCN2 mRNA and protein were upregulated after neuronal injury induced by kainite (Chia *et al.* 2011) or after neuroinflammation induced by systemic LPS injections (Ip *et al.* 2011). Some papers showed that astrocytes produced LCN2 (Bi *et al.* 2013), but other papers showed that LCN2 colocalized with neurons, not astrocytes or microglia (Jeon *et al.* 2013; Mucha *et al.* 2011; Skrzypiec *et al.* 2013). Our data suggest that ischemic neurons (not glia) produced LCN2 in rat and human stroke brains (Xing *et al.* 2014).

The effects of LCN2 are likely to be disease, model, and species-dependent. In a mouse model of renal damage, LCN2 protected the kidney against ischemia-reperfusion injury (Mori et al. 2005). Macrophages that overexpress anti-inflammatory factor IL-10 were protective in rat models of kidney dysfunction via iron-mediated upregulation of LCN2 and its receptors, eliciting both anti-inflammatory and proliferative responses (Jung et al. 2012). LCN2 is being increasingly explored in CNS disease. In models of amyotrophic lateral sclerosis and spinal cord trauma, LCN2 induced oxidative stress in neurons (Berard et al. 2012; Lee et al. 2009; Rathore et al. 2011). Recently, our findings provided proof of concept that LCN2 was released by injured neurons as a help-me signal that activated microglia and astrocytes into potentially prorecovery phenotypes (Xing et al. 2014). LCN2 was upregulated in injured neurons in rat cerebral ischemia and human stroke patients. The release of LCN2 increased in neuronal conditioned media after oxygen-glucose deprivation (OGD), but not detected in microglial or astrocytic cultures. After OGD in vitro or cerebral ischemia in vivo, LCN2 released by injured-but-not-dead neurons shifted astrocytes and microglia into beneficial phenotypes to protect neurons against OGD and promote neuroplasticity. A recent study showed that astrocytes expressed LCN2 and LCN2 deficiency attenuated neuroinflammation and tissue damage in mouse models of transient cerebral ischemia (Jin et al. 2014a), seemingly at odds with our hypothesis. Here, species differences may be critical because the mouse gene differs from rat and human homologs (Tsaparas et al. 2006; Zhao et al. 2004). Rigorously understanding how LCN2 help-me signaling contributes to the balance between injury and repair should be useful for pursuing future therapeutics for stroke recovery.

2.5 Neuron-derived IgG

Although IgG is most commonly thought of as a blood protein, it can also be produced by neurons. IgG-positive neurons are found in cerebral cortex, hippocampus, mesencephalon,

cerebellum, lower brainstem, dentate gyrus, and the spinal cord (Huang *et al.* 2008; Niu *et al.* 2011; Yoshimi *et al.* 2002; Zhang *et al.* 2013a; Zhang *et al.* 2013b). Although similar IgG-positive neurons are observed in rabbit, rat, and mouse brains, each species have a characteristic distribution. Compared to rat and mouse brains, IgG-positive neurons are more abundant in rabbit brains (Yoshimi *et al.* 2002). No positive IgG signals are detected in astrocytes and oligodendrocytes (Zhang *et al.* 2013b). But a fraction of microglia is IgG positive (Yoshimi *et al.* 2002; Zhang *et al.* 2013b). FcγRs (mainly CD64, the receptor with the highest affinity for IgG) is expressed in microglia (Niu *et al.* 2011; Vedeler *et al.* 1994; Zhang *et al.* 2013a). Astrocytes, oligodendrocytes and neurons do not appear to express FcRs (Vedeler *et al.* 1994).

Neuron-derived IgG protects neurons against cell death through CD64 and TLR4 pathway and attenuating the release of NO by microglia (Zhang *et al.* 2013a; Zhang *et al.* 2013b). IgG production increased in primary cultured neurons after exposure to 6-OHDA or complement, and neuron-derived IgG reduced apoptosis of neurons and inhibited secondary NO release from microglia in these models (Zhang *et al.* 2013a; Zhang *et al.* 2013b). Neuron-derived IgG triggered microglial activation, including morphological changes and production of TNFα and IL-10 to protective levels via the FcγR I and TLR4 pathways, and this effect could be attenuated by IgG blocking (Zhang *et al.* 2013b). Cultured microglia also showed FcR-mediated agglutination and phagocytosis of IgG-sensitized erythrocytes (Vedeler *et al.* 1994). Therefore, it is possible that under some specific circumstances, injured neurons may release extracellular IgG that serve as help-me signals that amplify endogenous protective responses against further neurotoxic stimuli. Further studies are warranted to explore these potential pathways in various models of stroke and brain injury.

3. Extracellular signals within the neurovascular unit for neuroprotection and neurorecovery

Besides neuronal help-me signals, other extracellular proteins may also be involved in the interaction between different cells in the neurovascular unit. Importantly, many of these mediators are biphasic in nature, comprising a complex mix of help-me signals, DAMPs and PAMPs. Nevertheless, in theory, if one can distinguish the differential signaling mechanisms of detrimental versus beneficial CNS responses, one may design combination therapies to protect and repair the neurovascular unit. Here, we select three representative examples (a cytokine TNFα, a chemokine CCL2, and a growth factor VEGF) to discuss the effects of extracellular help-me signals in non-cell autonomous mechanisms of neuroprotection and neurorecovery after ischemic stroke **(Figure 4)**.

3.1 Cytokines: tumor necrosis factor α

Cytokines comprise a group of multifunctional polypeptides with low molecular weight. Almost all cytokine family members possess broad-spectrum pleiotropic properties including the regulation of cell proliferation, differentiation, and activation (Sriram and O'Callaghan 2007). In the CNS, TNFα is a stereotypical cytokine that is central to multiple physiologic processes as well as classical inflammatory responses (Park and Bowers 2010). In the healthy brain, constitutive TNFα exerts a permissive and regulatory function on

crucial physiological processes, such as learning and memory, food and water intake, sleep, and synaptic plasticity, including astrocyte-induced synaptic strengthening (glial transmission) (Santello and Volterra 2012).

3.1.1 TNFα and its receptors—TNFα is synthesized as a 26kDa transmembrane protein precursor. Upon cleavage by TNFα converting enzyme, a soluble form is released as a homotrimer protein of 17kDa subunits that go onto act in various autocrine and paracrine pathways (Sriram and O'Callaghan 2007). TNFα can be produced by many cell types including macrophage, lymphocytes, monocytes, dendritic cells and natural killer cells (Kaltsonoudis *et al.* 2014). In the brain, microglia are a prominent source of TNFα, although TNFα can also be released by astrocytes and some populations of neurons under specific conditions (Figiel 2008; Montgomery and Bowers 2012).

The biological activities of TNFα take place via two receptors, TNFR1 (p55) and TNFR2 (p75), which belongs to the TNF receptor superfamily which includes other receptors such as Fas, CD40, p75 nerve growth factor receptor, lymphotoxin β receptor, etc (Kaltsonoudis *et al.* 2014; Sprang 1990; Sriram and O'Callaghan 2007; Tartaglia *et al.* 1991). TNFR1 may be expressed in most CNS cell types, whereas TNFR2 is mainly found on endothelium and microglia (Santello and Volterra 2012). TNFα signal transduction is complex, and the differential expression pattern of TNF receptors and downstream cascades may play a key role in determining beneficial or detrimental effects of TNFα (Santello and Volterra 2012). TNFα binding to TNFR1 affects biological processes including cell growth, cell death, and inflammation, whereas stimulation of TNFR2 preferentially leads to activation of anti-apoptotic and proinflammatory pathways (Santello and Volterra 2012). Although distinct cellular responses are mediated by different TNFα receptors, emerging data now demonstrate important overlap of two receptors in mediating its varied biological effects (Figiel 2008).

3.1.2 Profiles of TNFα expression after brain ischemia—In ischemic stroke patients, TNFα is elevated in serum, plasma and CSF samples (Intiso *et al.* 2004; Vila *et al.* 2000; Zaremba and Losy 2001). In animal models of cerebral ischemia, TNFα levels in the blood were rapidly increased during ischemia and early reperfusion (Lavine *et al.* 1998). In mouse models of global cerebral ischemia, TNFα increased in the brain 1.5 hours after injury, then decreased at 6 hours followed by a secondary increase again at 3 days (Uno *et al.* 1997). In models of focal ischemia, TNFα mRNA and protein levels were elevated by 3 hours in the ischemic hemisphere, peaked at 6 to 12 hours followed by a prolonged plateau that can persist for days (Buttini *et al.* 1996; Gong *et al.* 1998; Liu *et al.* 1994). In human ischemic brains, microglia probably constitutes the main cellular source of TNFα (Dziewulska and Mossakowski 2003). In animal models, TNFα may be mainly released from microglia and invading leukocytes (Buttini *et al.* 1996; Gregersen *et al.* 2000; Lambertsen *et al.* 2009; Sairanen *et al.* 2001). In addition, TNFα immunoreactivity was also showed in neurons, astrocytes, and endothelial cells (Botchkina *et al.* 1997). TNFα protein is localized with neurons in both infarct core and adjacent tissues at an early stage after ischemia and peaking bilaterally at 2-3 days, while TNFα expression in astrocytes and

macrophages may occur in later phases (Gong *et al.* 1998; Liu *et al.* 1994; Sairanen *et al.* 2001).

Focal cerebral ischemia also induced a significant up-regulation of TNF receptors, with an early peak of TNFR1 around 6 hours, and a later peak of TNFR2 around 24 hours post-ischemia (Botchkina *et al.* 1997). Besides neurons and blood vessels, expression of TNFα receptors may be induced in glial cells (astrocytes and microglia/macrophages) after ischemia (Dziewulska and Mossakowski 2003).

3.1.3 Neurotoxic and neuroprotective effects of TNFα in cerebral ischemia: opposite roles of TNFR1 and TNFR2—Exogenous TNFα increased the infarction induced by transient or permanent focal ischemia in a dose-related manner (Barone *et al.* 1997). Correspondingly, neutralizing antibodies against TNFα, compounds that inhibit endogenous TNFα synthesis, or soluble TNFR1 to inhibit the activity of TNFα all significantly attenuated microvessel perfusion impairment, enhanced reperfusion, reduced infarct volume, and improved functional outcome (Barone *et al.* 1997; Dawson *et al.* 1996; Lavine *et al.* 1998; Meistrell *et al.* 1997). In vitro, it seemed that TNFα itself alone failed to kill neurons in cultured cerebellar granule cells (Barone *et al.* 1997), but it might be harmful to neurons when acting synergistically with other deleterious factors released from glia in cocultures (Zhao *et al.* 2001).

In spite of these well-documented neurotoxic actions, some studies have suggested that TNFα may also possess neuroprotective effects. TNFα protects cultured hippocampal and cortical neurons and cerebellar granule cells against glucose deprivation, excitotoxicity and Aβ (Barger *et al.* 1995; Cheng *et al.* 1994; Kaltschmidt *et al.* 1999). Compared with wild-type mice, TNF knockout significantly exacerbated neuron damage, infarction and behavioral deficit caused by cerebral ischemia (Bruce *et al.* 1996; Lambertsen *et al.* 2009). TNFα may also contribute to neuroprotection by upregulating the expression of neurotrophic factors in astrocytes, including nerve growth factor, brain-derived neurotrophic factor and glial-derived neurotrophic factor (Appel *et al.* 1997; Hattori *et al.* 1993; Kuno *et al.* 2006; Saha *et al.* 2006).

In many experimental studies, predominant TNFR1 activation was associated with circuit alterations and neuronal damage, whereas TNFR2 activation was protective. However, TNFα/TNFRs action is more complex than initially thought. In primary cortical neurons, TNFα-mediated protection against N-methyl-D-aspartate (NMDA)-mediated excitotoxicity is TNFR2-independent and requires the activation of the TNFR1 plus the release of endogenous TNFα (Carlson *et al.* 1998). But beneficial effects of TNFα against glutamate excitotoxicity are mediated by TNFR2 (Marchetti *et al.* 2004). In ischemia-reperfusion-induced retinal damage in mice, absence of TNFR1 potently decreased neuronal death and lack of TNFR2 enhanced neuronal death (Fontaine *et al.* 2002). However, compared with wild-type and TNFR2 deficient mice, deficiency of TNFR1 significantly increased neuronal death after focal cerebral ischemia-reperfusion, and degeneration of CA3 hippocampal neurons after kainic acid injections (Gary *et al.* 1998). Compared with TNFR2 knockout and wild-type mice, TNFR1 knockout mice had increased infarction, suggesting that

neuroprotective effects of microglial-derived TNF may operate through TNFR1 (Lambertsen *et al.* 2009).

3.1.4 TNFα and Ischemic preconditioning—Preconditioning with TNFα may be protective against cerebral ischemia. TNFα levels in plasma were higher in acute stroke patients with prior TIA (Castillo *et al.* 2003). Infarct volumes and the frequency of poor outcome were significantly lower in stroke patients with prior TIA, and the TNFα/IL-6 index was associated with good outcome (Castillo *et al.* 2003). Preconditioning with intracisternal administration of TNFα significantly reduced infarct volume and inhibited microglial activation in a focal ischemia models (Nawashiro *et al.* 1997). Pre-exposure to TNFα caused a significant reduction in glutamate-induced Ca^{2+} influx in hippocampal cultures, and antagonism of TNFα completely reversed this effect (Watters *et al.* 2011). Ischemic preconditioning upregulated neuronal expression of TNFR1, and TNFR1 antisense oligodeoxynucleotide abolished the ischemic preconditioning-induced protective effect (Pradillo *et al.* 2005). These findings suggest that TNFα signaling participates in the phenomenon of ischemic tolerance.

TNFα is required for LPS-induced ischemic preconditioning as LPS-precondition was not protective in TNFα null mice cerebral ischemia (Rosenzweig *et al.* 2007), and treatment with a specific TNF antagonist reversed the protective effect of LPS preconditioning in permanent focal ischemia in mice (Tasaki *et al.* 1997). TNFα is also required for the preconditioning induced by tPA or TLR9 agonist unmethylated cytosine-phosphate-guanine-rich DNA oligonucleotides against the damaging effects of lethal neuronal hypoxia and cerebral ischemia (Haile *et al.* 2012; Packard *et al.* 2012).

3.1.5 Roles of TNFα in neurogenesis and angiogenesis—Neural stem cells or neural progenitor cells (NPCs) express TNFR1 and TNFR2 (Ben-Hur *et al.* 2003; Keohane *et al.* 2010)(Bernardino et al., 2008; Keohane et al., 2010), and TNFR1 and TNFR2 are also expressed in progenitor cells from hippocampal and subventricular zone (SVZ) (Iosif *et al.* 2008; Iosif *et al.* 2006).

To date, the effects of TNFα on neurogenesis remain controversial. In vitro, TNFα signaling through TNFR2 is required for NPC proliferation while signaling through TNFR1 impairs neural progenitor proliferation and induces cell death (Chen and Palmer 2013; Iosif *et al.* 2008). TNFα treatment inhibited the proliferation of neurospheres obtained from striatum and SVZ without affecting cell survival and did not affect NPCs lineage fate after differentiation (Ben-Hur *et al.* 2003; Iosif *et al.* 2008). In contrast, TNFα treatment promoted NPCs proliferation in culture (Widera *et al.* 2006). Exposure of NPCs to TNFα enhanced astrogliogenesis and inhibited neuronal differentiation, and percentages of newborn neurons reduced and percentages of astrocytes increased (Keohane *et al.* 2010; Lan *et al.* 2012; Liu *et al.* 2005). In contrast, exposure of NPCs to TNFα resulted in increased neuronal differentiation and axonogenesis, and the proneurogenic effect of TNFα is mediated via TNFR1 (Bernardino *et al.* 2008).

In vivo, TNFR1 may be involved in the negative regulation of neural progenitor proliferation in both normal and diseased brain. Baseline neurogenesis in the hippocampus elevated in

TNFα−/−, TNFR1−/− and TNFR1/R2−/− animals, whereas absence of TNFR2 decreased baseline neurogenesis or showed no significant changes (Chen and Palmer 2013; Iosif *et al.* 2006). After focal stroke, TNFα promoted the survival of newborn striatal and hippocampal neurons via TNFR2, and TNFα antibody-treated rats showed fewer new striatal and hippocampal neurons (Heldmann *et al.* 2005). Concommitantly, deficiency of TNFR1 enhanced proliferation and neuroblast formation in the subventricular zones after focal cerebral ischemia (Iosif *et al.* 2008).

Compared to neurogenesis, the effects of TNFα on angiogenesis are not as well studied. TNFα inhibited endothelial cell proliferation in vitro, including basal and FGF-stimulated proliferation (Frater-Schroder *et al.* 1987). Surprisingly, in vivo TNFα stimulated neovascularization in the rabbit cornea (Frater-Schroder *et al.* 1987). In addition, TNFα/TNFR1 signaling was found to upregulate the EPO receptor in endothelium, thus amplifying EPO-mediated activation of VEGF/VEGFR2 and Ang1/Tie2 angiogenic pathways (Wang *et al.* 2011b). In primary rat cerebral endothelial cultures, TNFα potently increased EPO receptor expression; further exposure to EPO in TNFα-treated cells significantly promoted matrigel tube formation, whereas blocking TNFR1 dampened TNFα-induced EPO receptor levels and prevented EPO-induced tube formation (Wang *et al.* 2011b). Recently, it has been proposed that microglia enhanced in vitro angiogenesis of brain microvascular endothelial cells by releasing TNFα and upregulating the expression of angiogenic factors ephrin-A3 and ephrin-A4 (Li *et al.* 2014). Altogether, these data are consistent with the idea that TNFα may act as a remodeling signal within the recovering neurovascular unit.

3.2 Chemokines: CCL2/CCR2

The monocyte chemoattractant proteins (MCPs) belong to the CC-chemokine sub-family. The five MCP members share approximately 60% sequence homology, but MCP-1 (CCL2) is the first discovered and best characterized MCP and signals through its receptor CCR2 (Conductier *et al.* 2010). CCL2 is a potent chemoattractant for monocytes, memory T-cells and natural killer cells (Allavena *et al.* 1994; Carr *et al.* 1994; Sozzani *et al.* 1994). In this section, we briefly review the roles of CCL2 as an intercellular signal that underlies non-cell autonomous interactions in the neurovascular unit.

3.2.1 Expression: the CCL2/CCR2 network in brain—Constitutive CCL2 expression in neurons has been documented in many brain regions including cortex, hippocampus, substantia nigra, globus pallidus, various nuclei in hypothalamus, and Purkinje cells of the cerebellum (Banisadr *et al.* 2005a; Banisadr *et al.* 2002; Coughlan *et al.* 2000; Gourmala *et al.* 1997; Stamatovic *et al.* 2005; van der Meer *et al.* 2000). Co-distribution of CCL2 with classical neurotransmitters such as acetylcholine and dopamine suggest that CCL2 may modulate neuronal and neuroendocrine functions (Banisadr *et al.* 2005a; Rostene *et al.* 2007). Adding CCL2 to dopaminergic neurons amplified dopamine release and neuronal excitability (Guyon *et al.* 2009). Colocalization of CCL2 with arginine vasopressin neurons and melanin-concentrating hormone expressing neurons in pituitary and hypothalamic areas support an interaction with neuroendocrine regulation (Banisadr *et al.* 2005a; Callewaere *et al.* 2007). Furthermore, besides neurons, CCL2 can also be found in astrocytes, endothelium, and perivascular microglia (Andjelkovic and Pachter 2000; Andjelkovic *et al.* 1999; Barna *et*

al. 1994; Berman *et al.* 1996; Glabinski *et al.* 1996; Gourmala *et al.* 1997; Hanisch 2002; Hayashi *et al.* 1995; Hurwitz *et al.* 1995; Kim *et al.* 1995). Altogether, this specific yet widespread network of CCL2 may be consistent with its key roles in CNS function.

In contrast to the ligand, its receptor CCR2 may participate in immune signaling. Monocytes, activated T cells, and dendritic cells, constitutively express CCR2 (Van Coillie *et al.* 1999). In the CNS, CCR2 can be found in microglia (Boddeke *et al.* 1999; Conductier *et al.* 2010), and reactive astrocytes that arise during neuroinflammation (Andjelkovic *et al.* 2002; Croitoru-Lamoury *et al.* 2003). CCR2 is also detected on large number of neurons, including cortex, hippocampus, striatum, hypothalamus, brainstem and cerebellum (Banisadr *et al.* 2005b; Rostene *et al.* 2007).

In ischemic stroke patients, CCL2 levels are increased in the blood and CSF (Arakelyan *et al.* 2005; Losy and Zaremba 2001; Sanchez-Moreno *et al.* 2004; Worthmann *et al.* 2010). In animal model of focal ischemia, mRNA and protein levels of CCL2 rapidly increase within hours and then remain elevated for days after ischemic onset (Wang *et al.* 1995; Yamagami *et al.* 1999). CCL2 tends to appear first in neurons in early stages of stroke, and then becomes upregulated in astrocytes later (Che *et al.* 2001).

3.2.2 Neurotoxicity and neuroprotection of CCL2 in ischemic stroke—Compared to normal mice, transgenic mice overexpressing CCL2 show larger infarct volumes and increased perivascular accumulation of neutrophils and macrophages in the brain (Chen *et al.* 2003). Conversely, focal ischemia in CCL2 deficient mice resulted in reduced infarct size, improved neurological functions, impaired leukocyte infiltration, and reduced inflammatory markers such as IL-6, IL-1β, and G-CSF (Hughes *et al.* 2002; Kumai *et al.* 2004; Strecker *et al.* 2011). CCL2 may be required for recruiting blood cells to damaged brain; neutrophils and macrophage infiltration was reduced in CCL2-deficient animals compared to wild type mice without a detectable effect on microglia (Schilling *et al.* 2009). Analogous findings have been obtained in receptor mutant mice. Compared with wildtypes, CCR2 knockouts were be protected against ischemia-reperfusion injury, along with a decrease in brain levels of cytokines, neutrophils, and monocytes (Dimitrijevic *et al.* 2007). However, as with any inflammatory mediator, its ultimate role in brain injury and recovery is complex and may depend on the context of stroke evolution over time. Using MRI, another study suggested that by 3 days after focal ischemia, brain infarction was essentially similar in wild-type mice and CCL2 knockout mice (Andres *et al.* 2011).

During the acute stage, CCL2-CCR2 signaling may be detrimental due to its effects on leukocyte targeting into damaged brain. But during the recovery stage, emerging data suggest a potentially positive role for this complex signaling network. In primary neurons, CCL2 was protective against oxygen-glucose deprivation or glutamate toxicity, in part by blocking intracellular calcium buildup, dampening secondary glutamate efflux, and ameliorating the subsequent loss of ATP (Madrigal *et al.* 2009). In mixed neuron-astrocyte cultures, CCL2 was protective against NMDA or Tat neurotoxicity by inhibiting increases in extracellular glutamate and NMDA receptor 1 expression (Bruno *et al.* 2000; Eugenin *et al.* 2003). In vivo, exogenous CCL2 was neuroprotective in the wild-type mice after HIV-1 Tat

injection into striatum, but not in CCR2 knockout mice, suggesting the neuroprotection of CCL2 is mediated by CCR2 (Yao *et al.* 2009).

Besides being a direct neuroprotective agent, CCL2 may also be involved in the regulation of other protective factors. The neuroprotective effects of norepinephrine were partially mediated by CCL2 released from astrocyte, and was blocked by neutralizing antibody of CCL2 (Madrigal *et al.* 2009). In hippocampal neurons subjected to glutamate or oxygen-glucose deprivation, the protective effect of CXCL16 was dramatically smaller when co-administered with CCL2 blocking antibodies (Rosito *et al.* 2012).

3.2.3 CCL2 and blood-brain barrier permeability and angiogenesis—Like many other factors that promote angiogenesis will increase vascular permeability, such as VEGF (see the discussion in next section), CCL2 may also possess biphasic properties. It may be deleterious in terms of reducing BBB integrity by regulating tight junctions and cytoskeleton. It may be beneficial because it may play a role in promoting neovascularization. CCL2 can affect BBB permeability, in part because of its ability to modulate the actin cytoskeleton and regulate the intracellular versus membrane localization of tight junction proteins such as ZO-1, claudin-5 and occludin (Stamatovic *et al.* 2003). In astrocyte-endothelial cocultures subjected to OGD, blocking CCL2 with antisense oligonucleotide or neutralizing antibody improved the distribution of tight junction proteins and rescued BBB function (Dimitrijevic *et al.* 2006). Intracerebral and intracerebroventricular administration of CCL2 induced a significant increase in the BBB permeability, whereas monocytes/macrophages depletion reduced the effect of CCL2 on BBB integrity (Stamatovic *et al.* 2005). Compared to wild-type mice, CCL2–deficient mice had better preservation of tight junction proteins and BBB function after transient focal cerebral ischemia (Strecker *et al.* 2013).

CCL2 is a key factor in angiogenesis (Keeley *et al.* 2008), and its function to promote neovascularization has been demonstrated in a wide spectrum of in vitro and in vivo models (Barcelos *et al.* 2004; Galvez *et al.* 2005; Goede *et al.* 1999; Niu *et al.* 2008; Salcedo *et al.* 2000; Stamatovic *et al.* 2006; Weber *et al.* 1999). CCL2 can act as a direct angiogenic factor (Salcedo *et al.* 2000). CCL2 increased the expression, clustering, and activity of membrane type 1-matrix metalloproteinase and promoted tube formation in human endothelium. Blocking membrane type 1-matrix metalloproteinase activity effectively negates the pro-angiogenic actions of CCL2 (Galvez *et al.* 2005). The transcription factors Ets-1 and MCP-1 induced protein play a critical role in CCL2-induced angiogenesis. CCL2 upregulates both factors, and Ets-1 antisense oligonucleotide or knockdown of MCP-1 induced protein by siRNA suppressed CCL2-induced angiogenesis (Niu *et al.* 2008; Stamatovic *et al.* 2006). Finally, CCL2 can also be linked with the two standard networks for angiogenesis, i.e. hypoxia-inducible factor 1α and vascular endothelial growth factor (VEGF) (Hong *et al.* 2005).

3.2.4 Roles of CCL2 in migration and differentiation of neural stem cells—NPCs are known to respond to chemokine gradients during migration and differentiation. In this context, the expression of CCR2 on NPCs may be relevant (Tran *et al.* 2004). Using a Boyden chamber assay, NPC migration increased in response to CCL2 in vitro (Magge *et al.*

2009; Widera *et al.* 2004). Time-lapse video microscopy visualized the migration of single stem cells from neurospheres in CCL2-treated cultures, whereas no migration occurred in untreated cultures (Widera *et al.* 2004). In vivo, infusion of CCL2 into the brain induced neuroblasts migration to the infusion site (Magge *et al.* 2009; Yan *et al.* 2007).

The putative role of CCL2 in adult neurogenesis has been explored in experimental stroke (Semple *et al.* 2010). After focal ischemia, neuroblasts derived from SVZ neural progenitors migrate towards the injured brain regions (Arvidsson *et al.* 2002; Jin *et al.* 2001a; Parent *et al.* 2002; Zhang *et al.* 2004), and CCL2 signaling may be involved in this phenomenon. During the migration of newly formed neuroblasts, CCL2 plays an important role. Transciptional analysis of SVZ NPCs in this model suggest that CCL2 is one of the most robustly upregulated genes after focal cerebral ischemia (Liu *et al.* 2007). CCL2 expression and the number of CCL2-positive cells were significantly increased in ischemic cortex, striatum and SVZ (Liu *et al.* 2007; Yan *et al.* 2007). CCL2 also promotes neuronal differentiation in vitro. Treating NPCs with CCL2 dose-dependently increased the number of Tuj1-positive cells (Liu *et al.* 2007). Ultimately, the migration and differentiation of NPCs is CCL2/CCR2-dependent since blocking CCL2 with neutralizing antibodies or gene knockdown of either CCL2 or CCR2 almost completely negates this phenomenon (Liu *et al.* 2007; Yan *et al.* 2007).

3.3 Vascular endothelial growth factors (VEGF)

VEGF is one of the most well characterized trophic factors in vascular development, homeostasis and pathology. In the context of stroke, brain injury and neurodegeneration, the various isoforms of VEGF have been implicated in atherosclerosis and blood vessel disease, BBB leakage and brain edema, neurogenesis and angiogenesis during CNS repair and remodeling, and the interactions between central and peripheral compartments during cell therapies (Greenberg and Jin 2013). VEGF-A and its receptor VEGFR-2 are considered to be the most active members of VEGF family to mediate these various effects. Here, we survey the literature that supports a role for VEGF as a non-cell autonomous mediator for help-me signaling between different elements in the neurovascular unit.

3.3.1 VEGF and its receptor family—VEGF is a member of the cysteine knot growth factor family (Keck *et al.* 1989; Leung *et al.* 1989; Senger *et al.* 1983). In humans, the VEGF family includes VEGF-A (typically just termed as VEGF in the literature), VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF) (Ma *et al.* 2012). Human VEGF-A gene contains eight exons and seven introns which undergo extensive alternative splicing following transcription and proteolytic processing, thereby leading to the production of several isoforms (Tischer *et al.* 1991). Isoforms of VEGF-A include: VEGF121, VEGF121b, VEGF145, VEGF145b, VEGF165, VEGF165b, VEGF183, VEGF189, and VEGF206 (Crafts *et al.* 2015).

Three different VEGF receptors (VEGFR-1, -2, -3), which belong to tyrosine kinase receptor family, bind differentially to the VEGF peptides. VEGFR-2, known as kinase domain-containing receptor in humans and Flk-1 in murine systems, is the main mediator of angiogenesis and vascular permeability by binding VEGF-A, VEGF-C and VEGF-D

(Matsumoto and Claesson-Welsh 2001; Shalaby *et al.* 1995). VEGFR-1, also known as Flt-1, binds VEGF-A, VEGF-B and PlGF. Although most VEGF signals are pro-angiogenic individually, network function is more complex in its entirety. For example, by acting as a decoy receptor, VEGFR-1 may downregulate angiogenesis by preventing VEGFR-2 from binding VEGF-A (Ferrara *et al.* 2003; Park *et al.* 1993; Roskoski 2008). VEGF signals operate outside of the main vascular system per se. VEGFR-3 (also called Flt-4) is involved in lymphangiogenesis (Gordon *et al.* 2013; Veikkola *et al.* 2001).

3.3.2 Regulation of VEGF signaling in cerebral ischemia—Changes in VEGF have been described in many studies of cerebral ischemia and brain injury. In focal stroke models, rapid upregulation of VEGF in the penumbra occurs within a few hours, peaks by 24 hours, and then is sustained at a lower elevated level up to a week later (Plate *et al.* 1999). Cellular distributions are complex. In transient models of focal ischemia, VEGF mRNA and protein levels are significantly increased within 1-3 hours after reperfusion in neurons and pial cells, and then decreased in neurons but sustained in the pia for up to a week post-reperfusion (Hayashi *et al.* 1997). Other studies have shown an even broader response, and under some conditions, VEGF immunoreactivity can be increased in both ipsilateral and contralateral hemispheres in neurons as well as blood vessels (Lennmyr *et al.* 1998). In the evolving ischemic penumbra, VEGF mRNA and protein can be detected in astrocytes over 24-48 hors after stroke onset (Cobbs *et al.* 1998), while another study suggested that microglia and invading macrophages may also upregulate some VEGF isoforms in the ischemic borderzones (Plate *et al.* 1999).

In concert with ligand responses, various receptors including VEGFR-1 and VEGFR-2 are also altered in cerebral ischemia. After focal stroke, vascular levels of VEGFR-1 may be elevated over days to weeks along with the development of angiogenesis (Kovacs *et al.* 1996). VEGFR-1 immunoreactivity was widely noted in neurons, glial and endothelial cells, while VEGFR-2 immunoreactivity was most often observed in glial cells (Lennmyr *et al.* 1998).

3.3.3 Effects of VEGF on vascular permeability and angiogenesis—VEGF was identified originally based on two biological effects - angiogenesis (Leung *et al.* 1989) and vascular permeability (Keck *et al.* 1989). In this respect, VEGF is a perfect example of the biphasic properties of non-cell autonomous signals in the recovering neurovascular unit. As a beneficial signal, VEGF may promote recovery angiogenesis by increasing the proliferation and migration of endothelial cells during in the recovery and repair phases of pathological conditions. But as a deleterious signal, VEGF may worsen BBB leakage and induce the formation of brain edema after brain injury. In rat models of stroke, early administration of VEGF (within 1 hour of onset) impaired outcome and exacerbated BBB permeability and hemorrhagic conversion, whereas delayed treatment (48 hours after onset) was beneficial by promoting neurovascular repair and recovery (Zhang *et al.* 2000). During the acute stage of focal cerebral ischemia, inhibition of VEGF by receptor antagonists or anti-VEGF antibodies prevented BBB leakage, ameliorated hemorrhagic conversion, and improved behavioral outcomes (Chi *et al.* 2007; Kimura *et al.* 2005; van Bruggen *et al.* 1999). Combination of angiopoietin-1 and VEGF or coexpression of angiopoietin-1 with

VEGF augmented BBB integrity and reduced edema and brain damage after ischemia, but did not affect the angiogenic effects of VEGF (Shen *et al.* 2011; Valable *et al.* 2005; Zhang *et al.* 2002). Thus further dissection of the complex VEGF signaling networks may ultimately provide ways of separating beneficial and deleterious effects for therapeutic gain.

As a potential pro-recovery molecule, VEGF enhances angiogenesis in the ischemic brain and reduces neurological deficits during delayed stages post-injury. Late intracerebroventricular administration (48 hours after focal ischemia) of VEGF165 dramatically improved microvascular perfusion and angiogenesis in the penumbra and improved neurological recovery (Zhang *et al.* 2000). Chronic intraventricular infusions of VEGF165 dose-dependently increased microvessel density (Harrigan *et al.* 2002). In a rat focal ischemia model, intracerebroventricular administration of VEGF between 1-3 days of reperfusion increased the number of von Willebrand factor-immunoreactive endothelial cells in the ischemic striatal core (Sun *et al.* 2003). Although network interactions between multiple ligand and receptor isoforms are complex, the primary pro-angiogenic effects of VEGF are thought to occur via VEGFR-2 (Ferrara *et al.* 2003), since VEGFR-2 deficient knockout die in utero because of defects in vasculogenesis (Shalaby *et al.* 1995).

3.3.4 Effects of VEGF on neuroprotection and neurogenesis—The sum of the literature suggests that VEGF may be a potent neuroprotector against cerebral ischemia. VEGF protected primary cultured neurons from excitotoxicity and OGD (Jin *et al.* 2000; Matsuzaki *et al.* 2001; Svensson *et al.* 2002). Direct VEGF treatments onto rat brain reduced infarct volume and neuronal damage post-ischemia-reperfusion (Hayashi *et al.* 1998). Intracerebroventricular infusion of VEGF165 after focal cerebral ischemia reduced infarction in a blood flow-independent manner(Harrigan *et al.* 2003), whereas intraventricular injection of VEGF antibody exacerbated infarction (Bao *et al.* 1999). Hence, VEGF may have non-vascular actions in the context of CNS injury. Overexpression of VEGF or treatments with VEGF decreased infarction (Wang *et al.* 2005), and improved functional recovery after focal ischemia by downregulating caspase-3 and preventing neuronal dropout without any direct effects in angiogenesis (Kaya *et al.* 2005; Sun *et al.* 2003; Wang *et al.* 2006).

Beyond angiogenesis per se, VEGF may also have effects in neurogenesis. In cortical neuronal precursors cultures, VEGF increased cell number and 5-bromo-2'-deoxyuridine (BrdU) incorporation, an effect that can be blocked by the VEGFR2 tyrosine kinase inhibitor SU1498 (Jin *et al.* 2002). In vivo, injections of VEGF into the ventricles increased BrdU-labeled cells in the two primary neurogenic zones, i.e. SVZ and subgranular zones of the dentate gyrus, and these signals were detected in multiple cell types comprising immature and mature neurons, glial cells, and endothelial cells (Jin *et al.* 2002). In adult rats, VEGF gene transfer into the hippocampus almost doubled rates of neurogenesis and augmented cognition, whereas inhibition of VEGF with RNA interference abolished this neurogenic response (Cao *et al.* 2004).

VEGF enhances neurogenesis not only in normal brain, but also in ischemic brain. Intraventricular injections of VEGF during early stages of reperfusion after focal stroke enhanced the survival of newborn neurons in the SVZ and dentate zones of neurogenesis

(Sun *et al.* 2003). VEGF overexpression amplified the proliferation of neural progenitors in the SVZ, subgranular zone and dentate gyrus, increased the numbers of immature and mature newborn neurons and significantly improved their migration towards lesioned brain (Li *et al.* 2009; Wang *et al.* 2007b). In transgenic mice overexpressing VEGF, SVZ neurogenesis markedly increased at 7-28 days after cerebral ischemia, neuroblasts appeared to extend into cortical penumbral regions, and the number of newly generated neurons may even persist for up to 14-28 days post-ischemia (Wang *et al.* 2007a).

3.4 Roles of help-me signals in neurogenesis and angiogenesis

The sections above briefly surveyed three representative examples of neurovascular unit signals drawn from cytokine, chemokine and growth factor families. In the context of endogenous protective programs, these various extracellular factors can also be interpreted as adaptive help-me signals that promote recovery by augmenting neurogenesis and angiogenesis in a damaged or diseased brain.

3.4.1 CX3CL1/CX3CR1 and neurogenesis—CX3CL1/CX3CR1 signaling is involved in neuroplasticity. It has been proposed that CX3CR1 deficiency may promote IL-1β signaling, thus interfering with synaptic homeostasis and cognition (Rogers *et al.* 2011). CX3CL1 is upregulated in the hippocampus during memory-associated synaptic plasticity (Sheridan *et al.* 2014), and CX3CL1/CX3CR1 signaling regulates hippocampal neurogenesis by directly modifying the niche environment (Bachstetter *et al.* 2011). Disruption in CX3CL1/CX3CR1 signaling in young adult rodents decreased survival and proliferation of neural progenitors through IL-1β (Bachstetter *et al.* 2011). Aged rats showed decreased CX3CL1 in hippocampus, and interruption of CX3CR1 in these aged brains did not yield further effects on neurogenesis (Bachstetter *et al.* 2011). Interestingly, injection of exogenous CX3CL1 reversed these age-related perturbations in hippocampal neurogenesis, but exogenous CX3CL1 did not change neurogenesis in young animals (Bachstetter *et al.* 2011). If CX3CL1 can be fully defined as a help-me signal, these pathways may provide new leads for regrowing neural circuits in order to repair damaged brain tissue.

3.4.2 IL-34 and blood-brain barrier and angiogenesis—CSF1R is also expressed in microvessel endothelial cells in the CNS (Jin *et al.* 2014b). A novel function of IL-34 in the BBB has been recently described. IL-34 upregulated the tight junction proteins claudin-5 and occluding, and reversed BBB disruption induced by pro-inflammatory cytokines (IL-1β and TNFα) (Jin *et al.* 2014b). In addition, IL-34 overexpression is associated with an increase of angiogenesis (Segaliny *et al.* 2014). In vitro, IL-34 stimulated endothelial cell proliferation and vascular cord formation, and pre-treatment of endothelial cells by chondroitinases/heparinases reduced matrigel tube formation and abolished the associated cell signaling (Segaliny *et al.* 2014). Hence, promoting IL-34 pathways may augment neurovascular repair.

3.4.3 Lipocalin-2 and angiogenesis—As a candidate help-me factor, LCN2 may also function as an angiogenic factor. LCN2 promoted angiogenesis in human breast cancer cells (Yang *et al.* 2013), and these effects are thought to occur via the upregulation of VEGF via hypoxia-inducible factor 1α and ERK signaling, suggesting that VEGF may be essential for

the angiogenic activity of LCN2 (Yang *et al.* 2013). LCN2 may also enhance angiogenesis in brain endothelial cells (Wu *et al.* 2015). LCN2 promoted matrigel tube formation and wound healing migration via iron and ROS-related pathways in rat brain endothelial cells, and ROS scavengers, Nox inhibitors and iron chelators all dampened the ability of LCN2 to enhance in vitro angiogenesis in brain endothelial cells (Wu *et al.* 2015). Because LCN2 can be released by damaged-but-not-dead neurons as a help-me signal, this factor could potentially serve a critical role not only in modulating neuroinflammation but also as a way for a damaged neurovascular system to repair itself.

4. Endogenous protective mechanisms and secreted help-me signals

In this review, we have attempted to introduce the concept of help-me signaling as a non-cell autonomous mechanism for neuroprotection and neurorepair. The accumulating literature has provided many candidate factors for this phenomenon. However, it is also clear that such signals cannot operate alone. It is likely that help-me signaling involves an integrated and recursive network of mediators. How would one begin to find more factors and build a representation of this network? Here, we propose that analyses of the transcriptome and secretome of the perturbed neurovascular unit may provide a way forward. The transcriptome should provide insight into intercellular mechanisms. The secretome should provide insight into extracellular mechanisms. And together, these databases may allow us to rigorously define the network of help-me signaling for neuroprotection and neurorecovery after stroke and brain injury.

4.1 Mapping the transcriptome

Mechanisms of damage and repair in cerebral ischemia are very complex, and analysis of the transcriptome by microarray is a useful tool for studying molecular pathophysiology and transcriptional changes (Cox-Limpens *et al.* 2014; Stenzel-Poore *et al.* 2007; VanGilder *et al.* 2012). Microarray studies investigating the transcriptome of both focal and global ischemia showed that the differentially expressed genes involved immediate early genes, stress response genes, apoptosis, signal transduction, neurotransmission, ion channels, inflammation, cytoskeleton, ribosome, and neurotrophic factors, et al (Buttner *et al.* 2009; Cox-Limpens *et al.* 2014; Gilbert *et al.* 2003; Hori *et al.* 2012; Jin *et al.* 2001b; Lu *et al.* 2003; Lu *et al.* 2004; Ramos-Cejudo *et al.* 2012; Sarabi *et al.* 2008; Schmidt-Kastner *et al.* 2002; Soriano *et al.* 2000; Sun *et al.* 2007; Tang *et al.* 2002; Wang *et al.* 2011a; Yakubov *et al.* 2004).

Preconditioning activates endogenous protective mechanisms by reprograming the brain transcriptome in order to achieve ischemic tolerance (Stenzel-Poore *et al.* 2007). Several studies have investigated preconditioning induced gene expression with microarrays (Bernaudin *et al.* 2002; Cox-Limpens *et al.* 2013; Feng *et al.* 2007; Gustavsson *et al.* 2007; Kawahara *et al.* 2004; Prasad *et al.* 2012; Stenzel-Poore *et al.* 2003; Tang *et al.* 2006; Truettner *et al.* 2002). Examining the genomic profile of focal ischemia with and without preconditioning demonstrates expression of similar genes; however, preconditioning results in a substantial down regulation of the common expressed genes (Stenzel-Poore *et al.* 2004). Severe and damaging levels of ischemia generally upregulated gene expression; whereas

ischemic preconditioning followed by a second damaging ischemic challenge generally downregulated overall gene expression (Della-Morte *et al.* 2012). The genomic profile of ischemic preconditioning is characterized by suppression of gene expression involved in ion channel regulation, control of membrane excitability, metabolism, ATP regulation, cell cycle regulation, immune responses, and decreased blood coagulation (Della-Morte *et al.* 2012; Van Elzen *et al.* 2008). In spite of the promise of these array approaches, replication of individual gene responses has not been easy, and may be highly system and model-dependent. For example, a comparison effort based on single-gene analyses revealed that only about 15 genes were common in two studies or more (Cox-Limpens *et al.* 2014). Further cluster-based investigation into these 15 genes suggested that their common signaling pathways may be related to ERK1/2 networks that underlie cell survival and proliferation (Cox-Limpens *et al.* 2014). Future studies are warranted to carefully define sources of similarity and variation in the transcriptome response that may require attention to specifics in experimental paradigms, such as age, insult type, gender, the investigated brain region, and selected cellular and functional endpoints (Cox-Limpens *et al.* 2014).

The experimental study of preconditioning contributes to the knowledge of endogenous neuroprotective mechanisms, which may eventually lead to potential pharmaceutical treatments. Several pharmacological approaches have been suggested, including stimulus mimetics such as PKC modifying agents, thioredoxin 1, resveratrol and statins (Della-Morte *et al.* 2012). Fundamentally, mapping the individual and integrated transcriptome of neural, glial and vascular cells after IPC should allow us to understand how intercellular mechanisms control the release of extracellular help-me signals that protect against acute damage and promote repair after stroke.

4.2 Mapping the secretome

If the transcriptome provides a window into the molecular mechanisms of intracellular control, then mapping the secretome should allow one to probe the entire network of extracellular factors that underlie non-cell autonomous mechanisms. This may be especially important in the CNS where crosstalk occurs between multiple cell types provide the basis for coordinating the communication between cells. In order to dissect the network of inter-cellular help-me signals and understand how cells to “talk to each other”, mapping the “secretome” (i.e. the subset of the entire cellular proteome) with advanced proteomic methods will be required (Colucci-D'Amato *et al.* 2011).

One of the initial proteomic maps of the neuronal secretome identified about 34 major secreted proteins belonging to families involved in neurite and axonal maintenance, synaptic transmission, proteases and protease inhibitors, and cell adhesion (Thouvenot *et al.* 2008). Among these 34 proteins, several proteins are secreted by cells via the classical vesicular pathway and encompassing a signal peptide at their N terminus (e.g., cystatin C, apolipoprotein E, matrix metalloprotease-inhibitor 2, carboxypeptidase E and several complement subunits), whereas a larger set of proteins are released following proteolytic cleavage of the ectodomain of a membrane-bound or a transmembrane precursor (Thouvenot *et al.* 2008). In addition, the characterization of proteins released from neurons, astrocytes and neural precursor cells shows that the extracellular space within the nervous system has a

more diverse protein composition than previously thought (Schubert *et al.* 2009). Although there is overlap between the different cell types, the extracellular protein pool is likely to be somewhat unique for each cell population. Neurons and neuronal precursor cells release a larger number of proteins with more functional diversity, while astrocytes release a relatively small number of proteins.

Recently, characterization of secretome from primary neurons was used to explore the mechanisms underlying neuronal death (Thouvenot *et al.* 2012) and to identify novel substrate candidates of protease BACE1 (Kuhn *et al.* 2012; Zhou *et al.* 2012). After comparing the secretome of apoptotic and surviving cerebellar granule neurons, 47 proteins in the supernatants were differentially expressed (Thouvenot *et al.* 2012). Among the 47 proteins, 31 proteins are secreted via either the vesicular pathway or a non-classical mechanism of secretion, while 13 of them, annotated as membrane proteins, might be released following proteolytic cleavage of the ectodomain of a transmembrane precursor (Thouvenot *et al.* 2012). Functional GO analysis of these 47 proteins revealed the enrichment in proteins residing in the extracellular compartment and in proteins involved in cell adhesion (Thouvenot *et al.* 2012). Secretome analysis of neuronal BACE1 revealed several novel substrates and suggested that this system may contribute the shedding and release of key inter-cellular signals in the CNS (Kuhn *et al.* 2012; Zhou *et al.* 2012), including molecules that may be essential for regulating neurite extension and synaptic integrity (Kuhn *et al.* 2012). These approaches may ultimately allow one to define novel molecular mechanisms underlying BACE1 activity in the CNS and perhaps even help predict potential side effects in BACE clinical trials for dementia.

Currently, extracellular vesicles (also known as exosomes, microvesicles, and microparticles, or other names) have gained attention as important factors in cell-cell communication. Extracellular vesicles are composed of a lipid bilayer enclosing proteins and RNAs, and modify the state and function of the recipient cells by inducing signaling via receptor-ligand interaction or delivering their content into the recipient cells (Tkach and Thery 2016). Extracellular vesicles can be formed by budding from plasma membrane, or originated from multivesicular endosomes or multivesicular bodies (MVBs) (Tkach and Thery 2016). Neurons can release exosomes that contain functionally active proteins and miRNAs, which can exert a neuroprotective or neurotoxic role (Ghidoni *et al.* 2011; Janas *et al.* 2016; Lachenal *et al.* 2011; Morel *et al.* 2013). Recent several reviews offer the roles of exosomes and microvesicles in normal function, the development of regeneration of CNS as well as in the onset and progression of of some neurodegenerative and neuroinflammatory diseases (Janas *et al.* 2016; Porro *et al.* 2015). As a key component of any cellular secretome, extracellular vesicles may then comprise logical candidates for help-me signaling in the context of damaged neurons. The fact that these vesicles may also be detected in plasma and serum may even pint toward a potential use of measurable biomarkers for measuring the dynamic balance between injury and repair in the CNS.

Of course, the secretome is a dynamic entity. So differential analyses will be necessary in order to investigate the proposed phenomenon of help-me signaling. Each cell type would be mapped under normal, sublethally stimulated, and lethally disrupted conditions. Acute versus chronic secretomes may also differ. And then each secretome “state” would be

validated against functional databases for paracrine effects on other cells. Theoretically, an integrated response profile can be built for each secreting cell type and responding cell type over time, and ultimately, the resulting linked database can then be mined for novel candidate help-me signals under various injury and disease conditions.

5. Conclusions and future opportunities

Help-me signals essentially comprise a subset of extracellular signals that reside within the larger family of damage signals (Kono and Rock 2008). Along with various find me signals, eat me signals and clean-up signals, these may form a complex web of interacting and recursive loops that underlie homeostasis in any multicellular system. From an evolutionary perspective, these networks provide a biological system with the ability to respond and adapt to external stimuli. In the context of brain injury and disease, help-me signaling defines a non-cell autonomous basis for preconditioning and tolerance. When applied in stroke, these signals may be essential in neuroprotection and neurorepair.

Standard experimental models have tended to emphasize the deleterious nature of intracellular signals and extracellular factors. Hence, translational research has traditionally focused on finding ways to block receptors or enzymes in order to prevent injury. Ultimately, however, any attempt to develop targeted therapies in brain injury and neurodegeneration must take into account the biphasic nature of all mediators in the entire remodeling neurovascular unit, comprising reactions to injury in neural, glial and vascular compartments. Deleterious mediators co-exist with beneficial ones, and help-me signals may define this dynamic balance between initial injury and subsequent repair. A better understanding of help-me signaling may eventually lead to novel therapeutic approaches for neuroprotection and neurorecovery.

Abbreviations

Aβ	β amyloid
BBB	blood brain barrier
BrdU	5-bromo-2'-deoxyuridine
CSF	cerebrospinal fluid
CSF1	colony stimulating factor-1
CSF1R	colony stimulating factor-1 receptor
DAMPs	damage associated molecular pattern family
EPO	erythropoietin
FGF	fibroblast growth factors
IL	interleukin
LCN2	Lipocalin-2

LPS	lipopolysaccharide
MCPs	monocyte chemoattractant proteins
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NPCs	neural progenitor cells
OGD	oxygen-glucose deprivation
6-OHDA	6-hydroxydopamine
SVZ	subventricular zone
TIA	transient ischemic attack
TNFα	tumor necrosis factor α
VEGF	vascular endothelial growth factor
ZO	zonula occludens

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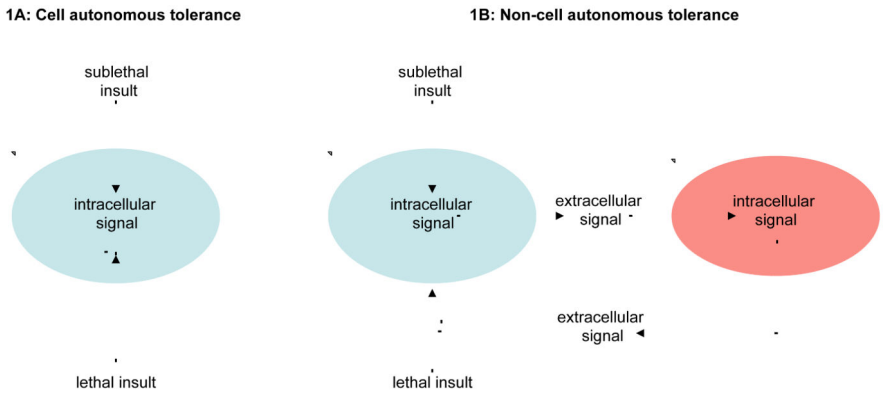

Figure 1. Cell autonomous tolerance (A) and non-cell autonomous tolerance (B)

(A) The initial sublethal insult induces intracellular signaling pathways that serve to block the second lethal insult. (B) The initial sublethal insult induces a cascade of intracellular signals that provoke the release of extracellular mediators that affect an adjacent cell. This second cell responds by releasing another set of extracellular signals that then block a lethal insult against the original cell.

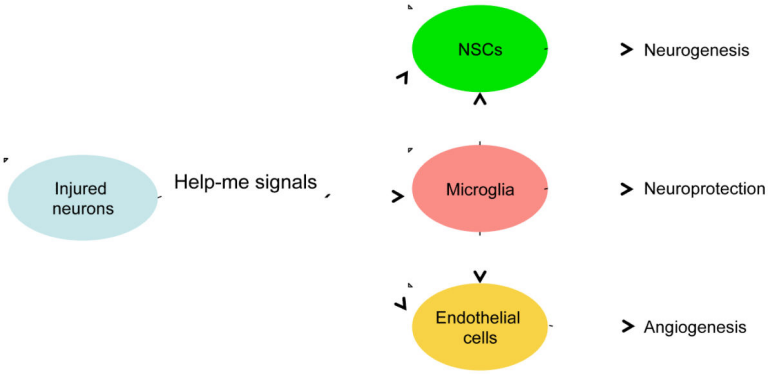

Figure 2. Help-me signals

Damaged or diseased neurons release signals that may shift glial and vascular cells into potentially beneficial phenotypes, i.e. providing neuroprotection and promoting neurogenesis and angiogenesis.

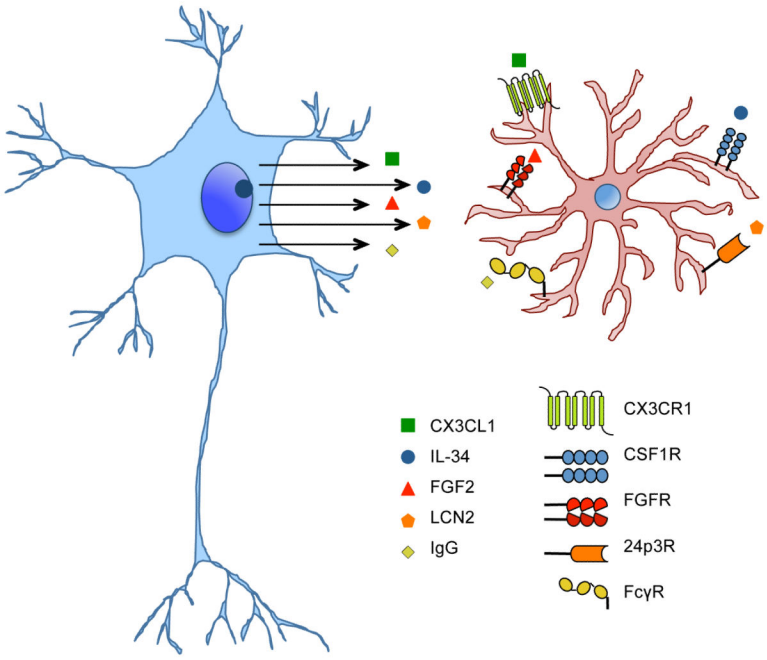

Figure 3. Neuronal help-me signals are involved in the interaction of neurons and microglia

After brain injury, neurons can release unique “help-me” signals, such as CX3CL1, IL-34, FGF2, LCN2, and IgG etc, which will interact with receptors expressed in microglia to guide microglial activation into a beneficial phenotype of neuroprotection and neurorecovery.

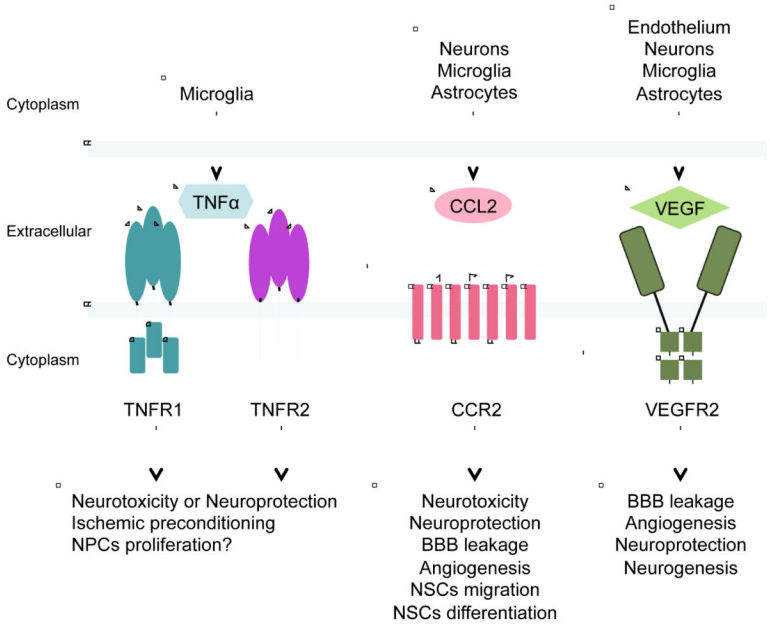

Figure 4. Extracellular signals within the neurovascular unit for neuroprotection and neurorecovery

Three representative examples (TNFα, CCL2, and VEGF) of extracellular signals may be involved in the interaction between different cells in the neurovascular unit and in non-cell autonomous mechanisms of neuroprotection and neurorecovery after ischemic stroke.