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REVIEW

Resolution of neuroinflammation: mechanisms and potential therapeutic option

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Abstract

The central nervous system (CNS) is comprised by an elaborate neural network that is under constant surveillance by tissue-intrinsic factors for maintenance of its homeostasis. Invading pathogens or sterile injuries might compromise vitally the CNS integrity and function. A prompt anti-inflammatory response is therefore essential to contain and repair the local tissue damage. Although the origin of the insults might be different, the principles of tissue backlashes, however, share striking similarities. CNS-resident cells, such as microglia and astrocytes, together with peripheral immune cells orchestrate an array of events that aim to functional restoration. If the acute inflammatory event remains unresolved, it becomes toxic leading to progressive CNS degeneration. Therefore, the cellular, molecular, and biochemical processes that regulate inflammation need to be on a fine balance with the intrinsic CNS repair mechanisms that influence tissue healing. The purpose of this review is to highlight aspects that facilitate the resolution of CNS inflammation, promote tissue repair, and functional recovery after acute injury and infection that could potentially contribute as therapeutic interventions.

Keywords Resolution of neuroinflammation · CNS infection · Traumatic brain injury · Spinal cord injury · Ischemic stroke

Introduction

Maintaining homeostasis in general is a highly dynamic process that requires a finely tuned system, rapidly responding to any disturbances by activating all necessary mechanisms which will help to restore the organism to its original state. Upon infection or tissue injury, the organism will activate its defense strategies to fight promptly and efficiently the insult. The immune system can sense homeostatic disturbances either by pathogen-associated molecular patterns (PAMPs), in case of infection, or by damage-associated molecular patterns (DAMPs) after tissue injury, which bind on pattern recognition receptors (PRRs) initiating a cascade of cellular activation that triggers the system's response. The PRRs comprise a family of membrane-bound toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and cytoplasmic receptors, RIG-like receptors (RLRs), and NOD-like receptors, expressed mainly on innate immune cells and recognize bacterial, viral, fungal, and parasitic material activating the cellular response [1, 2]. Activation of the PRRs on resident cells will result in the production of cytokines and chemokines which will attract peripheral immune cells in the injury site [3]. Lipid mediators play an essential role during the acute inflammatory phase, in addition to its resolution. Prostaglandins and leukotrienes produced by arachidonic acid derived from omega- 6-rich membranes are considered pro-inflammatory mediators. In contrast, resolvins, protectins, maresins, and lipoxins, collectively termed specialized pro-resolving mediators (SPM), derived by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) released from omega-3-rich membranes, seem to play a pivotal role in the resolution of inflammation in different tissues, including the CNS [4, 5].

In the central nervous system (CNS), resident glial cells are the first to respond in any potential insult (Fig. 1a). Microglial cells, the resident yolk sac-derived innate immune cells, are

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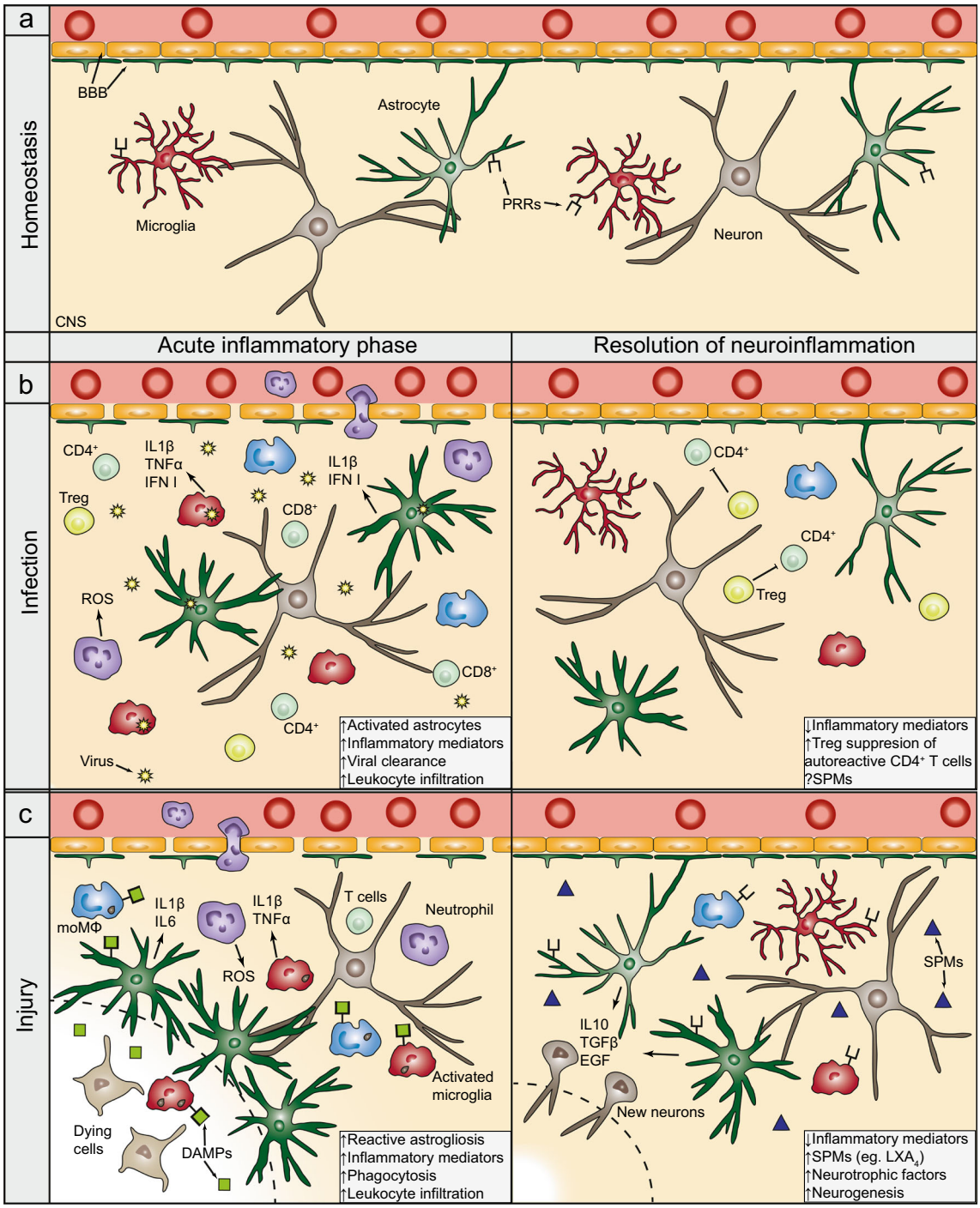

rapidly activated in CNS diseases, acquiring an amoeboid morphology and producing various pro-inflammatory mediators that attract peripheral cells to the site of the insult [6, 7]. In addition to microglia, astrocytes are key players in sensing homeostatic disturbances in the CNS, as well. Their activation contributes to the CNS response to injury, both by limiting inflammation and producing pro-inflammatory molecules. Being an integral part of the blood-brain barrier (BBB), astrocytes regulate its permeability and thereby indirectly the contribution of the periphery to the compromised area [8]. Activation of microglia and astrocytes is observed during virtually any CNS insult, such as infection, traumatic injury, or exposure to toxic elements. Inflammation of the CNS (i.e., neuroinflammation) is usually accompanied by the contribution of the peripheral immune system, a hallmark of the inflammatory process (reviewed in [9]). Acute neuroinflammation is an essential response to clear the tissue from pathogens or debris and to promote tissue repair. However, if unresolved,

◀ **Fig. 1** The inflammatory sequel during CNS viral infection and injury. **a** During homeostasis, the BBB separates the periphery from the CNS by tightly regulating the entrance of circulating molecules and nutrients as reviewed in Kierdorf et al. [113]. Astrocytes are part of the BBB and functionally support neurons, while microglia constantly survey the CNS parenchyma for potential factors that could compromise its integrity. **b** During viral infection, intracellular PRRs (not shown) recognize virus-derived material and activate resident CNS cells to produce cytokines (e.g., interferons), which recruit peripheral immune cells. $CD4^+$ and $CD8^+$ T cells play a prominent role for the effective clearance of the virus. During the resolution phase and after the clearance of the virus, Tregs action is important in silencing autoreactive $CD4^+$ T cells and promotes resolution. The contribution of SPMs following viral CNS infections remains largely unexplored. **c** In a generalized model of CNS injury, DAMPs are released from dying and stressed cells which bind to PRRs thereby activating the resident CNS cells. The BBB is consequently compromised, hypertrophic astrocytes surround the lesion core (dashed line), and microglia become activated. In turn, glial cells can release pro-inflammatory mediators (e.g., IL-1β), which attract peripheral leukocytes and augment the inflammatory response. During the resolution of the neuroinflammation following CNS injury, anti-inflammatory cytokines (e.g., IL-10) and trophic factors (e.g., EGF) are released, promoting neuronal tissue regeneration. SPMs, such as LXA_4, that are produced at the injured parenchyma facilitate, as well, in the resolution phase. BBB, blood-brain barrier; CNS, central nervous system; PRRs, pattern recognition receptors; moMΦ, monocyte-derived macrophages; ROS, reactive oxygen species; Treg, regulatory T cells; IFN, interferon; SPMs, specialized pro-resolving mediators; DAMPs, damage-associated molecular patterns

it can lead to chronic CNS inflammation and neurodegeneration. This review will focus on cellular and molecular aspects that contribute to the resolution of neuroinflammation after infection or sterile CNS injuries.

Initiation and resolution of pathogen-induced CNS infection

Upon viral infection of the CNS, viral particles, such as nucleic acids, will bind to members of the PRRs and lead to the transcriptional activation of so-called interferon regulatory factors (IRF) and a subsequent production of type I interferons (IFN I) which limit viral spread in the CNS [10]. An early IFN I response can be observed even in local CNS infections, as it is the case for the intranasally administered vesicular stomatitis virus (VSV), which sets the CNS in a state of alert, restricting viral dispersion until the specialized adaptive immune cells are recruited in the tissue (Fig. 1b) [11]. Bacterial infections in the CNS are sensed in a comparable manner. Bacterial components (e.g., lipopolysaccharides) trigger the inflammasome response through activation of absent in melanoma 2 (AIM2) and nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing receptor 3 (NLRP3) [12]. The cytoplasmic inflammasome multiprotein oligomers promote the proteolytic cleavage of pro-interleukin (IL-)1β and pro-IL-18 to their secreted active forms through recruitment of caspase 1. Both IL-1β and IL-18 are then needed to control infection and facilitate clearance of the tissue [12]. For example, CNS infection of apoptosis-associated speck-like protein containing a caspase 1 recruitment domain (ASC) or caspase 1/11, but not NLPR3-deficient mice, with *Staphylococcus aureus* results in a compromised inflammasome response leading to higher morbidity within 24 h. On the other hand, AIM2-deficient mice showed similar disease progression as the ASC knockout mice, highlighting AIM2 inflammasome as the main sensor in this model of infection [13]. Although microglia and other glial cells are the first line of defense against the infection, the recruitment of innate and adaptive peripheral immune cells is a critical component in the resolution of the inflammation. In the acute phase of herpes simplex virus 1 (HSV1) infection, microglia produce pro-inflammatory cytokines (e.g., IL1β, tumor necrosis factor α (TNFα) and chemokines (e.g., chemokine (C-C motif) ligand 5(CCL5)) that attract peripheral monocytes and neutrophils [14]. In parallel, activated astrocytes regulate BBB permeability and produce IFN I. During persistent infection of HSV1, $CD4^+$, and $CD8^+$ T cells are recruited, with the latter to produce interferon gamma (IFNγ) thereby exacerbating brain inflammation [14, 15]. A similar response can be observed following CNS infection with flaviviruses. In the rodent model of West Nile virus (WNV) infection, the upregulation of chemokine (C-X-C motif) ligand 12 (CXCL12) in the endothelial cells of the microvasculature attracts T cells which subsequently accumulate in perivascular spaces [16]. Astrocytes are also key players during WNV infection by producing pro-inflammatory molecules such as IFN I and IL-1β thereby regulating the permeability of the BBB [17].

Following infection, resident and peripherally recruited cells contain the spread and prevent excessive tissue damage. Infiltrating T cells, employ various mechanisms for viral clearance, like IFNγ-, TNFα-, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated antiviral responses that are either cytopathic (i.e., death of infected cells) or non-cytopathic (i.e., viral clearance without cellular damage) [18, 19]. Following lymphocytic choriomeningitis virus (LCMV) infection, $CD8^+$ T cells attract antigen-specific cytotoxic T lymphocytes resulting in fatal CNS vascular injury [20]. In contrast, persistently LCMV-infected mice exhibit, after administration of therapeutic antiviral T cells, IFNγ-dependent non-cytopathic clearance of virally infected microglia [21]. In the WNV infection model, $CD4^+$ and $CD8^+$ T cells act in favor of viral clearance by containing the virus in infected neurons and mediating recovery [18, 22], while regulatory T cells (Tregs) are beneficial at early stages of the infection, by suppressing the detrimental excessive response of virus-specific $CD8^+$ T cells [23]. During CNS infection with the mouse hepatitis virus (MHV), infiltrating $CD4^+$ and $CD8^+$ T cells triggers oligodendrocytic damage and demyelination in the spinal cord [24]. T helper cells control the function of cytotoxic $CD8^+$ T cells and regulate the containment of the

MHV virus [25]. In addition, depletion of Treg resulted in exacerbated neuroinflammation and increased neuronal damage contributed to lack of Treg-dependent control of autoreactive $CD4^+$ T cells proliferation, suggesting a potential therapeutic intervention of suppressing antiviral T cell activation in CNS infections (Fig. 1b) [26, 27]. While neuroinflammation is resolving, CXCR4-expressing oligodendrocyte progenitor cells (OPCs) are attracted to the demyelinated regions, where activated astrocytes express their ligand CXCL12. The OPC mature to oligodendrocytes initiating remyelination and repair of the damage [28].

Although the contribution of SPMs during acute inflammation and its resolution has been addressed in peripheral bacterial and viral infections (for review, see [5]), their role in CNS infections remains largely unknown. An in vitro study on cocultured human astrocytes with human immunodeficiency virus (HIV)-infected monocytes showed an elevated synthesis of leukotriene B4 and lipoxin LXA_4 linked to increased IL-1β and TNFα production [29]. In a murine model of *Toxoplasma gondii* infection, administration of lipoxin LXA_4 analogues in lipoxin-deficient mice reversed the fatal encephalitis phenotype linked to increased levels of IFNγ and IL-12, suggesting a protective role of LXA_4 for the resolution of inflammation by mitigation of pro-inflammatory molecules [30]. A similar effect was reported after parasitic infection with *Plasmodium berghei*, which causes cerebral malaria. Treatment with LXA_4 limited the disease burden in the brain of affected lipoxin-deficient mice and prolonged survival by attenuating the levels of IL-12 and IFNγ [31]. In a recent clinical study on adult patients with tuberculous meningitis (TBM), a meningeal infection by *Mycobacterium tuberculosis*, revealed that addition of aspirin to the existing treatment (dexamethasone) increased, among others, the cerebrospinal fluid (CSF) levels of protectins (e.g., PD1) and reduced the TBM-related infarcts [32]. In sum, these data suggest that during CNS infections, acute inflammation is essential to remove pathogens and infected cells, but a timely regulated and efficient resolution of neuroinflammation is essential to allow damage repair and restore homeostasis.

Inflammatory resolution of the injured CNS

The CNS innate immune system, comprised of microglia and non-parenchymal perivascular, meningeal, and choroid plexus macrophages [33], is also equipped to sense homeostatic disturbances caused by distal or local sterile injuries. Damage in peripheral cranial nerves, which project to specific nuclei in the CNS, leads to a local inflammatory response in the corresponding nucleus, due to retrograde neurodegeneration. In a murine model of facial nerve axotomy (FNX), lesion of the facial nerve results in progressive gliosis in the respective facial nucleus (FN), while its resolution and tissue regeneration occurs without the contribution of circulating monocytes [34]. We previously demonstrated that microglia clonally expand at the FN, with a peak of microgliosis to appear 7 days post-injury (dpi). During the resolution phase, at 30 dpi, the excess microglia are removed through apoptosis or by migrating out of the affected FN. Interestingly, transcriptomic profiling of microglia during the acute and resolved inflammatory phase revealed, in addition, upregulation of immune and lipid mediation pathways, suggesting the potential role of anti-inflammatory molecules and SPMs in the resolution of acute microgliosis [35]. In addition, astrocytic IL-10 expression has been reported to exert a neuroprotective effect during FNX-mediated inflammation, by regulating microglia response with the precise mechanism to remain unknown [36].

Local CNS injuries can occur after traumatic brain injury (TBI), spinal cord injury (SCI), and ischemic stroke. Regardless the nature of the insult (penetrating or not), there is a direct impact on the CNS, leading to long-lasting symptoms and noteworthy post-traumatic complications [37]. Both TBI and SCI are characterized by biphasic injuries. The primary mechanical insult (focal or diffused) results in disruption of micro- and macrostructures and subsequent tissue damage. The secondary phase involves neuronal excitotoxicity, electrolyte imbalance, mitochondrial dysfunction, and production of reactive oxygen (ROS) and nitrogen species (RNS) which contribute to a long-term progressive cellular stress and tissue pathology [38]. Ischemic injury is caused by temporally limited perfusion of a brain area that results in tissue necrosis and subsequent inflammatory response resulting in tissue clearance and repair [39]. Similar to pathogen detection, CNS cells are sensing DAMPs through the PRRs and trigger a robust immune response involving both resident and peripheral immune cells. For example, TLR4, a receptor strongly associated with detection of lipopolysaccharide (LPS) from Gram-negative bacteria, is able to recognize DAMPs, such as heat shock proteins (Hsp60, Hsp70), fibrinogen, fibronectin, and high-mobility group box 1 (HMGB1) that are all released after tissue injury [40]. Following CNS injury, adenosine triphosphate (ATP) is released by the damaged cells and recognized by the purinergic receptors (P2X4R, P2Y6R, P2Y12R) expressed on microglia cells. The activation of the purinergic receptors results in a rapid migration of microglia to the point of injury initiating a neuroprotective inflammatory response [41, 42].

Traumatic brain injury and its resolution

During the past years, various animal models of TBI have been established, simulating human injuries. Controlled cortical impact (CCI) and lateral fluid percussion injury (FPI) are mainly used to mimic focal injuries, while central FPI and weight drop models simulate diffuse injuries [43].

Depending on the origin and severity of the injury, the occurring tissue damage initiates a cascade of functional changes in the brain resident cells which subsequently express pro-inflammatory molecules that attract peripheral cells. Both resident and infiltrating cells remove damaged material and eventually facilitate in the repair of the tissue [44]. In general, in a model of cortical injury minutes to hours after the insult, DAMPs will activate the release of chemokines (e.g., CCL2, CCL5) and cytokines (e.g., IL-1β, TNFα) by resident glial cells, which in turn will recruit peripheral cells (Fig. 1c) [45–47]. Resident microglia are the first cells to respond to traumatic tissue disruption. At the core of the lesion, microglia will quickly get activated and change their arborized morphology to an amoeboid shape. In parallel, they release their pro-inflammatory secretome, which activates other resident glial cells, like astrocytes [48, 49]. In the consecutive reactive astrogliosis, astrocytes become hypertrophic and exhibit elongated processes. In severe cases, reactive astrocytes will form a characteristic structure (i.e., astrocytic "scar") which contains the damaged area and limits the infiltration of inflammatory peripheral cells in nearby unaffected tissue [50]. Since astrocytes are an essential part of the BBB, their activation inevitably affects the permeability of the brain's vasculature resulting in post-injury edema [51]. With the BBB compromised, the peripheral cells come in to play. The first event is a transient wave of infiltrating neutrophils, which release ROS and RNS in the brain parenchyma, followed by the second recruitment phase of mononuclear leukocytes that accumulate at greater numbers [52]. The most abundant infiltrating cells are $CD45^{hi}CCR2^{+}Ly\text{-}6C^{+}$ inflammatory monocytes with a small contribution of dendritic cells, natural killer cells, and T cells [53]. Interestingly, Morganti and colleagues managed to reduce the neurotoxic outcome of the neuroinflammatory response by administering a CCR2 antagonist that prevented the accumulation of $CCR2^{+}$ infiltrating monocytes, reduced the TBI-induced cognitive impairment and limited the pro-inflammatory phenotype 1 month after the insult [54]. At around 10–14 dpi, the acute inflammation was resolved and although the brain parenchyma has been cleared from peripheral infiltrates, $F4/80^{+}$ macrophages and reactive astrocytes remain present, even in sites far from the initial injury, such as regions with axonal projections of the damaged neurons [55, 56].

In the rodent model of CCI, microglia acquire an anti-inflammatory phenotype by upregulating CD206 and producing IL-10, arginase, chitinase, and transforming growth factor β (TGF-β), displaying increased phagocytosis and a neuroprotective phenotype [56–59]. However, this protective response is rather transient and microglia turn into a pro-inflammatory state by upregulating CD86, CD16/32, and iNOS, a long-lasting phenotype that is correlated with progressive white matter damage [57, 59]. Additionally, it was reported that activation of the adenosine receptor $A_{2A}R$ on microglia at the early phase after injury, in response to low glutamate levels, a marker for excitotoxicity, was beneficial. However, increasing levels of glutamate at later points result in a $A_{2A}R$-dependent microglia transition from anti- to pro-inflammatory phenotype [60]. In addition to microglia, astrocytes contribute to the inflammatory response as well. Depletion of proliferating reactive astrocytes after CCI resulted in exacerbated inflammation and extensive cortical degeneration [61]. Moreover, astrocytic IL-6 has been proposed to promote a neuroprotective phenotype under acute traumatic injury [62]. During the resolution phase, proliferation of glial and neural stem cell (NSC) initiates an innate repair machinery in the brain, with the exact molecular mechanism to remain unexplored [63, 64]. Insulin growth factor 1 (IGF-1) appears to promote neurogenesis in damaged areas after CCI [65]. In addition, IGF-1 overexpression in astrocytes enhanced gliosis and diminished hippocampal neurodegeneration [66]. Furthermore, voluntary exercise in mice after TBI has been reported to facilitate resolution of inflammation and functional recovery. More specifically, it increases the levels of IL-10, IGF-1, brain-derived neurotrophic factor (BDNF), and cAMP response element-binding protein (CREB) in the hippocampus; suppresses the chronic pro-inflammatory microglia activation status; promotes neurogenesis; and improves cognitive behavior [67].

Recent studies have focused on the role of SPMs in the resolution of neuroinflammation after TBI. Administration of the aspirin-triggered resolvin D1 (AT-RvD1) in a murine model of midline FPI resulted in improvement of motor and cognitive behavior, without any effect on the activation status of microglia [68]. In contrast, treatment with the resolvin RvE1 reduced microglia pro-inflammatory activation but had no impact on the behavioral output of the mice [68]. In addition, administration of a single dose of neuroprotectin-D1 intralesionally after severe focal penetrating TBI reduced the lesion size but had no impact on neurodegeneration or polarization of the immune cells (Fig. 1c) [69]. Finally, Luo and colleagues demonstrated that lipoxin LXA_4 reduces BBB leakage and lesion size by attenuating the production of IL-1β, IL-6, and TNFα, indicating a potential role in the resolution of inflammation after TBI [70]. Due to the high heterogeneity of TBI manifestation in the clinics, an efficient treatment strategy remains a challenge and the role of SPMs (or its precursors) as therapeutic supplements has yet to be explored. Although, only few case studies report ω-3 fatty acids to facilitate recovery after TBI (reviewed in [71]), ongoing and future clinical studies will reveal whether such nutritional supplementations are beneficial for TBI patients.

Spinal cord injury and its resolution

As discussed for the TBI, SCI as well is characterized by the primary mechanical insult, followed by a secondary injury and

inflammation. The spinal cord resident cells rapidly respond to the injury by expressing pro-inflammatory mediators, such as IL-1β and TNFα [72, 73]. Microglia appear to become activated even in distal areas from the site of injury, contributing to tissue reorganization and facilitating functional recovery [74]. Peripheral cells are additional players in the response after SCI. Transient infiltration of neutrophils is preceding the recruitment of monocytes at the injury site. The latter are comprised by either pro-inflammatory CX3CR1^{lo}CCR2^{hi}Ly-6C^{hi} cells with phagocytic capabilities, which enter first via the leptomeninges close to the injury through CCR2 signaling or anti-inflammatory CX3CR1^{hi}CCR2^{lo}Ly-6C^{lo} cells with tissue repair capacity that infiltrate in response to V-CAM1 via the choroid plexus and traffic through the CSF to the injury site [75]. T cells are also participating in the response to SCI. Their contribution is not only restricted to the functional characteristics of the cells but also to the timing in which they are recruited. At the early acute stage of SCI, CD4$^+$ T cells promote recruitment of monocytes at the injury site by producing IFNγ and facilitating functional recovery [76]. The presence of Foxp3$^+$ Tregs during this phase is rather detrimental, since their ablation promoted CD4$^+$ T cell recruitment and improved tissue repair [76]. In contrast, the contribution of these Tregs during the chronic stage is essential to suppress the prolonged and adverse activation of CD4$^+$ T cells and to resolve neuroinflammation. This early beneficial function of the CD4$^+$ T cells has been associated with the release of IL-4 which increased neuronal neurotrophin signaling and favored axonal regeneration [77]. These data highlight the important balance between pro- and anti-inflammatory mediators during the resolution phase that initiates tissue repair. Both microglia and monocyte-derived macrophages are actively removing myelin debris and engulf injured axons. However, a continual phagocytic activity oversaturates the macrophages resulting in iron accumulation and subsequent release of TNFα, potentially transitioning the cells from anti- to pro-inflammatory causing additional neurotoxicity [78]. As mentioned before for TBI, signaling through the $A_{2A}R$ can influence tissue damage and motor function following SCI, as well. While a beneficial neuroprotective outcome was mediated by $A_{2A}R$ activation on peripheral immune cells, inhibition of the receptor locally reduced glutamate-mediated excitotoxicity [79].

Astrocytes are also participating in the pathology of SCI. In their reactive state, they form the glial scar which surrounds the lesion and confines the highly active immune cells inside the injured area avoiding extensive damage of nearby healthy tissue [80]. In parallel, they exhibit anti-inflammatory properties by producing ependymal growth factor (EGF), TGF-β, IL-6, and IL-10 through activation of the STAT3 signaling contributing to resolution of the neuroinflammation [50, 81]. Nevertheless, this increase in astrocytic activity, although it contains the damage, potentially has suppressive effect on oligodendrocyte maturation and remyelination. Reactive astrocytes in the injured spinal cord produce bone morphogenetic protein 4 (BMP4) and chondroitin sulfate proteoglycans, which inhibit oligodendrocyte maturation and axonal myelination [82]. Recent studies have highlighted the role of pericytes, fibroblast-like cells that surround the endothelial cells of the vasculature, in scar formation, and affect resolution of neuroinflammation and repair after SCI. Type A pericytes, a subset of pericytes, migrate from vesicular structures to contribute to scar formation and fibrosis. Inhibition of type A pericyte migration to the lesion resulted in improved axonal regeneration and faster functional recovery [83, 84].

SPMs are also key players in the resolution of neuroinflammation after spinal cord injury. Administration of lipoxin LXA_4 in a rodent model of SCI attenuated microglia activation and TNFα production, by acting on ALX/FPR2 receptors, resulting in alleviation of SCI-induced neuropathic pain [85]. In another study using the same model, LXA_4 treatment had a neuroprotective effect, reducing the size of the lesion and improving locomotor behavior, by acting on the Akt/Nrf2/HO-1 signaling pathway [86]. The lipid mediator, maresin-1, was also shown to be implicated in resolution and neuroprotection after SCI. Treatment with maresin-1, in a murine model of SCI, promoted inflammatory resolution by reducing both pro-inflammatory cytokine release and intracellular STAT1,3,5-dependent inflammatory signaling, in addition to enhancing anti-inflammatory activation of macrophages and improving neurological recovery [87].

Resolution of ischemic injury

The outcome of ischemic stroke is closely associated with the post-ischemic inflammation. Nutrient deprivation and hypoxia at the core ischemic region will trigger the production of ROS resulting in cell death, neuronal damage, disruption of the BBB, and initiation of the inflammatory response [39]. Intracellular elements, such as nucleic acids (e.g., mitochondrial DNA) [88], lipids (e.g., oxidized phospholipids) [89], and proteins (e.g., HMGB1, peroxiredoxin) [90, 91] are escaping in the extracellular space acting as DAMPs on PRRs of resident cells activating the production of pro-inflammatory mediators. Neurons at the ischemic penumbra (the region surrounding the ischemic core) are also affected. Due to the low rate of perfusion, neuronal function is impaired and even if the blood flow is restored, the viability of the cells in the penumbra is potentially compromised by the excitotoxic effects of damaged neurons [92]. After brain ischemia, microglia proliferate and respond rapidly to the injury-induced DAMPs release. PRR activation in microglia leads to amoeboid morphology, clearance of apoptotic cells, and debris from the ischemic region, while in parallel, they produce pro-inflammatory IL-1β and TNFα [93]. The early activation of microglia has been suggested to be neuroprotective in the post-ischemic brain, by controlling neuronal Ca^{2+} overload

and limiting spreading depolarization. In this study, pharmacological ablation of microglia using the colony stimulating factor 1 receptor (CSF1R) antagonist, in a murine model of cerebral ischemia, resulted in higher infract size and dysregulation of the neuronal circuit, due to the excitotoxic effect of the depolarizing neurons, while microglia repopulation reversed the effect [94]. Reactive astrogliosis is another hallmark of the pathology following ischemic injury. Hypertrophic astrocytes exhibit increased Ca^{2+} signaling which result in the production of pro-inflammatory cytokines (IL-1β, IL-6) and chemokines (CCL3, CCL5), and formation of the glial scar demarcating the ischemic regions from the surrounding healthy tissue (Fig. 1c) [95]. The disruption of the BBB and the high levels of pro-inflammatory mediators produced by resident brain cells will attract peripheral immune cells in the ischemic area. Neutrophils are recruited early in the ischemic site, contributing in the BBB breakage, by metalloproteinase secretion, and in the production of ROS and RNS [96–98]. Monocyte infiltration starts with a pro-inflammatory phenotype followed by an anti-inflammatory state of monocytes [99]. T and B cells were also found to contribute to post-ischemic inflammation [100]. Depletion of IL-17-secreting γδ T cells limited ischemic injury, while the presence of IL-10-producing Tregs displayed a neuroprotective effect [101, 102]. In murine models of ischemic injury, the SPMs, protectins, and resolvins display neuroprotective role as well. Resolvins control leukocyte migration, attenuate neuronal damage, and reduce IL-1β production and NF-κB activation [103], while activation of neuroprotectin-D1 biosynthesis after stroke results in reduction of infract volume and diminished disease burden [104]. A protective role of LXA_4 has also been reported in the post-ischemic phase, where it mitigates astrogliosis, neutrophil infiltration, and production of IL-1β and TNFα [105], in addition to transitioning monocytes to an anti-inflammatory, tissue-repairing phenotype (Fig. 1c) [106]. Clinical studies on the effect of SPMs precursor molecules on stroke patients have been controversial. Tanaka and colleagues reported that during a clinical trial on the Japanese population, 5-year supplementation of purified EPA in hypercholesterolemic stroke patients reduced the risk of recurrent stroke [107]. In contrast, supplementation of fish oil (a natural rich source of EPA and DHA) on stroke patients for 12 weeks [108] or 12 months [109] had no significant improvement on the patients' clinical phenotype.

Concluding remarks

In response to CNS infection or injury, the initiation of a transient, acute inflammatory cascade is highly important to limit the damage, to clear the tissue from debris and damaged cells, and to trigger subsequent tissue repair. Failure to resolve the initial inflammation leads to an accumulation of pro-inflammatory molecules and cells in the tissue, which eventually become toxic and contribute to chronic inflammatory conditions with major impact on tissue integrity and function [110–112]. The identification of SPMs and their contribution in driving inflammatory resolution are rendering them as potent candidates for clinical application. Entering these compounds in clinical trial phase for stroke patients or patients with head and spinal cord injuries might result in new therapeutic interventions which will alleviate the disease burden, attributed to the prolonged toxic effects of unresolved inflammation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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