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Neuroinflammation after surgery: from mechanisms to therapeutic targets

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Abstract

Injury is a key driver of inflammation, a critical yet necessary response involving several mediators that is aimed at restoring tissue homeostasis. Inflammation in the central nervous system can be triggered by a variety of stimuli, some intrinsic to the brain and others arising from peripheral signals. Fine-tuned regulation of this response is crucial in a system that is vulnerable due to, for example, aging and ongoing neurodegeneration. In this context, seemingly harmless interventions like a common surgery to repair a broken limb can overwhelm the immune system and become the driver of further complications such as delirium and other perioperative neurocognitive disorders. Here, we discuss potential mechanisms by which the immune system affects the central nervous system after surgical trauma. Together, these neuroimmune interactions are becoming hallmarks of and potential therapeutic targets for multiple neurologic conditions, including those affecting the perioperative space.

The influence of systemic factors on the central nervous system (CNS) has long been shown; however, the molecular underpinnings of these factors and their effect on brain functioning have only recently become appreciated. It is becoming more apparent that, under certain conditions such as aging and neurodegeneration, systemic inflammatory mediators can influence the brain and ultimately impact cognition¹. For example, in stroke and traumatic brain injury, peripheral cells can directly enter the brain parenchyma and cause neuroinflammation, especially when the blood–brain barrier (BBB) is damaged^{2,3}.

Surgery can be lifesaving and can also vastly improve quality of life. Over the past decade, however, growing evidence has linked surgery, such as cardiac and orthopedic procedures, to brain pathology similar to that of other neurologic diseases in which the brain is the primary target of injury. This scenario is particularly true in older adults and frail patients who already experience limited cognitive reserves and are more vulnerable to cognitive

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deterioration and even dementia. Indeed, perioperative neurocognitive disorders (PNDs), which include acute delirium and longer-lasting cognitive decline, are now considered some of the most common postoperative complications among older adults⁴. PNDs can develop following major procedures, especially cardiac and orthopedic surgery. The strongest risk factors for postoperative delirium are advanced age and dementia; a thorough review of the relevant clinical literature is provided in ref.⁵. Notably, anesthesia has been implicated in the pathogenesis of PNDs, but clinically evident cognitive decline can occur after regional or general anesthesia, suggesting that other factors, such as surgical trauma, play a prominent role in causing cognitive deficits⁶. Indeed, orthopedic surgery is routinely performed in older adults, and as many as 50% of these patients suffer from postoperative delirium, an acute and fluctuating disturbance in awareness and attention⁷. Despite its acute course, typically 1–3 days after surgery and anesthesia, delirium has devastating consequences: increased 1-year postoperative mortality^{8,9}, decreased quality of life¹⁰ and an increased long-term risk for Alzheimer's disease (AD)^{11,12}. Importantly, PNDs have a synergistic relationship with neurodegenerative diseases, making their impact even more concerning¹³. In particular, an episode of delirium can accelerate the trajectory of cognitive decline, which can contribute to further dementia¹⁴. When delirium occurs in patients with underlying dementia, the prognosis is even worse^{15,16}. In fact, patients who suffer delirium after hip fracture surgery have a twofold increased risk for 1-year mortality as compared to patients who have had hip fracture surgery but do not have dementia or delirium¹⁷. Furthermore, delirium not only occurs after surgery but is frequently observed in the medical intensive care unit as a result of critical illness and mechanical ventilation, particularly relevant in the recent context of COVID-19, with an ~25% incidence, which is probably underestimated^{18,19}. Delirium already contributes an estimated \$150 billion per year to the soaring healthcare costs in the United States²⁰. These complications are generating new challenges for our aging society and are rapidly becoming a significant burden for families and healthcare providers²¹. Preclinical and early clinical studies continue to investigate putative mechanisms for PNDs, focusing in particular on a role for neuroinflammation. Perhaps such a role is not surprising; after all, surgery is a form of controlled trauma, trauma is an established source of tissue injury, and injury is a key driver of inflammation. Here, we will review key mechanisms related to postoperative inflammation and the implications for PND development, focusing on neuroinflammation and key cellular targets affected by surgical trauma.

Systemic inflammation and DAMPs after sterile injury

The brain has long been referred to as an immune-privileged organ, although it is becoming more apparent that neuroimmune interactions between the periphery and the CNS are not rare or restricted to brain neuropathology²². The presence of a physical barrier, the BBB, supported by different cell types, including brain endothelial cells, astrocytes and pericytes, prevents direct access of damaging molecules to the CNS²³. The role of the BBB in homeostasis and pathology has been extensively reviewed (see ref.²³). Here, we will focus on the emerging role of postoperative inflammation as a trigger for PND pathology.

Millions of patients worldwide undergo surgery routinely, including more invasive procedures that involve extensive tissue damage, hemorrhage and ischemic damage due to clamping or tourniquets, used in many cardiac and orthopedic procedures. These forms of

sterile trauma are associated with robust systemic inflammation that, in some cases, can lead to significant complications and even death. Cellular damage after surgical trauma triggers endogenous factors known as damage-associated molecular patterns (DAMPs), which activate immune cells such as neutrophils and monocytes to resolve the damage and restore homeostasis (reviewed in detail in ref.²⁴). Activation of these cells contributes to systemic inflammation, which can impact multiple organs, including the brain. The role of the innate immune response after trauma has been recently reviewed in ref.²⁵. There is growing evidence to suggest that dysregulated immune functions are a driver of PNDs.

HMGB1 is a prototypical DAMP with distinct roles in trauma and infection. HMGB1 is both a nuclear factor and a secreted protein that actively regulates several inflammatory processes²⁶. In the nucleus, it is responsible for chromatin packaging, and it can be rapidly released into the circulation following a mechanical injury such as incision of tissues or vessels²⁷. HMGB1 is detectable in the circulation within 30 minutes after surgery²⁸. Together with other cytokines such as tumor necrosis factor (TNF), it contributes to the early mobilization of immune cells after surgery and the subsequent engagement of bone-marrow-derived macrophages (BMDMs)²⁹. Indeed, exogenous administration of HMGB1 itself recapitulates similar neuroimmune and cognitive deficits found in PNDs, suggesting that early release of DAMPs jumpstarts the neuroinflammatory and behavioral responses to trauma. Soluble HMGB1 engages several pattern recognition receptors (PRRs), including Toll-like receptor (TLR) 2 and TLR4 as well as the receptor RAGE³⁰. Both TLR4 and MyD88 signaling have been implicated in PND pathology, as evidenced by mice genetically deficient for both genes that remain protected from surgery-induced inflammation and CNS dysfunction^{28,31}. Indeed, HMGB1 is a potent primer for CNS inflammation. Administration of antibodies selective for this DAMP can ‘desensitize’ resident microglia to peripheral inflammation caused by both infective and sterile trauma, including in models of PND^{29,32,33}. HMGB1 signaling can also interact with extracellular ATP, also commonly released after tissue/cellular trauma, and together, they can activate the inflammasome complex to release interleukin (IL)-1 β and IL-18³⁴. Although the role of IL-1 β in PNDs has been established through both preclinical models and the biofluids of postoperative patients^{35,36}, the regulation and characterization of the cellular source(s) of IL-1 remain poorly described. A study described a key role for P2X7 receptor signaling in postoperative neuroinflammation, suggesting that blocking ATP binding to this receptor prevents inflammasome activation and improves cognitive outcomes after surgery (Fig. 1)³⁷.

Postoperative complement system activation

The complement system is another key component in the inflammatory response, which can be activated by the ‘DAMPs surge’ after surgery. For example, C-reactive protein (CRP), a biomarker that has been well established by studies involving multiple cohorts of patients with delirium, can activate and regulate the classical complement pathway^{38–41}. While CRP is commonly used clinically as a biomarker, less attention has been devoted to the complement cascade and its potential implications for PNDs. Previous clinical investigations demonstrated that in patients who were postoperative or had multiple traumas, there is early complement component 3 (C3) activation, represented by plasma C3 depletion and upregulation of cleaved forms of C3 (including C3a and C3b)^{42–44}. In a murine model of

orthopedic surgery, C3 was upregulated in the CNS, with higher expression of C3 in hippocampal astrocytes and C3a receptor specifically in microglia⁴⁵. Although C3 and C3a concentrations were not measured in the plasma, the study showed that administration of a C3a receptor blocker improved choroidal blood–cerebrospinal fluid barrier integrity and hippocampal-dependent memory function, suggesting that complement activation may play a role in the mechanisms underlying PND development. Thus, interfering with the complement cascade, including C3, may provide promising therapeutic avenues for PND treatment. Indeed, aging and dementia, two well-established risk factors for delirium, are characterized by C3 accumulation on synapses. C3 gene deficiency reduced both synaptic loss near amyloid plaques and neurodegenerative pathology in an AD mouse model⁴⁶. The promising protective effects of complement system inhibition were also described in a stroke mouse model. Administration of B4Crry, a selective complement inhibitor, prevents microglial phagocytosis of stressed neurons, thereby improving neuroinflammation and functional outcomes⁴⁷. In addition to plasma C3, a study in hip fracture patients showed that the preoperative C3 concentration in cerebrospinal fluid (CSF) was significantly altered from normal levels in patients with postoperative delirium. Although the findings in two cohorts of patients were opposing, which may be due to multiple factors, including the duration of fracture and the sample analysis methodology⁴⁸, the association between preoperative C3 in CSF and postoperative delirium should be noted and requires further validation.

Coagulation cascade after surgery

Complement signaling closely interacts with the coagulation cascade, which plays a critical role in the inflammatory response. Together with the release of DAMPs from the injury site, coagulation and thrombosis are activated after trauma and are critically implicated in restoring tissue homeostasis⁴⁹. The fibrinolytic system, which leads to the conversion of fibrinogen to fibrin to initiate and resolve blood clotting, has well-established immune consequences. If fibrinogen enters the CNS parenchyma through a BBB opening, the insoluble fibrin becomes a strong immunogenic factor, known to bind to the CD11b I-domain of the CD11b/CD18 integrin receptor (also known as complement receptor 3 (CR3)) to further activate macrophages/resident microglia and drive cognitive deficits^{50–52}. Notably, the CR3 can also recognize cleaved C3b (iC3b) and cause complement-dependent macrophage⁵³ and microglia⁵⁴ activation. We found perivascular fibrinogen deposition in the hippocampus as early as 24 hours after orthopedic surgery^{52,55,56}. Therefore, fibrinogen may also represent a valuable peripheral biomarker to identify patients at risk for PNDs. Fibrin deposition has been implicated in several neurologic disorders, including multiple sclerosis, traumatic brain injury and AD (reviewed in ref.⁵⁷). Fibrin is also a well-established pathologic hallmark of BBB disruption and could represent a key mechanism for systemic inflammation leading to CNS inflammation and neuronal dysfunction after surgery. For example, plasma concentrations of the serine protease inhibitor PAI-1 are significantly associated with prolonged delirium in the emergency department and can be rapidly assayed in the circulation⁵⁸. Indeed, peripheral biomarkers of inflammation and CNS dysfunction are becoming valuable tools for characterizing patient recovery⁵⁹ and further highlight the complex interactions between systemic inflammation and CNS pathology. Thus, plasma

biomarkers, including coagulation factors, lipid mediators and more classical proinflammatory cytokines, may already provide valuable information on the likelihood of developing PNDs without needing to directly access the CSF.

Blood–brain barrier opening and cell infiltration after surgery

BBB dysfunction is becoming more appreciated in the context of aging and dementia, although not many studies have characterized it in PNDs. One study evaluated changes in the pre- to postoperative serum albumin ratio in patients who had hip fracture surgery. Significant changes were measured in patients who developed delirium, suggesting that BBB dysfunction is relevant to the occurrence of postoperative cognitive complications⁶⁰. Systemic biomarkers of BBB dysfunction and endothelial activation have also been described in critically ill patients with delirium⁶¹; thus, understanding the impact of inflammation on barrier function is paramount.

Preclinical models of postoperative neuroinflammation and PNDs have demonstrated that anesthesia and surgery can reduce tight junction (TJ) protein expression in the brain microvasculature, leading to increased BBB permeability and migration of CCR2⁺ ‘inflammatory’ macrophages into the hippocampus^{52,62,63}. A simple laparotomy under isoflurane anesthesia causes cognitive impairment and increases BBB permeability in aged mice in an IL-6-dependent manner⁶⁴. This change was accompanied by a decrease in β -catenin and TJ proteins such as claudin, occludin and zonula occludens-1 (ZO-1)⁶⁴. Notably, in this study, exposure to anesthesia alone was not sufficient to trigger BBB opening even in aged mice. Using our orthopedic model, we also found no significant effects of well-balanced anesthesia alone on the CNS, including no inflammatory changes or behavioral deficits. A recent study in older adults that volunteered to receive anesthesia alone (without surgery) found no evidence of immune or neuronal injury as detected by plasma biomarkers⁶⁵, suggesting that its combination with ensuing surgical trauma contributes to CNS impairments. After orthopedic surgery, blocking IL-6 receptor signaling with the monoclonal antibody tocilizumab effectively prevented BBB opening and the ensuing infiltration of CCR2⁺ cells into the hippocampus, and these effects were not observed in anesthesia-exposed mice⁶⁶. Using the same tibial fracture surgery model in aged mice, T cell activation and IL-17A were implicated in BBB breakdown and PND behavior⁶⁷. In this study, treatment with a monoclonal antibody reduced IL-17A expression in both the circulation and hippocampal tissue and also prevented BBB opening. Activation and degranulation of brain mast cells has also been causally implicated in microglial activation via MAPK signaling, resulting in neuronal loss in rats after orthopedic surgery⁶⁸. Thus, multiple cell types, including neutrophils, BMDMs, mast and T cells, have been shown to be involved in PND pathology and its resolution. The mechanisms responsible for cell infiltration into the brain after peripheral surgery need further clarification.

Matrix-metalloproteinase (MMP) 2 and MMP9 are known regulators of TJs in brain capillaries and the BBB⁶⁹. Peripheral surgery can elevate MMP2 and MMP9 expression in the hippocampus of aged mice and rats^{67,70}. These changes are accompanied by a reduction in occludin and ZO-1. The role of MMP9 in surgery-induced BBB dysfunction and cognitive decline has been further validated using gene-targeted MMP9-deficient mice⁷¹.

The role of BBB disruption has been highlighted during aging and AD. A recent study described age-dependent BBB opening in mice by albumin extravasation in the hippocampus, starting as early as 12 months old⁷². The extravasated albumin is primarily taken up by astrocytes and contributes to neural dysfunction via transforming growth factor- β (TGF- β) signaling⁷². Notably, fibrinogen is a carrier of latent TGF- β , which induces astrogliosis and inhibits neurite outgrowth⁷³. Indeed, disruption of the BBB is linked to multiple cell types involved in maintaining the neurovascular unit and may contribute to the onset of cognitive disorders. Age-dependent BBB breakdown has been described in humans using advanced, dynamic contrast-enhanced magnetic resonance imaging (MRI). In fact, progressive loss of hippocampal BBB integrity has already been measured in individuals without evident cognitive impairments⁷⁴. This pathologic change is worsened in individuals with mild cognitive impairment and is associated with pericyte injury, as evidenced by an increase in the soluble growth factor receptor sPDGFR- β in CSF⁷⁴. Taken together, during aging and neurodegeneration, peripheral inflammation can synergize with ongoing pathology, thus leading to worse outcomes in more frail individuals.

Glial activation after peripheral trauma

Microglia, the resident immune cells of the CNS, surveil the brain parenchyma and are rapidly activated following injury. Microglial ontogeny and biology have been extensively reviewed (for example, in ref.⁷⁵). Indeed, microglia and monocytes share the expression of several PRRs and can thus induce similar inflammatory responses. Microglia are central players in neuroinflammation, including inflammaging and neurodegeneration, and are one of the key cell types affected by surgical trauma. Their activation has been described in the human brain using positron emission tomography imaging, and it is associated with long lasting PNDs via higher [¹¹C]PBR28 in patients with cognitive deficits after abdominal surgery⁷⁶. PBR28 is a second-generation selective radiolabeled ligand for the 18-kDa translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor, which is a widely expressed transmembrane protein that resides in the outer mitochondrial membrane of microglia but is also expressed in monocyte-derived macrophages⁷⁷. Thus, changes in TSPO may not only reflect microglial dysfunction but also astrocytes and vascular endothelial cells, as well as systemic cells^{78,79}. In this context, peripheral factors can activate microglia via a permeable BBB. In fact, mice treated with PLX5622, a selective inhibitor of the receptor CSF1R that can deplete microglia, and subjected to surgery remain protected from monocyte infiltration and do not develop PND behavior⁸⁰. PLX5622 treatment is frequently billed as a highly specific method for microglial depletion⁸¹. Recent evidence indicates that it has minor yet consistent effects on other immune populations, namely, Ly6C^{lo} ‘patrolling’ monocytes, which are reduced by as much as 30% with PLX5622 treatment^{80,82}. Ablation of BMDMs using clodronate also prevents microglial activation after orthopedic surgery without altering monocyte chemoattractant protein-1 (MCP-1) expression in the brain. This suggests a critical role for resident microglia in actively recruiting peripheral leukocytes after surgery via MCP-1 signaling. Notably, increasing systemic concentrations of MCP-1 correlate with cognitive aging in older adults⁸³. Nevertheless, the mechanisms that drive blood–CSF–brain communication need significant clarification in this context. MCP-1, together with a plethora of other

chemokines, is upregulated in the systemic circulation after surgery, raising the possibility that other cellular sources, such as endothelial cells, can contribute to its upregulation in the CNS after surgery independently of BMDMs⁸⁴.

With several factors able to affect microglia after surgery, a common feature described across PND models is the modification of cellular morphology, concomitant with the increased expression of molecules such as Iba-1 and CD11b on these cells. The effect of these changes on microglial function remains poorly defined. Recently, higher concentrations of the soluble receptor sTREM2 in CSF were detected in patients with delirium after hip fracture repair, confirming that microglial ‘activation’ occurs in the human brain due to ligands more specific than ubiquitous cytokines and chemokines⁸⁵. TREM2 is a critical innate immune receptor that signals via the adaptor protein TYROBP/DAP12 and is expressed on microglia. Furthermore, TREM2 has established mutations associated with aging and neurodegenerative pathology⁷⁵. Importantly, its signaling is essential to maintaining microglial homeostasis and overall metabolic fitness. In fact, dysregulation of TREM2 is a key functional signature of the disease-associated microglial profile⁸⁶. During aging, TREM2 also contributes to microglial priming and inflammaging. Interestingly, several proinflammatory and oxidative genes, including C1q, C3 and CD11b, are downregulated in aged TREM2-deficient mice⁸⁷. Whether TREM2 is causally related to PNDs is not yet known, and whether postoperative microglia express a disease-associated microglial profile is the focus of current studies using next-generation genetic sequencing approaches. From a histologic perspective, both microglia and astrocytes show distinct morphologic changes after peripheral trauma, and it is possible that proinflammatory factors released by microglia contribute to the subsequent activation of astrocytes, including IL-1 α , TNF, and C1q⁸⁸. Together, these mediators are both necessary and sufficient to activate A1 astrocytes, a more toxic and harmful subtype of these cells that are able to exert a potent neurotoxic effect. A1 astrocytes have been described in the context of normal aging, which may account for the higher risk of developing neurodegenerative conditions such as AD. Astrocytes are well known to shape synapses during development via complement signaling⁸⁹. Notably, the aging brain expresses high levels of complement components, such as C1q, thus similar pathways may be engaged during aging as a result of microglial priming and stressors like lipopolysaccharide or surgery^{90–92}. In this regard, A1 astrocytes may be responsible for the acute changes in neuronal plasticity and PND behavior, and studies are urgently needed to clarify these glial interactions (Fig. 2).

Indeed, astrocytes are also key components of the BBB and closely interact with the cerebrovascular endothelium to maintain homeostasis. Surgery impairs expression of water channel proteins, such as aquaporin-4, which are critical to support astrocytic endfeet and BBB integrity^{55,56}. The effect of astrocytic dysfunction after surgery is measurable in fluid biomarkers of postoperative patients, suggesting that CNS dysfunction is a result of peripheral trauma. For example, concentrations of the calcium-binding protein S100 β and glial fibrillary acidic protein are elevated in the CSF and plasma of patients with cognitive impairments after cardiac and non-cardiac procedures^{93–96}. Interestingly, for patients with pre-existing dementia, there is an even stronger association with these biomarkers, further demonstrating the higher vulnerability of this population to complications from these common procedures⁹⁶. From these studies, it remains challenging to ascertain causality

between different cell types and factors released in the brain parenchyma, especially with regard to astrocytic dysfunction that possibly precedes microgliosis. A recent study demonstrated that microglia migrate toward cerebral blood vessels after systemic inflammation⁹⁷. Interestingly, the initial contact between microglia and cerebral vessels aims at preserving BBB integrity. However, with prolonged inflammation, microglia start to develop an activated phenotype and phagocytose astrocytic endfeet, thus leading to BBB breakdown⁹⁷. Indeed, the signals that trigger the initial microglial migration require further investigation and, in the acute postoperative setting, may indicate a protective response by microglia in PNDs. Therefore, trauma can trigger both specific and localized CNS responses, and studies aimed at characterizing the peripheral and central ‘signalome’ after surgery may reveal unique pathways as well as potential PND therapeutic targets.

Potential therapies and concluding remarks

As reviewed here, the immune response to surgical trauma involves multiple compartments and, overall, is triggered to protect organs and restore homeostasis. Targeting inflammation in this context presents unique challenges as well as opportunities. Challenges include the heightened risk for immunosuppression and disrupted healing, a major concern for patients after surgery and a significant limitation of many biologics and immune blockers discussed here. Opportunities include the very acute time course of PND (as compared, for example, to other neurodegenerative disorders that manifest over several years) and the predictability of the outcome of a good portion of surgical cases in the context of elective procedures. This latter point is attractive because knowing the time of injury can ensure timely treatment and possibly prevent the CNS sequelae.

In line with these concepts, a couple of new therapeutic approaches are emerging in the field that desperately need attention. Resolution of inflammation is gaining considerable interest due to the safety profile of endogenous mediators and their potent actions on immune cells⁹⁸. Indeed, it is now appreciated that the process of resolution is activated as soon as trauma occurs. This process is highly regulated by the biosynthesis of specialized proresolving lipid mediators (SPMs) from omega-3 polyunsaturated fatty acids, which include resolvins, protectins and maresins⁹⁹. SPMs act as agonists to shorten the resolution interval of acute inflammation, affecting the influx and clearance of polymorphonuclear neutrophils already at the site of injury^{100,101}. Importantly, they are not immunosuppressive, and, in the context of infection, SPMs can lower antibiotic requirements for bacterial clearance¹⁰². We have described the protective effects of D-series resolvins, including RvD1 and MaR1, which prevent surgery-induced microgliosis and PND-like behavior^{62,103}. Importantly, SPM profiles determined by targeted metabololipidomics may serve as valuable biomarkers for CNS pathology. For example, patients with multiple sclerosis have altered SPM profiles in the blood that contribute to the regulation of monocytic migration through the BBB via proresolvin receptors expressed on endothelial cells¹⁰⁴. We have found that surgery dynamically regulates expression of MaR1, an SPM specific to macrophages, in the human CSF, and this may have implications for BBB–monocyte transendothelial migration⁶².

SPMs are not the only target for PNDs, and other therapies aimed, for example, at stabilizing the BBB may precisely disengage this systemic-to-central immune response. One example is the use of targeted nanocarriers to finely regulate the cerebral vasculature, for example, via vascular cell adhesion molecule 1 (VCAM-1) expression¹⁰⁵. Notably, endothelial VCAM-1 has been described as a key regulator of inflammation during aging, and administration of an anti-VCAM1 antibody reduces neuroinflammation and improves cognition in these mice¹⁰⁶. We found that a mixed-lineage kinase (MLK) 3 inhibitor selectively protects the BBB after surgery without significantly affecting the systemic immune response or causing healing impairments at the fracture site following tibial fracture repair¹⁰⁷. Finally, specific antibodies, such as 5B8, which targets the cryptic fibrin epitope $\gamma_{377-395}$, thereby inhibiting fibrin-induced inflammation and oxidative stress without interfering with clotting¹⁰⁸, may offer attractive strategies to safely prevent memory impairments. To date, only a few studies have evaluated the effects of anti-inflammatories on PNDs, partly because inflammation is a necessary response to injury, and tampering with this process can negatively impact healing and the host response. Thus, therapies that target dysfunctional inflammation may offer safer and more focused approaches to protect the brain from overactivation of the immune system.

In the *Bucoliche* (Egloga IX, written circa 39 BC), Virgil wrote “Time carries away everything, even our memory” (*Omnia fert aetas, animum quoque*). In this dialogue, Lycidas and Moeris reminisce on how difficult it has become to remember songs they used to sing in their youth and to recollect not only the actual words but also their intonation as they aged. This observation may be trivial. After all, we all have a hard time remembering things from the distant past. However, fast forward to the present time and, while forgetting remains a key manifestation of aging, it has also become an earlier pathologic hallmark of many debilitating neurologic disorders, including PNDs. If time slowly steals our memories, let us at least ensure that interventions like surgery do not accelerate the natural course of time, especially on an already vulnerable brain.

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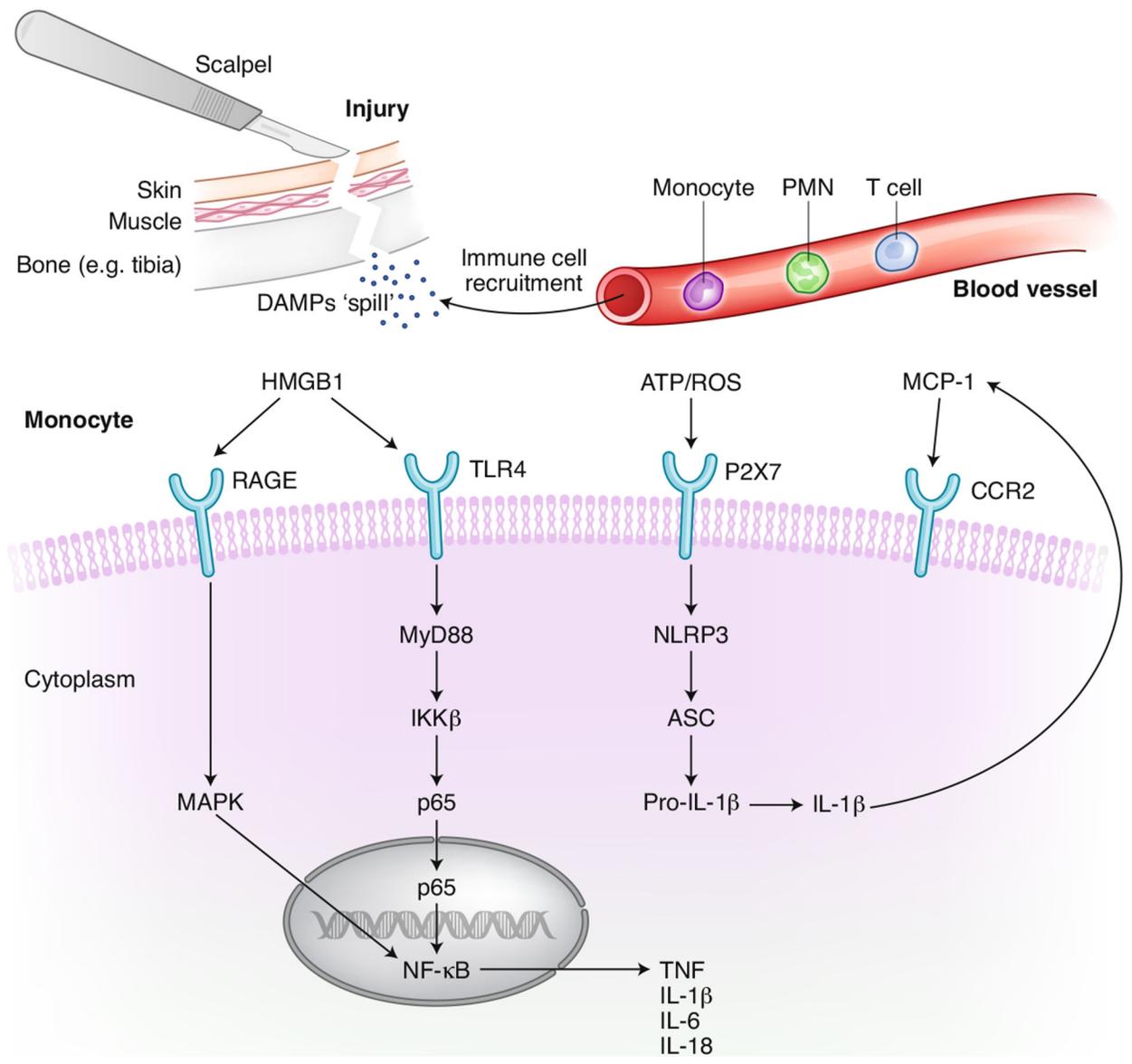


Fig. 1 | Innate immune response to sterile surgical trauma. Aseptic surgical trauma triggers acute inflammation by inducing inflammatory cytokines and DAMPs. This inflammatory milieu contributes to the recruitment of immune cells at the site of injury, for example, the tibia following intramedullary pinning and fixation, but also affects functions in other organs, including the brain. Monocyte activation is one of the drivers for postoperative neuroinflammation, as found in both preclinical and clinical PND studies. Key PRRs expressed on the surface of monocytes have been implicated in this signaling. HMGB1 binds to TLR4 and RAGE to activate NF- κ B, which further transcribes de novo cytokines. This process can synergize with the activation of the NLRP3 inflammasome complex to further elevate the production of IL-1. Plasma and CSF levels of IL-1 β have been described in individuals with PNDs. IL-1 induces expression of MCP-1 and facilitates access of CCR2⁺ monocytes in the CNS, possibly contributing to a feed-forward

loop leading to non-resolving inflammation and neurologic pathology. NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells.

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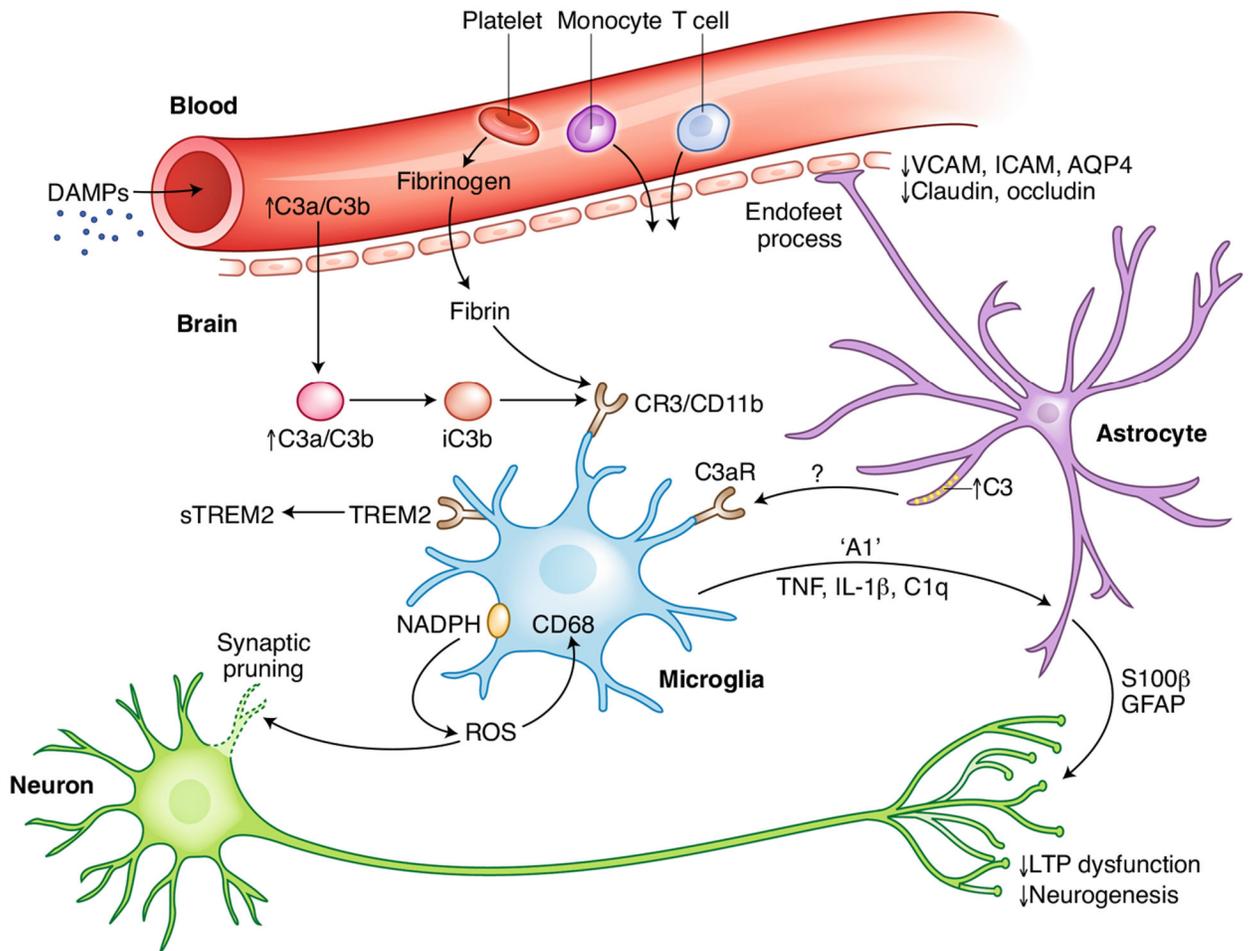


Fig. 2 |. Neuro-immune interactions in the brain after peripheral trauma.

The proinflammatory surgical milieu (including cytokines, chemokines, DAMPs, coagulation factors, immunocytes, and so on) impacts the BBB, thus contributing to ensuing CNS pathology. Microglia, as first responders to changes in the CNS microenvironment, sense the changes following endothelial and BBB openings. Orthopedic surgery causes complement signaling activation in the brain and the deposition of fibrin(ogen) in the hippocampal brain parenchyma. Fibrin(ogen) and complement factors (such as activated forms of C3) are potent activators of microglia via CD11b signaling. reactive microglia release proinflammatory factors, which further contribute to neuroinflammation. In particular, microglia can activate A1 astrocytes via IL-1, C1q and TNF to impact synapses and overall neuronal plasticity. Notably, the increased C3 in A1 astrocytes may in turn contribute to the microglial activation via C3aR. Surgery may also contribute to a DAM-like state, which requires further characterization in various preclinical models. Notably, sTREM2 is elevated in the CSF of patients with delirium after hip fracture, suggesting surgery impacts homeostatic DAM genes and microglial activity following surgical trauma.