CNS sterile injury: just another wound healing?

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The poor recovery of the central nervous system (CNS) after injury, coupled with its complex and immunologically-privileged nature, led to the belief that CNS repair is different from the repair of other tissues. Here, we consider CNS repair from a novel perspective, suggesting that CNS responses to injury resemble wound healing. Extrapolating the classical wound healing model suggests that poor CNS recovery is an outcome of insufficient resolution of intermin reparative events that precede tissue regeneration and renewal, a state reminiscent of chronic/unresolved wounds. This comparison requires reevaluation of the inflammatory response, glial scarring, and barrier permeability, traditionally considered obstacles to CNS repair. Understanding the similarity to wound healing suggests new research directions and therapeutic avenues for CNS injuries.

Add insult to CNS injury

Injury to the CNS (see Glossary), including the brain and spinal cord, is a major cause of disability. Annually, more than 2 million people in the US alone suffer traumatic brain injuries, over 500,000 people are afflicted by stroke, and at least 10,000 people are victims of spinal cord injuries. At least 10% of people experiencing CNS injuries are left with irreversible disabilities, ranging from paralysis to cognitive dysfunctions. Following the primary insult, secondary degeneration of the surrounding healthy neural tissue, initially spared but located adjacent to irreversibly damaged tissue, accelerates neuronal damage. Biochemical processes occurring at the lesion site, such as inflammation and increased barrier permeability, accelerate secondary degeneration. In addition, the CNS exhibits poor regenerative capacity, with the microenvironment at the lesion parenchyma (characterized mainly by pronounced glial scar formation) acting as a physical and biochemical obstruction to regeneration.

The poor regeneration that takes place in the CNS, along with the complex and immunologically-privileged nature of this tissue, led to the widespread dogma that repair processes within the CNS are different from those of any other tissues. Such a view led to the common assumption that numerous factors, some of which are pivotal players in skin wound healing, act as inhibitory components at the injured CNS: the transient permeability of the CNS barrier [blood–brain barrier (BBB) and blood–cerebrospinal fluid barrier (BCSFB)] has been interpreted as a breach in tissue isolation and homeostasis, causing accelerated tissue damage; the glial scar has mainly been studied in the context of its

Glossary

Astrocytes: a star-shaped type of glial cell in the CNS. Astrocytes are the most abundant cell of the CNS, providing biochemical support for endothelial cells of the BBB, supplying nutrients to the nervous tissue, and supporting maintenance of extracellular ion balance.

Blood–brain barrier (BBB): the physiological separation between the blood and CNS parenchyma, which restricts molecular diffusion, while actively transporting metabolic products. This barrier is formed by endothelial cells interconnected by tight junctions, thick basement membrane, and astrocytic endfeet.

Central nervous system (CNS): the part of the nervous system that includes the brain and the spinal cord, required for information integration.

Cytokines: small cell signaling proteins that are secreted by numerous cells, mainly known for their immunomodulating activities. Cytokines are important for regulating intercellular communication, cell function, and cell survival of many cell types.

Diapedesis: the movement of blood cells, especially leukocytes, through intact capillary walls into surrounding body tissue, in a process that does not damage the vessels.

Epithelium: one of the four basic types of tissues, lining the cavities and surfaces of structures throughout the body.

Fibroblast: a cell type of mesenchymal origin; fibroblasts maintain structural integrity of connective tissues by synthesis of extracellular matrix.

Fibrosis: development of excess fibrous connective tissue, usually as a result of injury or infection. Fibrosis promotes scar formation during wound healing.

Glia: as implied by their Greek name, glia are commonly known as the glue of the nervous system. They are non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for neurons.

Glia limitans: a thin barrier of astrocyte foot processes associated with the parenchymal basal lamina surrounding the brain and spinal cord parenchyma. The glia limitans is the outermost layer of neural tissue.

Inflammation: the complex biological response of tissues to injury or pathogen, involving local and recruited immune cells. Derived from the Latin ‘inflammare’ (to set on fire), inflammation was historically defined by the clinical signs of redness, heat, and swelling.

Leukocyte: a white blood cell derived from multipotent hematopoietic stem cells in the bone marrow.

Monocyte: circulating precursor of tissue macrophages, originating from the bone marrow.

Neurons: electrically excitable nerve cells that transmit information by electrical and chemical signaling.

Oligodendrocytes: a type of CNS glia, providing axon myelination required for action potential transmission.

Platelets: irregular shaped clear cell fragments circulating in the blood involved in homeostasis and formation of blood clots. Platelets are also known as thrombocytes.

Proteoglycans: heavily glycosylated proteins, consisting of a core protein attached to glycosaminoglycan (GAG) chains.

Resident microglia: a type of CNS glial cells, which are the primary immune sentinel of the CNS; microglia are derived from primitive macrophage progenitors in the yolk sac that colonize the CNS during development. They are considered the CNS equivalent of tissue macrophages.

Scarring: a confluent fibrosis that obliterates the architecture of the underlying organ or tissue.

Trophic factors: factors that promote cellular growth, differentiation, and survival. In the context of the CNS, the term is mainly used in relation to neurons.
growth inhibitory properties, causing the collapse of axonal growth cone and neurite sprouting [1]; and finally, inflammation is mainly viewed as neurotoxic, limiting tissue rejuvenation and the primary cause of secondary degeneration [2]. The linkage made between any event occurring at the injured CNS and the poor repair observed in these tissues has led to viewing the processes otherwise universally associated with healing as detrimental CNS responses to injury that should be mitigated.

Importantly, however, outside the CNS, healing is an orderly process in which only the final phase involves regeneration and tissue restoration [3,4] (Box 1). Sequential events, including disruption of homeostasis, exposure to plasma components, scarring, and inflammation, are all needed for creating the platform for the subsequent regenerative phase [3,4].

Therefore, we reexamine the processes occurring at sites of CNS trauma from the reverse perspective – relative to the traditional view – by focusing not on the inhibition of CNS regenerative capacity, but by revealing the similarity of CNS repair to the regular wound healing process. We use skin as our comparative paradigm, although other tissues engage similar pathways. At first glance, one can easily recognize that similar cellular and biochemical components and major events characterize both processes (Figure 1); in both, blood flow is disrupted, coagulation is initiated, synchronized inflammation is observed, and scar tissue is formed. Thus, by reevaluating the fundamental process occurring at the CNS lesion site, such as the inflammatory response, glial scarring, and barrier permeability, we suggest that the four sequential phases of the classical wound healing model (Box 1) can be extrapolated to the CNS response to sterile injuries. Accordingly, we suggest that the insufficient axonal regeneration and cell renewal in the CNS do not reflect an overall lack of repair capacity, but the insufficient resolution of preceding reparative events, which must be terminated prior to tissue regeneration and cell renewal, suggesting that the overall CNS response to insults has characteristics similar to an unresolved wound.

Notably, factors that limit CNS axonal regeneration have been extensively reviewed elsewhere and are beyond the scope of this viewpoint. Rather, we believe that identifying the common denominator(s) between CNS healing and that of other tissues, despite the often insufficient repair, will shed light on many open questions in the field, and may reveal therapeutic avenues and repair strategies for CNS injuries.

**Box 1. Lessons from the classical wound healing model**

Wound healing is an intricate process in which the skin repairs itself after injury via a complex process requiring the collaborative efforts of many cell lineages, extensively reviewed elsewhere [3,4]. According to the classical model, wound healing has four sequential, though overlapping, phases.

(i) Homeostasis (seconds–minutes) in which coagulation occurs at the ruptured vessels, platelets (thrombocytes) adhere and aggregate at the cracked vessel, and a fibrin plug is formed. The blood clot partially re-establishes tissue homeostasis and seclusion, and provides a provisional extracellular matrix for cell migration, thereby controlling bleeding.

(ii) Inflammation (hours–days), in which well-orchestrated leukocyte infiltration occurs, first of neutrophils, followed by monocytes. Tissue debris and invading bacteria are phagocytosed or killed. Leukocytes are also a major source for trophic support, encouraging the migration and division of cells involved in the subsequent proliferative phase.

(iii) Proliferation (days–weeks), also known as the repair phase, in which fibroblasts enter the wound, the scar is organized, the extracellular matrix is re-established (mainly collagen, which increases the strength of the wound), endothelial cells invade, and angiogenesis (neovascularization) is established to ensure oxygen supply; granulation tissue, containing macrophages, capillaries, fibroblasts, and provisional extracellular matrix, is formed. The provisional extracellular matrix, a fibroblast-derived platform, facilitates cell migration.

(iv) Remodeling or maturation (weeks–months–years, depending on wound type). In this phase, granulation gradually ceases, the collagen matrix is reorganized and realigned along tension lines; the wound contracts along the ‘axis of constriction’ by the action of myofibroblasts, anchoring the wound ends, and unneeded cells undergo apoptosis. Finally, the wound is covered by tissue in a process of epithelialization. Keratinocytes migrate to establish the new basement membrane.

The phases of wound healing normally progress in a predictable, timely manner; if they do not, healing may progress inappropriately to either a chronic wound or pathological scarring.

**Linking CNS recovery with wound healing – the steps preceding regeneration**

Research focus on the limited regeneration of the injured CNS [1] has resulted in the conventional view in which the term ‘CNS repair’ is used almost interchangeably with ‘CNS regeneration’. In view of this, we suggest a conceptual transition from viewing the CNS response to insult as a form of ‘limited neural regeneration’ to the understanding that it is ‘a failure of tissue remodeling’, meaning a failure to orchestrate – in a timely manner – the preceding reparative events needed for creating the scaffold for subsequent regeneration. Inspired by knowledge regarding wound healing, we thus suggest re-assessing CNS reparative capacity beyond regeneration by focusing on the phases preceding it, BBB breakdown, inflammation, and scarring.

**Breaking homeostasis via BBB breakdown – initiation of healing?**

In CNS injury, the mechanical insult ruptures the BBB and intra-parenchymal bleeding occurs, traditionally viewed as a violation of CNS homeostasis. Similarly, homeostasis disruption, vessel destruction, and leakage of blood take place in any wound. As in regular wound healing, in the minutes following CNS injury a clot is formed that acts as a temporary shield, protecting the exposed tissue and separating the tissue from the circulation [5]. Platelets adhere and a fibrin plug is formed, limiting bleeding and restoring primary homeostasis as coagulation occurs.

The glial scar also participates in the re-established separation and resealing of the breached BBB [6–8]. The end result is a tissue consisting predominantly of tightly packed, hyperfilamentous astrocytes, with many of their processes tightly apposed to one another, connected by numerous gap and tight junctions [9,10]. Migrating meningeal cells also take part in re-establishing the CNS glial limitans [11]. Like wound vasculature, the BBB is most permeable to proteins in the first 24 h following the
damage, and is largely resealed thereafter [12,13]. In the CNS, such leakiness, often termed ‘impaired BBB function’, is viewed as detrimental; plasma proteins such as thrombin, plasmin, fibrinogen, and circulating antibodies have been extensively investigated for their neurotoxic and demyelination effects [14]. However, transient opening of barriers and exposure to plasma proteins can actually promote cellular activation and healing; plasma fibronectin supports neuronal survival and mitigates brain injury [15], regulating inflammation, remyelination, glial activation, and scar formation [16,17]. As blood accumulates in the lesioned CNS, the oncotic pressure within the tissue increases, causing edema (swelling of tissue due to excess interstitial fluid retention). However, edema is a natural part of the orderly progression of wound healing events, essential for cell activation, catabolism, and the dilution of toxic debris.

As in a non-CNS wound, the clot itself participates in the healing – serving as a reservoir of cytokines, chemokines, and growth factors that are released as activated platelets degranulate – and thereby coordinates and amplifies CNS inflammation, facilitating the establishment of the subsequent phases.

When discussing vascular outcomes, hypoxia must also be mentioned. Hypoxia, as seen in the CNS, is a characteristic of all lesioned tissues and is considered a fundamental trigger of wound healing, contributing to endothelial and fibroblast proliferation and the excretion of growth/angiogenic factors. Nevertheless, severe hypoxia can lead to excessive inflammation and cell death. Thus, hypoxia seems to act as a two-edged sword for healing in general, and more specifically in the injured neural tissue, which is highly dependent on oxygen and extremely sensitive to its absence, which leads to neuronal damage within seconds. Thus, angiogenesis is fundamental for healing, restoring oxygen, and metabolite support to the tissue. Such neurovascularization, although limited, is also observed in CNS lesion sites [18]. Neovessels can also serve as scaffolds for regenerating axons and cell renewal by progenitor cells [18].

These lines of evidence are consistent with the suggestion that although breaching the BBB can undoubtedly facilitate neuronal death, it has additional effects that resemble, in many aspects, vessel breaching in skin wounds, and is an integral feature of the response to injury; if transient, interruption of the BBB seal contributes to the sub-acute events occurring at the injured parenchyma.
Inflammation – a universal healing player?

The CNS is a well-known immune-privileged site. Therefore, the inflammatory response at the injured neural tissue was traditionally viewed as detrimental to the healing process [2]. Indeed, many substances produced by leukocytes are neurotoxic and amplify glial scarring, as extensively reviewed elsewhere [2]. However, controlled inflammation and immune invasion are fundamental processes characterizing any wound healing pathway: leukocytes clean damaged sites, protect against potential infection of the exposed parenchyma, and promote tissue regeneration.

Similar to wound healing, leukocytes are actively recruited to the CNS (rather than entering due to barrier leakiness [19]) in sequential phases, in which early neutrophil recruitment is followed by monocyte infiltration and delayed lymphocyte entry [2, 20]. Similar to the well-described leukocyte diapedesis to wounds, entry to the CNS occurs through a regulated extravasation process involving selectins, integrins, and chemokines. Just as in regular wound healing, damage-associated molecular patterns (DAMPs), ATP, heat shock proteins, and matrix cleavage products are released from the injured tissue and coordinate inflammation. TLRs, NLR, and RAGE are also utilized by leukocytes in their response to CNS trauma, serving as damage sensors and activators.

Similar to their essential role in wound healing, accumulating data highlight the fact that circulating leukocytes [21–24] can support CNS repair through a multifunctional mechanism. Neutrophils, although generally viewed as an enemy of the CNS [25], have also been shown to support recovery [26] by reducing oxidized proteins [27], promoting astrocyte activation, and facilitating early production of growth factors [26]. In other tissues, they were even found to terminate inflammation [28], though such a role has not yet been demonstrated in the context of the CNS. Upon completing their tasks, a critical phase in inflammation resolution, skin wound infiltrating neutrophils undergo apoptosis and are engulfed by macrophages; it is not yet known if a similar mechanism operates following CNS trauma.

Similarly to the guiding role attributed to the extracellular matrix (ECM) for macrophage differentiation in wounds, in the lesioned spinal cord, chondroitin sulfate proteoglycan (CSPG), the major ECM component of the glial scar, is necessary for macrophage segregation at the lesion site and the acquisition of beneficial anti-inflammatory properties and growth factor secretion [29, 30]. Like their essential phagocytic role in wounds, macrophages engulf myelin debris as well as phagocytosing red blood cells, facilitating the safe elimination of highly toxic redox-active iron [31]. As in wounds [32, 33] and other diseases [34], macrophages within the CNS lesion have a pivotal role in the transition between the post-injury phase of cleaning the lesion and its preparation for subsequent remodeling, supporting tissue regeneration and ECM modulation. Myeloid cells support axonal regeneration [35–37] by clearing growth-inhibitory myelin debris [38], neurotrophic synthesis [30, 39], supporting blood vessel formation/maintenance [40], and resolving scar deposition [29]. The features of macrophages that support regeneration differ depending on the cell subset; whereas M1 cells induce stunted, short neurites with multiple branches, M2 macrophages promote extensive, long neurites [41]. Mononuclear phagocytes, as part of tissue regeneration, also support oligodendrocyte remyelination, as well as oligodendrocyte progenitor cell proliferation and differentiation [42–45], and retinal progenitor cell (RPC) colony expansion in the eye-ciliary body [24].

When considering inflammation in the CNS, special attention must be paid to resident microglia, a type of glial cell derived from embryonic yolk-sac macrophages [46] that are often viewed as CNS-native phagocytes. Their recently revealed yolk-sac origin suggests their comparison to epidermal Langerhans cells [47]. Just like skin Langerhans cells, the so-called quiescent microglia are highly mobile, continually surveying their environment with their fine processes [48]. Although microglia have many common characteristics reminiscent of monocyte-derived macrophages, accumulated evidence suggests that they are not redundant players in repair [23]. Upon traumatic brain injury, microglial processes rapidly and autonomously converge on the site of injury without cell body movement, establishing a potential barrier between the healthy and injured tissue. Similar to the occurrence in wounds, this rapid chemotactic response is guided by extracellular ATP released from damaged cells [49, 50]. Similar to macrophages, microglial activation is usually linked to the release of toxic factors and proinflammatory cytokines [51]; however, over a period of time that is prolonged relative to wound macrophages, microglia also start to secrete growth factors [30].

The termination of inflammation is essential for progression to the next healing phase in any wound. Similar to the pivotal resolving role attributed to macrophages in peripheral injury [32, 33], CNS infiltrating monocyte-derived macrophages play an essential resolving role, limiting the microglial response and local inflammation by secreting the anti-inflammatory cytokine interleukin 10 (IL-10) [23].

Glial scarring – a necessary interim fibrotic response

The CNS-associated scar, often referred to as the ‘glial-scar’ owing to its abundance of astrocytes, is mainly known for its growth-inhibitory properties [1]. The dense astroglial structure, along with the extensive ECM produced, are viewed mainly as physical and biochemical obstructions to regenerating neurites and axons. However, ECM production, as well as scarring, are fundamental and natural events in any wound healing process, serving as a temporary replacement for the damaged tissue, which is essential for the first steps of healing. A recent innovative study demonstrated that although the scar in the CNS is traditionally referred to as the glial scar, and thus is believed to be of cellular origin distinct from other scar tissues, pericytes (fibroblast-like cells covering capillaries) give rise to scar-forming stromal cells, which outnumber astrocytes, providing an initial origin-linkage to fibrosis [52]. As discussed below, many other common mediators exist between the fibrotic tissue and the glial scar.

Similar to the provisional matrix produced predominantly by fibroblasts in skin wounds (which provide a
scaffold for cell migration and thereby facilitate the formation of granulation tissue, discussed below), ECM is produced following CNS insults. Analogous to the well-described replacement of provisional matrix with normal ECM, a dynamic exchange of extracellular matrices is also evident in the injured CNS. Collagen, the predominant matrix in non-CNS wounds, is also a component of the glial scar; likewise, CSPG, the most predominant matrix of the glial scar is not unique to CNS injuries. Although in the context of CNS trauma, CSPG matrix (a known growth inhibitory component [1]) is generally considered a consequence of repair failure, CSPG upregulation in skin wounds represents breakdown of the provisional matrix and progression to the next stage of wound healing [53]. In this stage, CSPG enables wound closure, fibroblast proliferation, and, gradually, adhesion. We demonstrated that although CSPG is indeed an obstacle for regeneration and thus inhibits repair in the chronic phase, just as in non-CNS wounds, it is essential in the sub-acute response to spinal cord injury, controlling secondary degeneration and CNS inflammation [30]. Similar to the role of matrices in wound healing, CSPG regulates cellular migration and compartmentalization at the lesion site and skews infiltrating monocyte and microglial cell proliferation, cytokine secretion, and neurotrophic potential [29,30,53]. Moreover, by extrapolating from wound healing, in which it is known that the fibroblast–matrix composition resembles that of normal tissue but in a form that is crosslinked to enhance the strength of the structure, it becomes easier to understand why CSPG, a major component of the normal perineuronal CNS net, is the predominant glial scar matrix.

Like fibroblasts, astrocytes form a scar that stabilizes the injured parenchyma and efficiently isolates the injury site from intact neural tissue, limiting the spread of toxic compounds and preventing a cascading wave of uncontrolled tissue damage. This feature of the glial scar is clearly advantageous, because diminished glial scarring induced by astrocyte depletion, inhibition of astrocyte migration, or the blocking of CSPG synthesis exacerbates neuroinflammation, causes failure of BBB repair, and failure of wound contraction, leading to severe demyelination and neurodegeneration, as well as pronounced functional deficits [6–8,30]. Like fibroblasts, reactive astrocytes also exhibit paracrine trophic activities, triggering neuronal plasticity at the border of the trauma [54].

While evaluating matrix reorganization and scar creation at a site of injury, ‘granulation tissue’ formation should be discussed. Granulation tissue, new tissue growth that acquired the name based on its granular appearance, is a hallmark of the wound healing process, functioning as a rudimentary replacement tissue consisting of new blood vessels, fibroblasts, inflammatory cells, and the components of a new provisional ECM. Within days following spinal cord injury, a structure rich in ECM and many types of cellular components with a granular appearance also develops in place of native neural tissue. Surprisingly, although in a peripheral wound this is a sign of correct healing, in the CNS, the presence of such tissue is generally believed to indicate healing failure, probably due to its prolonged persistence. However, analogous to its role in establishing new tissue in wounds, this semi-granulation tissue in the CNS, with its newly formed microvasculature, serves as a scaffold for neural progenitors, suggesting its potential contribution to healing [55,56]. Similarly, whereas the next reorganization step – the transformation of the wound from cell-rich granulation tissue to cell-poor scar tissue with an excess of ECM – indicates advanced stages of skin wound healing (in which wound contraction occurs and many type of cells undergo apoptosis), such transition to scarring in the CNS was traditionally believed to represent malfunction of repair based on its growth-inhibitory properties.

Finally, an additional major event related to the scar is that of ‘scar contraction’. Contraction is a key healing phase in which the wound fibroblasts transform into myofibroblasts, which are capable of generating strong contractile forces. Although it is not yet clear if a similar process occurs in CNS lesions, it has been demonstrated in vitro that astrocytes can undergo contraction in response to stretching forces in a process involving the actin/myosin cytoskeleton network [57]; this might explain the enlarged lesion site seen in mice with astrocyte malfunction [7]. Increased immunoreactivity against glial fibrillary acidic protein (GFAP), a cytoskeleton protein seen in astrocytes demarcating the lesion site, might reflect cell contraction and cytoskeletal fasciculation. The concurrent progression towards the lesion center of GFAP immunoreactivity with advancing repair might reflect such partial scar contraction.

CNS response to injury takes the form of a chronic wound

Based on the evidence summarized above, we suggest that the four phases of classical wound healing also apply to the complex CNS healing response (Figure 2): (i) homeostasis, in which coagulation occurs, BBB structure is re-established, and plasma proteins and hypoxia activate the subsequent phases; (ii) inflammation, in which microglia and astrocytes become activated and well-orchestrated leukocyte infiltration occurs, facilitating phagocytosis of debris and trophic support; (iii) proliferation, in which gliosis occurs, the scar is organized, extracellular matrix is produced, and semi-granulation tissue containing macrophages/microglia, astrocytes, capillaries, pericytes, and provisional extracellular matrix is formed; and (iv) remodeling, in which the scar tissue is reorganized and neural tissue is regenerated.

The final stage of remodeling is a complex process in which the preceding stages are resolved and new tissue is established. As the early stages are resolved, the matrix is reorganized, inflammation is reduced, the wound contracts, and unwanted cells undergo apoptosis; as new tissue is created, tissue specific cells (in the skin epithelium and in the CNS neural lineage) are generated, organized, and integrated to replace the provisional tissue. To what extent does this occur in the case of CNS healing? It is well accepted that regeneration and cell renewal, the final step in the remodeling phase, is limited in the CNS [1,58,59]. This does not reflect an intrinsic property of neural cells, but rather the manifestation of a non-supportive environment. We propose that abortive repair of the injured CNS resembles chronic wounds that fail to complete the healing
phases and are characterized by excessive scarring, persistence of inflammation, and insufficient tissue regeneration. Abortive repair also occurs under scenarios where the area of damage exceeds the area that can be repaired (as occurs in severe skin burns), characterized by persistent scar tissue. Here, we summarize data suggesting that ineffective scar contraction, prolonged inflammation, and extensive edema, all basic characteristics of chronic wounds and scarring, often occur in the CNS, possibly underlying its limited regeneration.

**Prolonged healing – ‘the friend becomes a foe’**

**Vascular leakiness** Although the BBB is resealed during the sub-acute response, the secondary inflammatory response results in a secondary wave of permeability [60] in which the barrier remains permeable for over a month to small molecules, causing extensive edema. Given that the skull encloses the CNS, the local edema can result in increased intracranial pressure, less of a problem in soft tissue, which is often linked to increased morbidity and mortality. In addition, limited neovascularization that causes prolonged hypoxia further amplifies tissue damage.

**Inflammation** The microenvironment of the injured spinal cord is suggested to favor proinflammatory polarization, which has detrimental effects on tissue viability and regeneration [41]. A recent publication described this prolonged inflammation using quantitative measures to estimate inflammation resolution after spinal cord injury. The ‘resolution interval’, the time between maximum cell infiltration and the point at which cell number is reduced to 50%, was estimated to be 55 days for macrophages/microglia, and the ‘resolution plateau’ – the persisting inflammatory cellular component – was 45% for macrophages at 10 weeks [61]. These resolution indexes demonstrate that the acute immune response in CNS lesions is not fully self-limiting, resulting in a chronic inflammatory response. The nature of the persisting cells was not analyzed. We have demonstrated that some monocyte-derived macrophages can themselves serve as a source of inflammation termination, providing an essential resolving role via the secretion of the anti-inflammatory cytokine IL-10 [23,24]. This unique property of the macrophages is essential for controlling the proinflammatory resident microglia, for limiting secondary degeneration, and for motor function repair. The recruitment of these ‘alternatively activated’ or resolving macrophages in the physiological response seems to be insufficient for complete resolution of the local inflammation, and thus can benefit from augmentation [23,24]. However, a prolonged anti-inflammatory response may also be unfavorable for repair because it can promote fibrosis and scarring. Prolonged activation of immune cells also results in their dysfunction, as was demonstrated by iron-cleaning macrophages that, with time, develop toxic ferrous iron leakiness [31], which further amplifies the damage. Prolonged inflammation, which can persist as long as debris are present in the wound, also results in tissue damage in non-privileged organs, leading to chronic wounds.

**Scarring** In the CNS, the glial scar and granulation tissue are maintained long after injury. Many cells in the granulation tissue do not undergo apoptosis; even in the rodent where these cells are eliminated, such cellular apoptosis leaves a CSF-filled cyst, bordered by a thin, dense layer of reactive astrocytes, excluding the axons, and thus tissue function is never regained. CSPGs, the main glial scar matrix components, are secreted by lesion demarcating reactive astrocytes within 24 h after injury but continue to be present for months thereafter [1]. The hypertrophic astrocytes intertwined around the lesion site become more condensed with time. If it occurs in the CNS, scar contraction is insufficient, leaving excessive scar tissue. The persistence of the glial scar inhibits axonal regeneration and further accelerates damage, as associated with astrocyte production of cytokines and radicals. Excess scarring, which is suggested here to reflect the fate of the glial scar in CNS injuries, occurs in other unresolved wounds.

Many of the factors that participate in healing, such as plasma proteins, hypoxia, cytokines, and radicals, are neurotoxic and have demyelinating effects. They act as part of a vicious cycle escalating tissue damage, promoting BBB leakiness, and maintaining inflammation and...
scarring. Inefficient clearance of debris, an outcome of continuous cellular damage, provides constant signals that cause the persistence of inflammation and scarring, prolonging the healing phases preceding remodeling, as is observed for chronic wounds. In this unfortunate cycle, insufficient neovascularization increases tissue hypoxia, damaging the sensitive neural tissue that strongly depends on oxygen metabolism, skews the immune response towards a pro-inflammatory one, and promotes scarring. Whereas in the context of peripheral acute wound healing these phases are resolved, remodeling is achieved, and the healing process spontaneously terminates, in the CNS, the vicious cycle described above results in the persistence of many so-called ‘healer’ components (such as inflammatory cells and the glial scar) (Figure 2). In such a situation, the friend becomes a foe, further fueling the vicious cycle. Such prolonged activation of key players in the healing process, which, with time, accelerates tissue damage and limits regeneration, is characteristic of chronic wounds (Figure 3). Thus, we suggest that CNS response to injury takes a form similar to that of chronic wounds. Macrophages can provide the missing link for orchestrating healing — terminating the first non-resolving steps (by contributing to glial scar degradation [29], inflammation resolution [23, 24], and resealing of the breached BBB [40]), and creating the platform for the next regenerative phase [24, 39, 41–43].

**Concluding remarks**

By revealing countless similarities to wound healing, we suggest that many events occurring at the CNS lesion represent purposeful processes aimed at supporting tissue healing, rather than signifying a malfunction of regeneration. Such a novel view, revealing the fundamental functions of these processes, calls for a re-evaluation of many events that occur following CNS trauma, such as inflammation, BBB permeability, and glial scarring, which were hitherto viewed as impediments for tissue restoration that should be altogether eliminated. By viewing this milieu as ‘a step in healing’, we suggest that healing might be enhanced by their timely resolution rather than complete abolishment. We further suggest that the CNS response to sterile insults resembles that of chronic wounds, suggesting that limited CNS tissue remodeling/regeneration represents unsuccessful or insufficient resolution of preceding and essential phases of repair. A major goal of neurobiology is to determine how the CNS can be induced to engage in more effective damage repair. The comparison to wound healing presented in this article enlighten gaps in our knowledge and future directions in the field of CNS insults that have not previously been considered, and may open up therapeutic avenues for CNS repair by adopting therapies currently used to treat chronic wounds (Box 2).
Box 2. Outstanding questions

CNS response to insult as a type of wound healing – what is still unknown? Projecting the current knowledge in wound healing to recovery after CNS injury opens up future research directions, revealing many still open questions:

- Do macrophages or microglia engulf neutrophils, and if so, does this process trigger M2 skewing?
- Does myelin engulfment regulate macrophage/microglial phenotype?
- Does reorganization and re-alignment of the glial scar matrix occur? Do the glial scar or astrocytes create a scar contraction ring in vivo, and if so, what factors regulate this process?
- To what degree does angiogenesis occur following CNS trauma? What regulates it? Does increasing angiogenesis resolve scar gliosis?
- Does the CNS microenvironment restrict the microglia/macrophage skewing capacity?
- Does the delayed acquisition of an M2-like phenotype by microglia support prolonged scarring, as observed in lung fibrosis?
- Does the glial scar, and specifically ECM CSPG, serve as a conduit for cell migration, including leukocytes as well as neural progenitor cells?
- Does regulated apoptosis occur in the semi-granulation tissue seen in the damaged CNS? What limits this apoptosis in the CNS?
- Is there a bright side to CNS edema? Is it needed for cellular activation and debris dilution, as in wounds?
- What is the role of hypoxia in the CNS response to trauma? Does it trigger cellular proliferation and activation, initiating inflammation or regeneration?
- Do leukocytes, and specifically neutrophils and CD8 lymphocytes, protect the exposed CNS parenchyma from circulating pathogens?

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