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B cells and Autoantibodies: Complex Roles in CNS Injury

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Abstract

Emerging data indicate that traumatic injury to the brain or spinal cord activates B lymphocytes, culminating in the production of antibodies specific for antigens found within and outside the central nervous system (CNS). In this article, we summarize what is known about the effects of CNS injury on B cells. We outline the potential mechanisms for CNS trauma-induced B cell activation and discuss the potential consequences of these injury-induced B cell responses. Based on recent data, we hypothesize that a subset of autoimmune B cell responses initiated by CNS injury are pathogenic and that targeted inhibition of B cells could improve recovery in brain and spinal cord injured patients.

B cells as participants in central nervous system (CNS) injury immune responses

Historically, research efforts exploring interactions between the immune system and the diseased CNS have focused on neuroinflammation as well as immune regulation in multiple sclerosis (MS) and classical neurodegenerative diseases (e.g. Alzheimer's and Parkinson's disease). Less is known about how the immune system is affected by traumatic injury to the brain or spinal cord, but emerging data indicate that T and B cells play key roles in regulating CNS injury and repair[1–3]. In particular, recent studies implicate B cells, and the antibodies they produce, as pivotal players in the post-traumatic immune responses triggered by spinal cord injury (SCI). In vivo models show that B cells and SCI-induced antibodies exacerbate tissue damage and impair neurological recovery after SCI[1,2]. In this article, we summarize these data and discuss the implications of post-traumatic B cell activation, both in the context of host immunity and repair of the injured CNS. We also contemplate different mechanisms that may help to explain how trauma leads to dysregulation of B cell function and related mechanisms of neuroinflammation.

How and why does CNS injury activate B cells?

The canonical pathway for B cell activation involves recognition of a cognate antigen via mature B cell receptors and co-receptors with concomitant costimulation by T cells. These antigens, typically "non-self" pathogenic proteins, elicit a coordinated host immune response culminating in removal of antigen from the body. However, when the activating antigens are non-pathogenic host peptides, proteins, lipids or nucleic acids, autoimmune responses are elicited. Due to receptor editing and negative selection, most highly-autoreactive lymphocytes

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are deleted or inactivated in the thymus during development. However, during positive selection, "sub-threshold" stimulation of lymphocytes by self-peptides helps increase the sensitivity of lymphocytes to pathogenic proteins[4]. Thus, autoimmune recognition plays a physiological role in adjusting the strength of an immune response and only when a given threshold of activation is surpassed do autoreactive cells cause pathology. Current data suggest that after traumatic CNS injury, T-dependent- and perhaps T-independent self-antigens elicit adaptive immune responses with important functional consequences[1,2,5–7]. However, the nature and diversity of these autoantigens are presently unknown.

CNS antigens draining into peripheral lymphoid tissues after CNS injury might activate naïve neuroantigen-reactive lymphocytes (Figure 1). In support of this hypothesis, T cells in the spleen and lymph node become activated by spinal cord proteins including myelin basic protein (MBP)[6]. Indeed, after SCI, naïve T cells proliferate and when expanded *ex vivo* with MBP (or polyclonal stimuli), they can transfer a mild neuroinflammatory disease in naïve recipient animals[6]. The onset and progression of T cell-mediated autoimmune pathology is more striking when SCI is performed in $CD4^+$ MBP T cell receptor transgenic mice[8]. T cells in these mice are naïve but are genetically predisposed to recognize and respond to the encephalitogenic epitope of MBP. After SCI, MBP-reactive T cells expand in the periphery then traffic to the traumatized CNS where they exacerbate pathology[8]. A similar expansion of MBP-reactive T cells occurs in SCI humans[5].

Given that titers of anti-MBP antibodies increase after SCI in humans[9–11], it is likely that B cells are also affected by SCI. Indeed, an analysis of B cell responses in SCI mice revealed a marked increase in the number of $CD45R/B220^+CD19^+$ B cells and IgM- and IgG-antibody secreting cells in bone marrow and spleen[2]. Accompanying these cellular changes was an increase in total (polyclonal) and CNS-reactive serum antibodies[2], suggesting that activated B cells release autoantibodies into the circulation after SCI. At later times post-injury, B cells accumulate at the site of injury where they form intraspinal structures that are reminiscent of the ectopic follicles that develop in chronic MS[1,2]. Intraspinal B cell accumulation following SCI was accompanied by upregulated expression of genes encoding autoreactive immunoglobulins, suggesting that B cell-mediated autoimmunity is initiated or maintained within the CNS after injury.

The above experimental data provide a mechanistic explanation for older clinical research studies. In the 1970s, studies revealed that supraphysiological levels of antibodies specific for gangliosides and other phospholipids were enriched in the sera of humans that had suffered a traumatic brain injury (TBI)[12]. It was shown that autoantibodies specific for MBP and galactocerebroside were elevated in the sera of individuals with a traumatic SCI[11]. More recent studies have shown that ~50–60% of people with TBI or SCI produce antibodies that target a range of CNS proteins and glycoproteins including GM1 gangliosides, myelin-associated glycoprotein, AMPA and NMDA glutamate receptors, β-III-tubulin and nuclear antigens[9,13]. These data suggest that post-traumatic autoimmunity is common but is not an inevitable consequence of TBI or SCI. More comprehensive proteomic and lipidomic analyses of clinical autoantibody samples are needed to establish the true prevalence and specificity of SCI (or TBI)-induced autoimmune reactions in humans.

Systemic polyclonal B cell activation after CNS injury

Naïve, CNS antigen-specific B cells might become activated in peripheral lymphoid tissues by injury as described above (also see Fig. 1). However, reactivation of memory T and B cells that had previously responded to bacterial-, viral- or non-CNS self-antigens could also be responsible for trauma-induced autoimmunity[14]. Indeed, lymphocytes with receptors that recognize pathogenic or systemic antigens (e.g., nucleic acids) can cross-react with CNS

antigens. This concept of lymphocyte “polyspecificity”, previously referred to as molecular mimicry, could explain the increase in the prevalence of anti-CNS T and B cell responses after CNS injury. These lymphocytes could respond to CNS antigens directly or become re-activated by their cognate antigens or by polyclonal stimuli.

Traumatic CNS injury in humans is often associated with concurrent polytrauma, including concomitant head injuries or major injuries to the chest, pelvis, skin or extremities. These injuries facilitate entry of environmental pathogens, including bacteria and viruses that can prime or reactivate resting or memory B cells. CNS trauma also can increase intestinal permeability, promoting movement of commensal bacteria from the intestines into the circulation (i.e., bacterial translocation)[15,16]. Although commensals should not reactivate pathogen-specific B cells as cognate antigens, these endogenous bacteria could trigger polyclonal activation of B cells via toll-like receptors (TLRs) including TLR4 and RP105. Ligation of these receptors on B cells has been shown to exacerbate inflammatory disease[17]. Through these interactions, exogenous or endogenous microorganisms could amplify B cell responses, leading to enhanced neuroinflammatory reactions after CNS injury. Commensal microbiota have also been implicated in regulating the balance between inflammatory (e.g., Th17) and regulatory T cells (Tregs)[18]. As discussed below, trauma-induced activation of Tregs could be important for regulating B cell activation and pathogenic neuroinflammation.

Other non-pathogenic TLR ligands are released or are upregulated at sites of tissue injury[19]. Necrotic cells expel nucleic acids which ligate TLRs and form immune complexes, leading to activation of autoreactive B cells[20,21]. As a consequence of cell stress and tissue remodeling, damage-associated molecular patterns (i.e., DAMPs) including heat shock proteins, fibronectin and hyaluronan are increased at sites of tissue damage. All are considered endogenous TLR ligands that can initiate or enhance B cell responses[19,20,22]. Apoptotic cells also produce polyclonal stimuli that appear to act independent of TLRs. Indeed, when present at high concentration, phosphatidyl serines, cardiolipin and other antigens found on apoptotic cells activate B cells resulting in autoantibody production[23].

The site of CNS injury and time post-injury can influence B cell activation

Despite evidence that B cells are activated by injuries to the brain or spinal cord[1,2], other data show that CNS injury potently suppresses cellular and humoral immunity, which could explain the high incidence of mortality caused by infection in neurotrauma patients[24]. How is it then that SCI and TBI cause immune suppression while activating T and B cells that can exacerbate tissue injury? The key to resolving this paradox is to recognize that all immune cells are not equally affected by injury and that effects on the immune system vary over time.

During the first few days or weeks after injury to the CNS, a subset of human immune cells are anergic or otherwise blunted in their responses to immune challenge[25,26]. For example, within 24 hours of TBI, the total number of circulating T cells is decreased, as is the ability of T cells to proliferate or produce cytokines in response to mitogens[27]. Similar studies in SCI patients revealed defects in T cell and NK cell responses between 2 weeks and 5 months post-injury[28].

Despite these acute deficits in immune function, other clinical studies suggest that cognate T and B cell interactions are unaffected by SCI. Specifically, prophylactic pneumococcal and influenza vaccines were able to elicit immune responses with an expected increase in antibody synthesis[29,30]. Although the efficacy of these vaccinations was not affected by time post-injury, injury severity or injury location, the control groups were heterogeneous and group sizes small. Additional work is needed to fully characterize post-injury immune function, especially because newer data generated in controlled models of rat and mouse SCI show that post-injury B cell responses to specific, foreign antigens are blunted during the first few days to weeks

after SCI[31–33]. Specifically, when antigen is injected into the spinal intrathecal space of rats with a high-thoracic (T4 level) SCI, the antibody response to that antigen is reduced relative to the response elicited in uninjured mice receiving an identical immunization protocol[33]. Subsequent studies in mice proved that the immune suppressive effects of SCI on B cell activation and antibody synthesis are injury level-dependent, i.e., antibody synthesis is suppressed after high thoracic (T3) SCI but not after injury to the mid-thoracic (T9) spinal cord[31]. This is likely because sympathetic innervation of peripheral lymphoid tissues is regulated in part via the thoracic spinal cord[34]. When SCI occurs at or above the T3 spinal level, supraspinal control of sympathetic preganglionic neurons in the spinal cord is abolished. In contrast, some sympathetic outflow is preserved when SCI occurs at lower levels (e.g., T9 spinal cord). A post-injury surge in serum corticosterone (CORT) and splenic norepinephrine (NE) was found to be one mechanism responsible for the acute suppression of B cell function after high-level SCI. Specifically, CORT upregulates beta-2 adrenergic receptors on lymphocytes which, when subsequently activated by NE, initiates apoptotic signaling in immune cells[31,32,35]. When considered together, these data indicate that impaired supraspinal control of spinal sympathetic outflow to the immune system causes significant immunological deficits, at least during the first few weeks post-injury. This could explain the increased incidence of infection in humans with TBI, stroke or high-level SCI. Whether dysregulation of the sympathetic-immune system axis also augments pathological autoimmune responses after CNS injury has not been determined. Indeed, profound leukocyte apoptosis with impaired clearance of dying cells, similar to that caused by high-level SCI, is a suspected mechanism of autoimmunity in rheumatoid arthritis (RA), systemic lupus erythramatosus (SLE) and other rheumatic diseases[23,36].

Future studies also should determine whether the cholinergic anti-inflammatory reflex is involved in regulating B cell activation and autoantibody synthesis. To date, this neural-immune reflex has been characterized as an important regulator of proinflammatory macrophage functions through reflex activation of the vagus nerve[37]. Vagal release of acetylcholine (ACh) with subsequent ligation of α7 nicotinic ACh receptors on macrophages results in decreased release of pro-inflammatory cytokines (e.g., TNF-α). Nicotinic ACh receptors may also influence B cell development and activation, suggesting that enhanced vagus nerve activation could limit B cell hyperactivity[38]. To date, this hypothesis has not been formally tested in models of CNS injury; however, a recent report suggests that the cholinergic anti-inflammatory pathway can suppress lymphocyte activation and/or migration in response to mild neurodegeneration but it cannot ameliorate pathogenic neuroinflammation caused by CNS autoimmune disease[39].

Functional implications of B cell responses after spinal cord injury

Mice lacking B cells show improved locomotor function and reduced spinal pathology compared to wild-type mice after SCI, suggesting a pathogenic role for B cells[1]. The intraspinal pathology caused by B cells in wild-type mice is due in part to antibody-mediated ligation of Fc receptors and complement activation[1,2]. Even though intraspinal B cell clusters and autoantibodies are maintained indefinitely in injured mouse spinal cord and human cerebrospinal fluid, there is no proof that these immune responses cause protracted neurological deterioration. If they did, there would be a precipitous decline in function in both mice and humans as B cells became activated and autoantibodies were synthesized. Instead, delayed pathogenic autoimmune responses may target compensatory mechanisms of CNS repair. In human and animal models of SCI, spontaneous recovery of function stabilizes after a period of weeks or months post-injury, coincident with B cell activation and autoantibody synthesis. If B cells and autoantibodies are responding to proteins that are newly expressed in growing axons, remyelinating oligodendrocytes, stem cells or new endothelia, little or no additional gain of function beyond that achieved prior to the onset of the autoimmune response would be

expected. In this way, chronic autoimmune reactions might be responsible for regenerative axon growth failure and permanent loss of function after CNS injury in mammals.

It is also likely that as pathogenic immune responses become activated, regulatory cascades are activated in parallel (or shortly thereafter) that limit chronic B cell/autoantibody toxicity. Indeed, clusterin and factor H, proteins that counteract complement-mediated tissue damage, are induced after CNS injury[40]. Myeloid suppressor cells, Tregs and B regulatory cells (Bregs) also have been shown to inhibit or titer the potentially injurious consequences of inflammation and autoimmunity. How these distinct cell populations might regulate pathogenic immune responses after CNS injury is comprehensively reviewed elsewhere[18,41,42]. Although these suppressor/regulatory cells are undoubtedly important for controlling neuroinflammation, none have been adequately studied in the context of SCI or TBI. There are limited data exploring the role of Tregs, but the data are not easily reconciled. On the one hand, Tregs were shown to inhibit a naturally-occurring T cell-mediated “protective autoimmune” response induced by injury to the optic nerve; in the absence of Tregs, injury-induced neuron loss was exacerbated[43]. Conversely, intraspinal inflammation and pathology were worse after traumatic SCI in mice lacking CD4+ Tregs[44]. How or if B cells or autoantibodies were influenced by Tregs was not considered in either study. A key variable important for the induction and differentiation of regulatory immune cells, whether they be monocyte/macrophages or lymphocytes, is the microenvironment in which these cells become active. As can be assumed from the two examples provided above, different types and locations of CNS injury will undoubtedly create unique lesion environments. Accordingly, the relative composition and participation of immune regulatory cells is expected to vary. In models of traumatic SCI, the lesion environment seems to favor the development and protracted activation of inflammatory macrophages[45], T helper 1 lymphocytes[8] and pathogenic B cells[1,3]. Future studies must attempt to reveal whether these potentially injurious neuroinflammatory cascades engage self-correcting regulatory or immune-suppressive networks. By understanding the breadth of regulatory networks that are involved, it might be possible to accelerate or augment their actions to limit any pathogenic effects caused by B cells or other destructive neuroinflammatory cascades.

Additional experiments also are needed to reveal the origin of autoantibody synthesis (i.e., within vs. outside the CNS) and the breadth of CNS and non-CNS antigens that elicit antibody production after injury. Moreover, the functional significance of natural autoantibodies, i.e., self-reactive antibodies that are found in all individuals in the absence of inflammation or injury[46], have not been explored in the context of CNS injury and repair. Natural autoantibodies are produced by a primordial subset of lymphocytes called B-1 cells and bind a range of highly conserved (T-independent) self-antigens, including carbohydrates, phospholipids and oxidized lipoproteins. Natural autoantibodies have been implicated as effectors of pathology after ischemia/reperfusion injury in muscle and gut[47]. However, they also might help coordinate neuroprotective functions in microglia and macrophages, including the induction of recycling endocytosis and TNF-α release, ligation of anti-inflammatory FcRs and induction of remyelination via stimulation of oligodendrocyte progenitor cells[48,49]. The induction of these protective mechanisms during an immune response might explain the therapeutic benefit of intravenous immunoglobulin (IVIG) therapy for CNS and non-CNS diseases[49,50].

Do B cells and autoantibodies cause systemic pathology after CNS injury?

After CNS injury, B cells and autoantibodies might cause or influence systemic pathology, in addition to mediating adverse CNS effects. Serum rheumatoid factor (both IgM- and IgG-RF) is increased in SCI subjects[51], leading to the conclusion that circulating levels of RF could serve as a biomarker capable of predicting injury severity. There is a growing interest in identifying acute serum or cerebrospinal fluid biomarkers as prognostic indicators of chronic

outcome after TBI, SCI and stroke but it is not known if measurement of RF or other autoantibodies will be useful for this purpose. Autoantibodies produced in mice after SCI bind double stranded DNA (ds-DNA), chromatin and other nuclear antigens[2] and autoantibodies with similar binding specificities to those antibodies found in the blood of patients with systemic autoimmune diseases including RA and SLE[36,52]. In both RA and SLE, immune complex formation and the coordinated activation of innate and adaptive immune responses are implicated in disease pathogenesis[1,2]. A similar cause-effect relationship in post-CNS injury systemic complications has not been proven but remains an intriguing possibility, especially because loss of neurological function cannot explain many of the co-morbidities that accompany CNS injuries. For example, male sexual infertility that is unrelated to erectile dysfunction, kidney disease/failure and aberrant skin inflammation (e.g., seborrheic dermatitis) are chronic problems after SCI, but dennervation has not proven to be a universally compelling argument to explain these problems.

Recently, it was shown that SCI primes oxidative metabolism, inflammatory signaling and trafficking of neutrophils and monocytes to lung and kidney after traumatic SCI in humans and rodents[53,54]. The enhanced production of autoantibodies specific for spermatozoa antigens, DNA or other nuclear antigens might help explain some of the systemic comorbidities associated with SCI and other forms of CNS injury[2,55–57].

Manipulating B cell function as therapeutic approach for CNS injury

To date, most data indicate that B cell activation after a traumatic CNS injury, especially SCI, causes pathology leading to impaired recovery of neurological function[1,2]; therefore, it is logical to explore inhibition of B cell function as a therapeutic option. A number of B cell-directed therapies (e.g., B cell-depleting monoclonal antibodies including Rituxan® or Ocrelizumab®) already exist or are in clinical trials for treating SLE, RA and most recently, MS[58]. However, to date, there have been no attempts to use similar approaches for treating individuals with traumatic CNS injuries. The use of alternative therapies, including IVIG therapy, plasmapheresis or biologics that target endogenous factors that regulate B cell growth/differentiation (e.g., BAFF or APRIL) should also be considered for limiting the accumulation of potentially pathogenic antibodies in the circulation. In mice, intralesional B cell follicles form, and gene expression arrays indicate that B cell growth and differentiation occurs within the chronically injured CNS[1,2,59]. Therefore, the intraspinal or intracranial delivery of antibodies or pharmacological agents that block BAFF and APRIL is feasible and would presumably limit the effects of B cells and antibodies within the CNS parenchyma. However, as with other strategies that interfere with T cell or macrophage function, B cell inhibition strategies can also be associated with severe immunological complications, [such as the development of progressive multifocal leukoencephalopathy (PML)], which must be a strong consideration when contemplating immune-based interventions in patient populations[60].

Future research might also show that even though pathogenic B cell responses are activated after injury, safe and efficient vaccine therapies could be exploited for CNS repair. Pre-clinical vaccination protocols have been developed with the goal of enhancing anti-myelin antibody synthesis for accelerating the removal of axon growth inhibitory myelin debris[61]. Clinical trials are underway to test whether exogenous monoclonal antibodies specific for Nogo-A and other repair-inhibiting myelin antigens can be used to safely treat patients with CNS injuries (clinicaltrials.gov). The administration of exogenous antibodies has the benefit of potentially inducing repair without directly activating (or re-activating) B cell clones that are set in motion by CNS injury.

Conclusions

It is clear that B cells are activated by traumatic CNS injury and that these cells participate in ongoing cascades of CNS injury. After SCI in mice, B cells produce pathogenic antibodies that cause neuroinflammation, cell death and sustained neurological dysfunction. Accordingly, strategies that inhibit B cell function after SCI could be therapeutic. Based on the overlapping specificities of autoantibodies produced after SCI and in autoimmune diseases like RA and SLE, future studies should determine if SCI autoantibodies also cause immune complex disease, cognitive deficits and kidney or sexual dysfunction in SCI subjects. Indeed, RA and SLE autoantibodies are known to cause systemic and cognitive impairments that mimic those described in people with SCI. As with any new and emerging area of biomedical research, there are many fundamental questions that remain unanswered (see Box 1). Hopefully, the answers to these questions can be used to develop more effective therapies for individuals who sustain a CNS injury.

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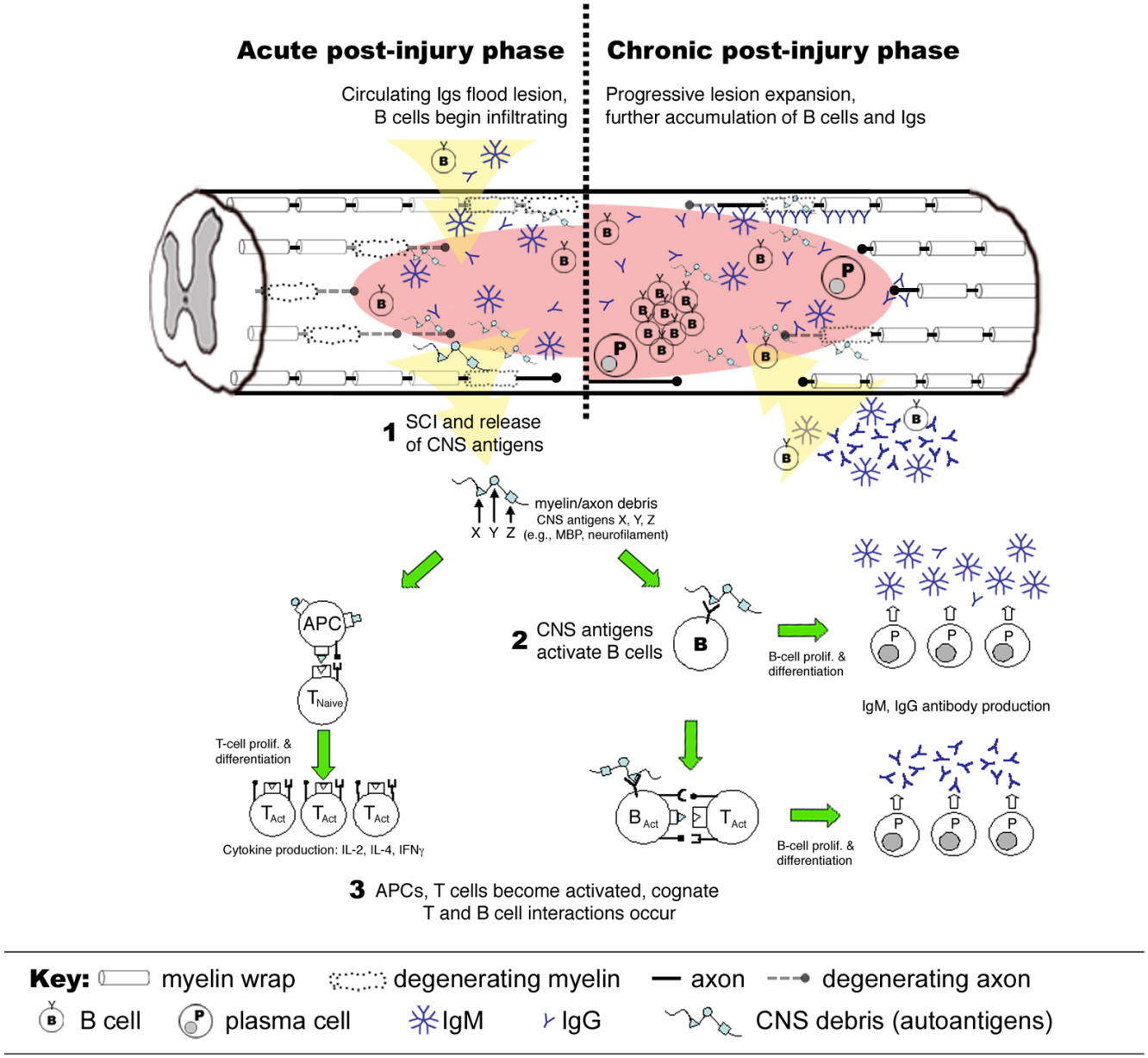

Figure 1.

Putative mechanisms of B cell activation after traumatic SCI. SCI causes cell death and blood-spinal cord barrier (BSCB) damage (1). At this time, circulating B cells and (pre-formed) immunoglobulins (Igs) cross the BSCB and accumulate at the injury site. BSCB also facilitates drainage of CNS antigens to peripheral lymphoid organs with subsequent B cell recognition of CNS antigens causing B cell proliferation and antibody production (2). Concurrently, APCs present CNS antigens to T cells (3). Cognate interactions between T and B cells amplifies the autoimmune response to CNS antigens such that during the chronic post-injury phase (weeks to months post-SCI), B cells and antibodies continue to accumulate at the injury site forming ectopic follicle-like structures with Igs decorating cells and tissues in and nearby the site of injury.

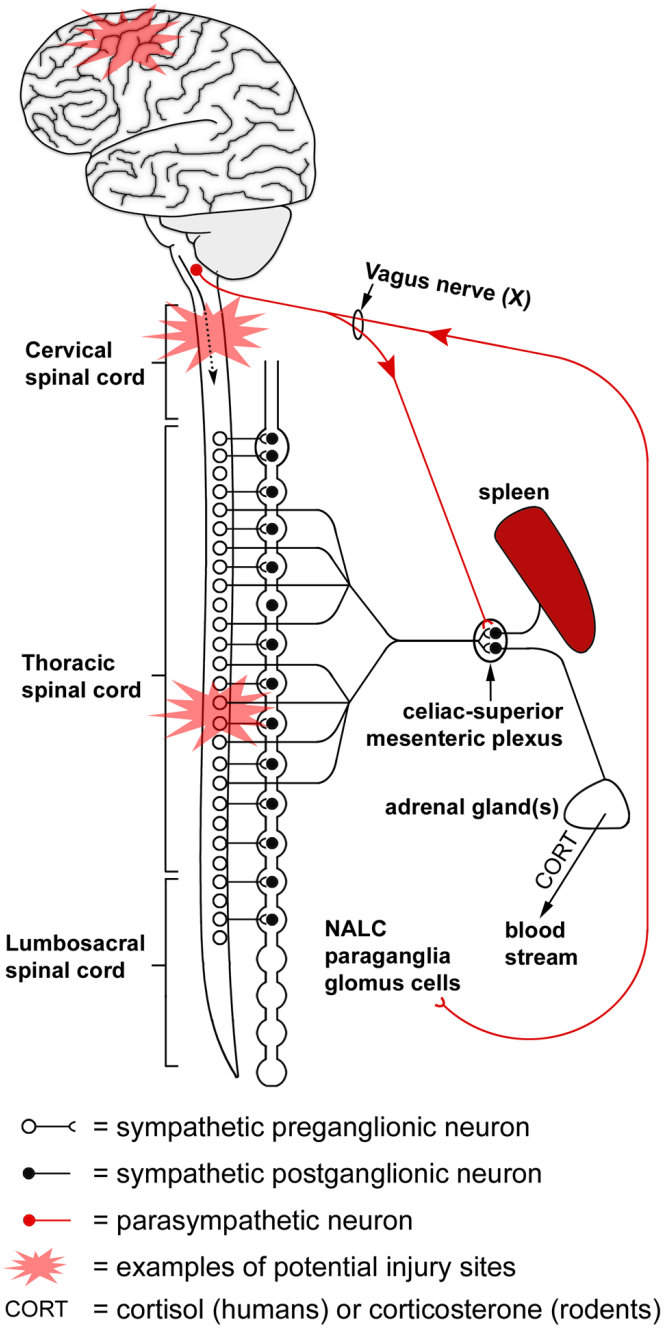

Figure 2.

Autonomic nervous system innervation to the spleen, nerve-associated lymphoid cells (NALC) and adrenal glands. Injuries sustained at different levels of the neuraxis differentially influence immune function. Injuries to the brain or brainstem will block supraspinal control of (dashed arrow) sympathetic preganglionic neurons which in turn regulate noradrenergic postganglionic neurons in the sympathetic chain ganglia. The latter innervate the spleen and adrenal glands. Dysregulation of this “hard-wiring” will adversely affect immune function. Immune function in the periphery and the CNS may also be adversely affected by CNS injury if reflex activation via the vagus nerve is damaged. Normally, this “cholinergic anti-inflammatory vagal reflex” helps limit inflammatory signaling cascades generated in the periphery (see [37] for review).