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Spinal cord injury, immunodepression, and antigenic challenge

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Abstract

The inability to effectively control microbial infection is a leading cause of morbidity and mortality in individuals affected by spinal cord injury (SCI). Available evidence from clinical studies as well as animal models of SCI demonstrate that increased susceptibility to infection is derived from disruption of central nervous system (CNS) communication with the host immune system that ultimately leads to immunodepression. Understanding the molecular and cellular mechanisms governing muted cellular and humoral responses that occur post-injury resulting in impaired host defense following infection is critical for improving the overall quality of life of individuals with SCI. This review focuses on studies performed using preclinical animal models of SCI to evaluate how injury impacts T and B lymphocyte responses following either viral infection or antigenic challenge.

Keywords

Spinal cord injury; Infection; Immune response; Immunologic memory

1. Introduction

Spinal cord injury (SCI) is a dramatic and devastating condition affecting approximately 1.3 million people within the United States [1,2]. Aside from the varying severity of motor skill impairment, SCI results in numerous metabolic and immune problems that can last the lifetime of the injured individual. With regards to the latter, SCI-induced immunodeficiency leads to increased susceptibility to infection resulting in elevated morbidity and mortality. For over 40 years, researchers have made efforts to characterize the molecular and cellular interactions between the nervous, endocrine and immune systems which facilitate immune regulation and physiological homeostasis. Early findings have elucidated the mechanisms

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controlling the important interplay between these systems related to cause and effect relationships of inflammation and physiological changes such as observed in fever. More recently, researchers have described suppression of immune responses in response to external factors that disrupt neuroendocrine-mediated regulation. The interactions between the neural and immune systems is a complex process involving bidirectional communication of neurotransmitters, hormones, and immune cells/lymphoid tissues which highlights the lack of autonomy between these two organ systems [3–7]. Understanding the multifactorial balance of immune regulation continues to be a growing interest especially in the field of neurotrauma research.

Many factors, including stroke, traumatic brain injury (TBI), and SCI are known to have detrimental effects to the immune system [8] and this is collectively referred to as CNS injury-induced immunodepression (CIDS) [9]. Following stroke, TBI or SCI, patients exhibit an increased rate of infection and mortality [9]. Complications from infection are the leading cause of re-hospitalization and death in the post-acute phase following SCI [10,11], and immune dysfunction can impede neurologic recovery in stroke patients [12,13]. Evidence supporting neuroendocrine involvement in immune dysfunction was shown in 2000 by Cruse and colleagues in clinical studies that correlated suppression of immune functions with increased cortisol levels in patients with SCI [5,14,15]. Therefore, understanding the mechanisms underlying immunodepression following SCI have been the focus of many clinicians and researchers for the purpose of improving therapeutic intervention and the quality of life for those with SCI. This brief review article will focus on SCI-induced deregulation of neuroimmune pathways and provide perspective on how the severity of immunodepression may be influenced by the level of SCI. Specifically, we will focus on how primary adaptive immune responses and immunological memory are impacted following SCI within the context of both viral infection and responses to defined chemical antigens.

2. Neuroimmune connection and modulation of immune responses

The CNS provides a network of pathways to regulate inflammation, resolve infection and maintain homeostasis. The immune system can be modulated by the CNS via the hypothalomo-pituitary-adrenal axis (HPAA), the sympathetic nervous system (SNS) and the parasympathetic nervous system. In general, these components maintain homeostasis via anti-inflammatory mediators that counterbalance inflammation at both systemic and cellular levels (Fig. 1). Among the various effects on the immune system, the HPAA and autonomic regulation via glucocorticoid, catecholamine and cholinergic signals, respectively, target leukocytes and have been implicated in modulating circulating and lymphoid tissue cell numbers. In addition, numerous biological functions critical in host defense in response to microbial infection including migration, proliferation, phagocytosis, and cytokine secretion are controlled by these pathways [4,16–18]. Cells of the immune system express receptors for these transmitters, which reach their cellular targets via circulating blood or by proximal nerve terminal-cell interaction. While increasing evidence supports a vagus nerve based anti-inflammatory pathway [17], the majority of data indicate neuroimmune interaction is dominated by sympathetic modulation via norepinephrine (NE) [3]. Anatomical studies mapping neuroimmune pathways reveal the majority of primary and secondary lymphoid

organ innervation is sympathetic [19,20]. Furthermore, leukocytes express adrenergic receptors and the influence of NE on immune cell functions and been studied in detail [3].

Proinflammatory cytokines such as IL-1β, TNF-α and IL-6 are produced by the immune system in response to stress, injury or infection, and these factors signal to the CNS resulting in immune modulation; activation of the HPAA leads to the release of the humoral immunosuppressive glucocorticoids [6], and increased NE turnover rate in the spleen correlates with suppression of immune cells [21]. Meltzer and colleagues show that the SNS is primarily responsible for the immunosuppressive effects of stress rather than HPAA, using combinations of experimental splenic nerve cuts, adrenalectomies and adrenual demedullations [22]. Interestingly, activation of the SNS can inhibit or enhance lymphocyte immune function, yet inhibits the function of innate immunity [19]. NE signaling contributes to CD4+ T cell development to Th1 subtype and balance of Th1/Th2 associated immune responses [23,24]. The duration and timing of catecholoamine exposure to lymphocytes relative to their maturation phase may influence the effector function, indicating additional complexity to neuroimmune regulation [19,24]. Furthermore, the negative-feedback paradigm of neuroimmune interaction may be over simplified and Nance and Metlzer argue CNS outputs are delayed relative to ongoing immune reactions, and thus may instead provide a greater influence to delimit the duration of an immune response [16]. Nonetheless, the CNS and immune system share a counter-balance relationship that is disrupted following CNS-injury. As a result, injury to the CNS presents a unique situation in which there is a defined period of elevated inflammation within the CNS exacerbating neuropathology, yet there is a long-lasting impairment with regards to controlling peripheral microbial infection that relies on inflammation in order to eliminate the invading pathogen. This scenario ultimately leads to immunodepression and emphasizes the importance of the SNS and HPAA pathways in contributing to regulating immune responses to infection [9]. Understanding the underpinnings involved in immune deregulation following SCI has been the focus of ongoing research by many investigators.

3. Disruption of neuroimmune regulation following SCI

SCI and the resulting physiological changes have been studied extensively in both experimental and clinical settings. The severity and location of injury to the spinal cord influences the outcome of paralysis, muscle atrophy, loss of sensory, bowel, bladder and sexual function and may influence the degree of immune suppression. Importantly, complications from infections are a leading cause of re-hospitalization and death in the post-acute phase of SCI [10,11]. The normally well-balanced neuroimmune interactions are disrupted following SCI, resulting in immune suppression and increase susceptibility to infection. Despite the immune suppressive effects of methylprednisolone acute SCI-therapy, immunodepression and increased sensitivity to infection can occur in the absence of treatment [9,25,26]. Therefore, SCI itself is a primary factor in dictating the severity of immune suppression.

SCI can interrupt neural pathways involved in neuroimmune balance, most notably, central autonomic pathways that descend via the spinal cord. Output signals by preganglionic sympathetic axons that innervate lymphoid organs and the adrenal gland are modulated post-

SCI [27,28]. Although the peripheral nerves are intact following SCI, the output to these peripheral tissues would no longer be regulated by supraspinal control. The majority of meaningful SNS activity evolves from thoracic level T6 and above, and innervation to key lymphoid tissues such as the spleen and the adrenal medulla arise from the mid-thoracic and lumbar spinal cord [29,30]. Therefore, SCI at or above T6 level may damage SNS pathways resulting in greater loss of neuroimmune regulation compared to lower level injury which would conserve normal central connectivity. Other physiological processes normally influenced by the SNS, such as blood pressure regulation, also experience level-dependent changes following SCI. Reduced sympathetic activity, morphological changes in sympathetic preganaglionic neurons and peripheral alpha-adrenoceptor hyperresponsiveness are observed following loss of supraspinal control following injury at or above T6, which leads to dynamic changes in cardiovascular function over time and may manifest in bouts of sympathetic hyperactivity, i.e. autonomic dysreflexia [31,32]. Indeed, exaggerated catecholamine release during episodes of automonic dysreflexia caused secondary immune deficiency after SCI in mouse and human [32].

Deregulation of SNS below the level of injury may result in dynamic changes in sympathetic activity, which can modulate immune function both systemically and locally at lymphoid tissues. As an example, NE has been shown to modulate multiple components of an immune response including expression of TNF-α which is inhibited by increased NE levels [27]. Significant increases in NE levels within the spleen have been observed following acute and chronic injury in mice with T3-injury, but not with T9-injury, indicating a potential reduction in proinflammatory responses [28,32]. Investigation into SNS activity in response to systemic administration of LPS following high thoracic injury in rats revealed plasma levels of catecholamines were dramatically reduced. Splenic TNF-α expression was elevated in injured rats, however, the NE levels within the spleen were unchanged in response to stimulation [27]. The authors suggest that while NE nerve fibers remain present within the spleen, no significant amount of NE is released in response to stimulation. More importantly, these studies highlight the need for adequate methods to evaluate SNS activity within the spleen using readout techniques to accurately monitor NE production, release, diffusion/metabolism, and transmitter reuptake that may change over time following injury. Finally, it would be interesting to assess how SCI affects expression of adrenergic receptor sensitivity at defined times following injury. Recent findings show the expression and affinity of beta-2 adrenergic receptors on lymphocytes is increased following early-acute high thoracic SCI, thereby increasing sensitivity to glucocorticoid and NE mediated immune suppression and apoptosis [33]. Further insight to the consequences of adrenergic receptor changes on lymphocytes may be gained in future in vivo experimental mouse studies using lymphocyte adoptive transfer of SCI-derived leukocytes into un-injured mice stimulated with immunogen to evaluate cellular homeostasis.

In addition to deregulation of SNS-immune connections, the HPAA also contributes to immune suppression following SCI. Glucocorticoids have an array of effects in modulating innate and adaptive immunity that contribute to resolution of inflammation and infection. Acute SCI initiates a stress response resulting in glucocorticoid production and immune suppression, and in the absence of systemic inflammation to provide negative feedback to the HPAA, the anti-inflammatory effects may compromise immune defenses and increase

susceptibility to infection. An increase in levels of glucocorticoid and cortisol are observed both clinically and in experimental SCI rodent models [14,28,34]. Cruse and colleagues have correlated the inverse relationship of elevated urine-free cortisol with decreased T cell functions (evaluated by IL-2R expression and proliferation), and showed immune function was lowest at 3 months post-injury [14]. In rodent SCI models, elevated levels of circulating corticosterone (CORT) are observed early in the acute phase following high and low thoracic injury in mice [28]. Day 3 post-severe SCI (complete transection of the spinal cord) at T3 resulted in significant increase in CORT levels compared to surgical control, while both moderate-contusive or severe injury at T9 resulted in non-significant increase relative to surgical control. However, this increase may be transient as others have found no change at 1-week post-injury in rat receiving moderate-injury at T1–T3 [27]. Still others have reported elevated CORT levels up to 28 days following severe-injury [32,34]. For example, both laminectomy surgical control and mice receiving T3- or T9-level complete SCI (crush-injury) had elevated plasma CORT relative to un-injured mice at day 8 and approximately one month later, only mice with injury had sustained increased in CORT [34]. These data indicate that the level and severity of SCI may influence the outcome of HPAA activity and duration of potential immune suppression.

4. Immunodepression following SCI

Clinical and experimental SCI studies provide evidence of depressed innate and adaptive leukocyte responses. The effect on leukocytes and immune function is modulated over time following SCI and in many cases deficiencies are dependent on injury level. Table 1 provides an overview of immune components modulated post-injury in relation the level of injury and tissue evaluated. Following acute injury a dramatic decrease in circulating leukocytes and HLA-DR (MHC II) expression is observed by 24 h post-injury [25,35]. Immune functions are altered throughout acute and chronic injury, and evidence support pronounced deficits are observed with injury above T6 (Table 1). In general, decreased leukocyte numbers are restored within one week, but deficits in cell effector function may persist for months, indicating that systemic stress signals and decentralization of lymphoid tissues, which support leukocytes, contribute to immune depression [32,34]. The instability of neuroimmune interactions following SCI is complex and adherent responses to stress can lead to periods of immune suppression as observed in autonomic dysreflexia [32]. Furthermore, deficits in immune function may also be influenced by the severity of injury [36]. A prospective multicenter clinical study to define the spinal cord injury-induced immune depression syndrome is currently in progress to explore influencial factors such as injury-level, injury severity and monocyte HLA-DR expression that are linked to increased incidence of infection [37]. Publicaiton of data from this study are anticipated for late 2014, and findings may ultimately lead to improved spinal cord injury medical care.

5. SCI and adaptive immunity

The adaptive immune system plays a critical role in resolving infection and establishing immunological memory. Lymphocyte genesis, numbers, and effector functions are negatively impacted following SCI, indicating that both quantitative and qualitative decreases may contribute to increased incidence of infection. More importantly, evidence

from experimental studies support adherent SNS and HPAA signaling post-SCI directly influences adaptive immunity. For example, mitogen-induced T cell proliferative response is dramatically diminished at 3 months post-injury and correlates to elevated urine-free cortisol levels in SCI patients [14]. Others studies have characterized how the intensity, level and phase of SCI can differentially alter the function of T cell proliferation and thymus-dependent antibody response using innocuous antigen [36]. However, SCI patients are faced with an increased susceptibility to infection highlighting the need to examine how SCI affects host response to microbial infection. We employed an experimental SCI-infection model using mouse hepatitis virus (MHV). Anti-viral host defense to MHV infection involves a robust T cell-mediated immune response. One week following complete SCI at T3 or T9, mice exhibited increased mortality and higher viral infection compared to uninjured infected mice (Fig. 2A and B) [26]. The increased sensitivity following injury was independent of injury level and quantitative difference in T cell splenic levels. Following infection of injured mice, antigen-presenting cell activation and viral-specific T cell number, proliferation and IFN-γ production were significantly reduced. Although, SNS and HPAA activities were not evaluated in this study, it is likely elevated splenic NE and systemic CORT exacerbated suppression of anti-viral immune responses and increased the sensitivity to infection at both acute and chronic stages post-injury (Fig. 2B).

Increasing evidence support SCI-induced disruption of B cells and humoral functions. For example, increased B cell apoptosis and glucocorticoid and beta-2 adrenergic receptor sensitivity observed during acute-SCI correlates to increased NE and CORT levels [33]. In addition, pharmacological inhibition of glucocorticoid and beta-2 adrenergic receptors rescues B cell number and humoral activity [28,32,33]. B cell genesis is also dramatically affected following acute-SCI, thus reduction in cell survival and lymphopoiesis contributes to B cell leukopenia. Lymphopoiesis is restored after about one month, however the magnitude of thymus-dependent responses is diminished following SCI and greater deficits are observed in mice with high thoracic-level injury [28,32,34]. Interestingly, thymus-independent type 2 response is profoundly decreased after chronic T3-level injury. Marginal zone B cells are critical for thymus-independent response, and although there are inconsistent findings in quantitative effects during chronic-SCI, qualitatively, up to 3–4 fold reduction in IgM production and increased sensitivity to apoptosis has been shown in mice chronically injury at T3 [32,34]. These findings indicate that primary B cell responses are not intact following SCI, which may contribute to decreased ability to form memory B cells and long-lived plasma cells needed for protection against re-infection or secondary-challenge. In attempt to address how memory responses may be affected following SCI, Oropallo and colleagues [32] immunized mice and established memory pools prior to SCI and then re-challenged mice with antigen (Fig. 3A). Strikingly, resting and boosted memory responses are unchanged; frequency and number of high-affinity splenic antibody secreting cells, and the concentration of high affinity antibody is unaltered following high or low-thoracic SCI (Fig. 3B and C). These findings revealed secondary humoral responses are intact following chronic SCI. Therefore, the results suggest memory B cells may be refractory to neuroimmune deregulation following SCI, and immunity to prior vaccination or pathogen will remain unperturbed. However, it is still to be determined whether protective immunity and memory can be established upon exposure to new antigens after SCI.

6. Conclusion

SCI results in a lifetime of paralysis associated with a spectrum of medical complications including metabolic problems as well as increased susceptibility to microbial infection. With regards to the latter, research within the clinical setting as well as using preclinical animal models of SCI have revealed new insight into mechanisms associated with immunodepression following SCI. A new understanding of how injury affects B cell genesis, antibody formation, and memory responses has now been characterized as well as new information on how injury influences the biology of antigen-presenting cells and subsequent activation of T cells following viral infection. Nonetheless, much work needs to be performed in order to help individuals with SCI combat and control infections. For example, the effects of SCI on innate immune responses following infection e.g. pattern recognition receptors (PRRs) needs to be better defined as well as characterizing how SCI influences host defense in models of infection using clinically relevant viruses such as influenza needs to be examined in detail. In addition, the effect of lymphocyte exhaustion in the face of infection needs to better characterized. Finally, the ability to effectively immunize and maintain stable lymphocyte memory pools in injured individuals needs to be examined in more detail. A broader knowledge of how injury subverts innate and adaptive immune responses in the face of infection will enable clinicians to more effectively treat people with SCI and improve the overall quality of life.

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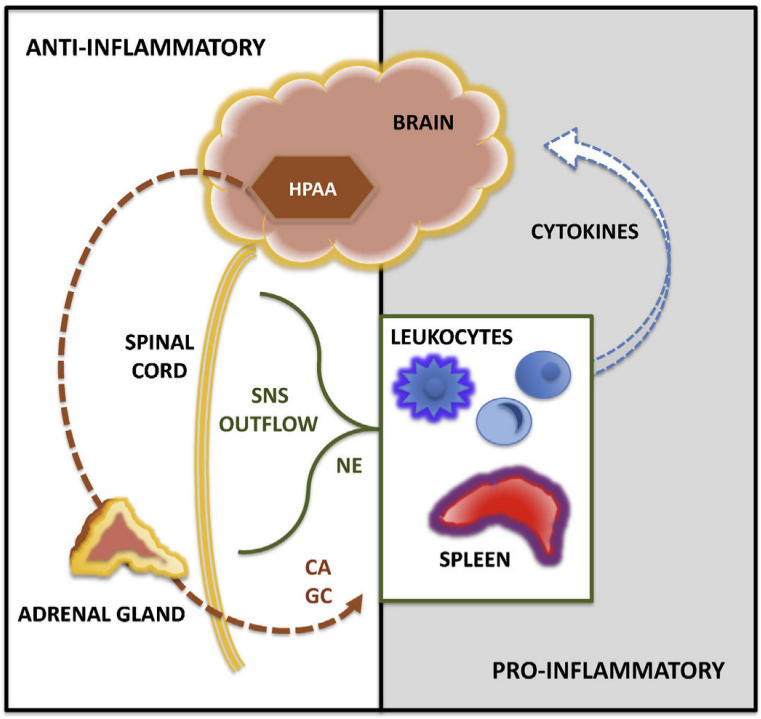

Fig. 1.

Neuroimmune connection and modulation of immune responses. The CNS and immune system interact to balance inflammatory responses. Pro-inflammatory cytokines released during an immune response are processed by the CNS resulting in anti-inflammatory signals from the HPAA and SNS. Activation of the HPAA results in production of glucocorticoid hormones (GCs) and catecholamines (CAs), which have systemic effects on leukocytes and lymphoid tissues. Activation of the SNS results in production of norepinephrine (NE), which reach leukocytes via hardwire connection to lymphoid tissues. The counter anti-inflammatory response from the CNS and interactions between these systems helps to maintain homeostasis.

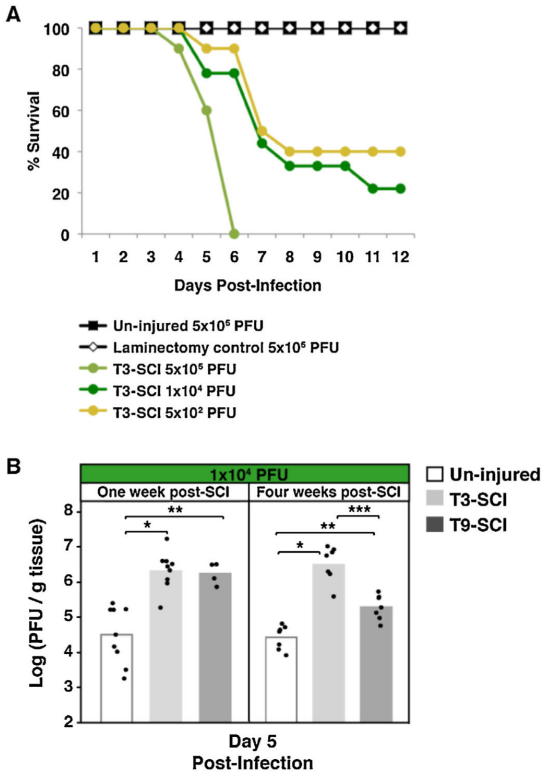

Fig. 2.

Spinal cord injured mice exhibit increased mortality and higher viral titer following viral infection compared to un-injured infected mice. At one-week post-SCI, mice were infected with decreasing dosages of MHV and mortality recorded. (A) The survival of T3-injured mice following the highest dosage of MHV infection resulted in mortality, yet 100% survival was observed in un-injured mice and laminectomy surgery-control mice. Survival of T3-injured mice was prolonged following infection at lower dosages. (B) Viral titers were recorded following day 5 post-infection, and injured mice showed higher viral titers compared to un-injured mice. Following infection at one-week post-SCI with 1×10^4 plaque forming units (PFU), T3- and T9-injured mice had significantly higher titers compared to un-injured mice ($*p \leq 0.001$ and $**p \leq 0.006$, respectively). At four weeks post-SCI another cohort of mice was infected with 1×10^4 PFU and titers examined at day 5 post-infection. T3- and T9-injured mice had significantly higher titers compared to un-injured mice ($*p \leq 0.002$ and $**p \leq 0.003$, respectively). T3-injured mice also had significantly higher titer compared to T9-injured mice ($***p \leq 0.003$). Survival studies began with 10–8 mice in each infection group. Viral titers are presented as logarithmic means of PFU per gram of liver, as shown in columns in *B*, with each data point representing one mouse. The limit of detection was ~200 PFU/g liver.

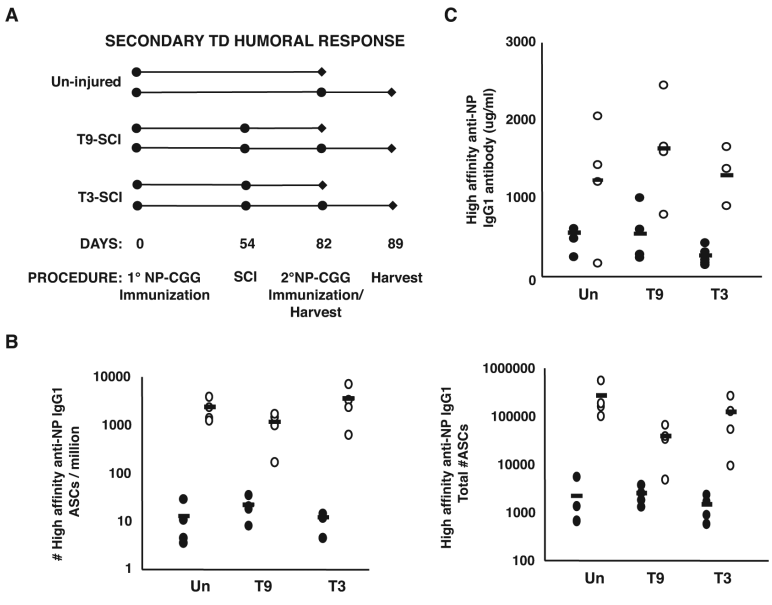

Fig. 3.

Secondary humoral responses are intact following chronic SCI. (A) Diagram of experimental procedures showing assessment of secondary thymus-dependent responses in injured and un-injured mice. Mice were immunized i.p. with 50 μg of NP_{15}-CGG 54 days prior to SCI, then 28 days post-injury resting (closed circles), and boosted (open circles) memory responses were assessed. (B) The frequency/million and total number of splenic high affinity IgG1 antibody secreting cells (ASCs). (C) High affinity IgG1 anti-NP antibody in treatment groups both before and after secondary challenge is shown (n = 4–5 mice per group). Data are representative of two experiments.

Source: Permission for use of this figure was kindly granted from Oropallo et al. [34].

Table 1

SCI-induced immune depression.

Immune component	Alteration following SCI and evaluated (tissue)	Level-dependent	References
Neutrophil/granulocyte	Reduced phagocytosis, and cell number remains unchanged, except for a transient increase occurring 24-h post-injury (blood)	Yes	[25,35,38]
Natural killer cells	Decreased number and cytotoxicity-conflicting observations supporting greater losses when injury occurs above T6 (blood)	No, yes	[14,35,39]
Monocyte/macrophage	Reduced number (blood, spleen)	No	[25,32,35]
Dendritic cells	Reduced number; more pronounce deficiency in decentralized tissues (spleen, BM)	Yes	[25,32,40]
HLA-DR	Reduced expression (blood)	N/D	[25,35]
B lymphocyte	Reduced number (immature and mature), genesis, and humoral function; more pronounce deficiency in centralized tissues (spleen, BM). Secondary humoral response is unaffected (spleen)	Yes	[25,26,28,32,34,35]
T lymphocyte	Reduced number, cytotoxicity* (blood), proliferation, and proinflammatory secretion; more pronounce deficiency in decentralized lymphoid tissues (spleen, lymph node)	Yes/no	[14,25,26,28,32,35,36,41]
Spleen size	Atrophy during acute and chronic stages	Yes	[26,28,32]