Examining mechanisms underlying how spinal cord injuries worsen neuroimmune signaling and immune function

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Abstract

Spinal cord injury (SCI) is defined as damage to the bundle of nerves and nerve fibers that transmit signals throughout the body. SCI is commonly linked to paralysis and loss of sensation, but it can also have a profound impact on the immune system. Examples of these impacts include changes in the timing of the immune response, immune organ dysfunction, and excessive inflammation. The present literature review examines the consequences of SCI on immune function, evaluating changes in inflammatory signaling, immune organ function, and communication between the nervous and immune systems. Evidence suggests that SCI can cause overactive inflammation and immune suppression, leaving one vulnerable to infections and other long-term complications. The severity of these effects often depends on the region where the injury happens as well as the completeness of the injury. Recent studies have suggested classifying SCI as a neurological and immunological disorder and that a deeper understanding of neuroimmune interactions may help in developing better future treatments and patient outcomes.

Introduction

Annually, approximately 18,000 people in the United States experience a traumatic spinal cord injury (SCI) (Spinal Cord Injury Facts and Figures at a Glance 2012). SCI is defined as damage to the bundles of nerves and nerve fibers that transmit signals across the body (*Spinal Cord Injury*, n.d.). Primary causes of SCI include automobile crashes, falls, gunshot wounds, and more (Chen et al., 2013). Paralysis and loss of sensation are the most common consequences of SCI, but the effects go far beyond the nervous system (Bauman et al., 2012). Increasingly, research has demonstrated that spinal cord injuries can result in profound changes in immune function, leading to a greater susceptibility to infections and other health issues. For example, people with SCI are estimated to be 37 times more likely to die from pneumonia than people without such injuries, due to the serious consequences of immune dysfunction after SCI (Burns, 2007).

Infections continue to be one of the leading causes of illness and death in persons with SCI despite advances in emergency care and rehabilitation. Scientists have come to understand that spinal cord damage disrupts communication between the nervous system and the immune system, altering inflammatory signaling, immune organ function, and even the body's ability to fight disease. It is important to understand these changes not only to explain why infections are so common after SCI but also to develop new treatments that can improve long-term outcomes. This review examines how SCI alters immune function and considers whether immune dysfunction is best understood as a core feature of SCI rather than a secondary complication.

Body Section 1: An in-depth look at Spinal Cord Injuries

The spinal cord is crucial for communication between the brain and the rest of the body. For this reason, the spinal cord is an important component of the central nervous system (CNS), which consists of the brain and spinal cord and is important for coordinating many functions throughout the body. Structurally, the spinal cord is divided into many different regions. From top to bottom, the regions are cervical, thoracic, lumbar, sacral, and coccygeal. Each region of the spinal cord controls different sensory functions.

Spinal cord injuries

Spinal Cord Injuries (SCI) occur when trauma or disease damages the neural pathways in the spine, disrupting the transmission of signals between the brain and the organs. The

location of spinal cord injury varies from person to person. The severity and symptoms of the injury depend on the location and the extent of the damage. For example, cervical spine injuries, which occur near the neck region, are often the most severe and will most likely result in tetraplegia (paralysis affecting all of the limbs as well as the torso region). In addition, cervical spine injuries lead to impaired respiratory control due to the disruption of nerves that help control the diaphragm. Other SCIs include thoracic spinal cord injuries that affect the upper torso and may lead to paraplegia, and lumbar injuries that generally impair lower limb movement and sensory function.

Beyond the loss of motor function and sensory abilities, injuries to the spinal cord initiate a cascade of physiological consequences that extend far beyond the site of impact. SCI can be very broadly categorized into primary and secondary injury phases. The primary injury refers to the initial damage to neurons, glial cells (support cells that protect, regulate, and nourish neurons), and blood vessels at the moment of trauma. However, much of the long-term damage associated with SCI occurs during the secondary injury phase. This phase involves hyperinflammation and neuronal cell death. These processes can unfold over hours to weeks following the initial injury, and they significantly contribute to the progression of neurological damage. Patients with SCI often experience both acute symptoms, such as swelling, hemorrhage, and neurological impairment, and chronic complications, including inflammation, pain, dysfunction, and an increased chance of getting infections. These effects can lead to a weakened immune system.

To understand how SCI weakens the immune system, it is essential to understand the immune system itself. The immune system is composed of various cells, proteins, and pathways that work together to defend against infection or injury by providing rapid and effective immune responses to protect the body. The immune system is generally divided into two main categories: the innate and adaptive immune systems.

Innate and adaptive immune system

The innate immune response is considered the first line of defense (Dettmer, 2021, #) It consists of immediate immune responses to an infectious invasion or tissue damage. Some examples of the main cells (lymphocytes) in the innate immune response include macrophages and neutrophils. Macrophages are cells that engulf pathogens and damaged tissue while releasing cytokines (signaling molecules), while neutrophils release antibacterial substances and enzymes to eliminate pathogens (Dettmer, 2021, #).

Dendritic cells are important in linking the innate and adaptive sides of the immune system. Dendritic cells capture pathogens and break them into smaller pieces for the lymphocytes to build a more specific immune response (Harryvan et al., 2021). The circulating proteins of the complement system, located in plasma, are additional components and can directly destroy cells through the membrane attack complex (MAC) system or indirectly by supporting phagocytosis in other cells (Dettmer, 2021, #). But if the pathogens are not beaten after several hours, the innate response begins to slow down. This is when the adaptive immune system is necessary, as it can allow for long-term immunity against a disease that is causing a large problem in the body.

The adaptive component of the immune system is more specialized and longer-lasting when responding to pathogens. The adaptive immune system works by recognizing an antigen in a highly specific way (Dettmer, 2021, #). The adaptive immune system is activated when dendritic cells present processed antigen to T-cells in lymphoid tissue. Once a T-cell becomes activated, it will then undergo differentiation into T-cell subsets: T-helper cells and T-cytotoxic

cells (Dettmer, 2021, #). B-cells are also an important component of adaptive immunity. After being activated by T-helper cells, they differentiate into plasma cells, which generate antibodies. Antibodies are proteins that bind specifically to foreign antigens and neutralize pathogens and allow for more leukocyte communication (Dettmer, 2021, #).

However, after an SCI, the immune system starts to behave differently. Without help from the spinal cord, the immune system is unable to coordinate like normal.

Section 2: Cytokines

Cytokines are small proteins that act as vital chemical messengers in the immune system. Cytokines coordinate the start of inflammation, which immune cells are recruited, how strongly the cells respond, and whether the tissue shifts toward damage containment or repair. After SCI, cytokines do not simply turn on after injury and then turn off again. Instead, research shows a more complicated pattern. Cytokine signaling is necessary for debris clearance and wound response, but when it becomes excessive or dysregulated, it contributes to secondary damage, chronic inflammation, and impaired host defense. This is why cytokine signaling after SCI is often described as both protective and pathological.

SCI rapidly induces pro-inflammatory and chemoattractant cytokines at the lesion site (site of injury or inflammation), showing that inflammatory signaling is not a secondary side note to injury, but part of the core pathophysiology of SCI itself (Pineau & Lacroix, 2006). In a mouse model, Bartholdi and Schwab reported early expression of pro-inflammatory cytokines and chemokines (a subsection of cytokines that lead leukocytes to the site of injury) after SCI, helping define the now widely accepted idea that trauma to the cord triggers an immediate molecular inflammatory cascade (Bartholdi & Schwab, 1997).

Within that acute cascade, several cytokines repeatedly appear as central mediators. Some main examples are TNF-α, IL-1β, IL-6, and interferon-related signaling pathways. The literature generally agrees that TNF-α and IL-1β are among the earliest and most strongly pro-inflammatory signals after SCI (Li et al., 2022). Their early rise helps activate resident glia and increase endothelial permeability (Li et al., 2022). These cytokines can also recruit additional immune cells into the damaged cord, which can support clearance of necrotic debris but can also intensify secondary tissue injury (Li et al., 2022). Reviews on inflammatory cytokine regulation in SCI emphasize that cytokines operate in a context-dependent manner (Bartholdi & Schwab, 1997). Some signals that amplify inflammation in the acute stage may also participate in survival and repair depending on timing and cellular context (Bartholdi & Schwab, 1997). In that sense, the field has moved away from a simple “pro-inflammatory bad, anti-inflammatory good” framework and toward a temporal interpretation, where the same signaling pathway may be adaptive early and maladaptive if sustained (Bartholdi & Schwab, 1997).

This timing issue is one of the most important themes in the SCI inflammation literature. Acute inflammation is usually framed as an unavoidable and functional response to injury, whereas chronic inflammation is framed as a major contributor to long-term morbidity. One key finding shifts attention away from the lesion alone and toward the broader systemic inflammatory state that often persists after SCI (Allison & Ditor, 2014). The findings of this study suggest that SCI is commonly associated with a chronic low-grade inflammatory condition rather than a short-lived immune event, and they connect this persistent inflammation to autonomic disruption, endocrine changes, recurrent infections, reduced mobility, altered body composition, and other secondary complications (Allison & Ditor, 2014). Their framing is important because it expands the inflammatory story beyond the acute injury site: inflammation after SCI is not just

local neuroinflammation in the cord, but an ongoing whole-body problem that may shape long-term health and recovery (Allison & Ditor, 2014).

Taken together, research presents cytokine signaling after SCI as a temporal and functionally complex process. In the acute phase, cytokines such as TNF-α, IL-1β, and IL-6 support inflammation and tissue response. But when these signals persist or become dysregulated, they contribute to chronic inflammation and immune dysfunction. This combined perspective underscores that cytokine activity after SCI is not simply excessive but fundamentally misregulated, making it a critical target for understanding both recovery and long-term complications.

Section 3: Immune Organs

Spinal cord injury not only alters immune signaling at the lesion site. It can also suppress the function of major immune organs, including the spleen, bone marrow, and lymphatic system. The spleen is especially important because it stores immune cells and supports antibody responses while acting as a major site where innate and adaptive immune responses interact. The spleen is described as the largest mammalian lymphatic organ, and it plays an important role in immune defense and blood filtration (Noble et al., 2018). After SCI, however, the spleen can become a site of neuroimmune dysfunction rather than normal immune coordination. A key primary study showed that SCI can impair antibody synthesis in a lesion-level-dependent manner (Lucin et al., 2007). Their study measured HPA-axis activity, splenic norepinephrine, and antigen-specific antibody production after high- versus low-level SCI, directly linking spinal injury level with altered splenic immune regulation. The research supports the idea that splenic immune suppression is not random, but connected to loss of descending nervous system control over sympathetic preganglionic neurons (Lucin et al., 2007). Later work also found that norepinephrine levels in the spleen rise early after SCI, and splenic sympathetic signaling contributes to neutrophil infiltration into the injured spinal cord (Monteiro et al., 2020). Together, these studies suggest that SCI can distort splenic function through sympathetic dysregulation. The spleen may release or alter immune cells in ways that intensify acute inflammation while weakening normal adaptive immunity.

Bone Marrow Alterations

The bone marrow is another major immune organ affected by SCI because it is responsible for hematopoiesis, the production of new blood and immune cells. Carpenter et al. showed in mice that SCI causes a rapid and chronic bone marrow failure syndrome marked by excessive hematopoietic stem and progenitor cell proliferation, accumulation, and impaired function (Carpenter et al., 2020). Their finding is important because it connects SCI to long-term immune consequences beyond the spinal cord itself. If bone marrow output becomes abnormal, the body may struggle to generate properly functioning immune cells, helping explain why immune dysfunction can persist chronically after SCI. This bone marrow disruption fits into the broader framework of spinal cord injury-induced immune depression syndrome, or SCI-IDS. In a major clinical study, Kopp et al. found that SCI patients can develop a secondary neurogenic immune deficiency characterized by reduced monocytic HLA-DR (specific cell receptors on B cells) expression and relative hypogammaglobulinemia (an immune disorder characterized by low levels of antibodies), reflecting both cellular and humoral immune impairment (Kopp et al., 2023). Earlier work on humans also showed that immune suppression can begin rapidly after SCI, with major reductions in monocytes, T lymphocytes, B lymphocytes, and HLA-DR-positive cells within 24 hours (Riegger et al., 2008). These findings show that SCI-IDS is not simply a

late complication. Immune suppression can begin early and can continue through chronic changes in immune-cell production and function.

Section 4: Impact of spinal cord injury level and severity on immune dysfunction

Not all spinal cord injuries affect the immune system in the same way. One of the most important findings in SCI research is that the level and severity of the injury strongly influence how much immune dysfunction develops afterward. In general, injuries higher on the spinal cord, such as the cervical and thoracic, tend to produce more severe immune suppression because they disrupt more autonomic nervous system pathways. The autonomic nervous system controls automatic body functions such as heart rate, blood pressure, hormone release, and communication with immune organs like the spleen. When these pathways are damaged, the brain can no longer properly regulate immune activity.

A study clearly demonstrated this idea by using mouse models. The researchers compared mice with high thoracic injuries at the T3 level to mice with lower thoracic injuries at T9. They found that mice with T3 injuries produced significantly fewer antibodies after immune stimulation than mice with T9 injuries (Lucin et al., 2007). Lower antibody production means that the adaptive immune system is significantly weaker. The researchers made another connection due to the alteration of the sympathetic nervous system's control of the spleen. In particular, spinal cord injuries above the level of T3 resulted in changes in the concentration of norepinephrine in the spleen. Norepinephrine is the neurotransmitter that plays a role in the stress response. However, at elevated concentrations, norepinephrine tends to suppress immune responses. As T3 injuries lead to more interruptions in the functioning of the sympathetic nervous system compared to T9 injuries, their impact is more destructive (Lucin et al., 2007). Further investigation has shown that communication within the neuroendocrine-immune system is impaired following SCI. According to research, changes in autonomic and hormonal messaging in the post-injury state can cause a suppression of immune cells' function and result in infections like pneumonia and UTIs (Rodgers et al., 2022).

However, injury level alone does not fully predict immune outcomes. Many studies focused on complete SCIs, where communication through the spinal cord is almost entirely lost below where the injury happened. However, incomplete SCIs are more common in patients, meaning that not all nerve tracts are damaged. One study has shown that incomplete injuries do not necessarily result in the conventional finding of increased immune suppression the higher the level of injury (Hong et al., 2019). Some autonomic tracts are left functional after injury (Hong et al., 2019). This finding is clinically important because incomplete SCIs are common in human patients. Immune outcomes seem to exist along a spectrum that is affected by injury severity and the extent of remaining neural connectivity rather than a simple rule that greater injury necessarily leads to more immune dysfunction. Recognizing these differences could help investigators develop more personalized strategies to predict risk of infection and treat immune dysfunction after SCI (Kopp et al., 2023).

Section 5: Therapeutic Implications

The increasing recognition of immune dysregulation following spinal cord injury (SCI) has significant implications for patient management and future treatment development. For many years, SCI was seen as a neurological problem involving movement and sensation. However, today's research suggests that SCI can also influence normal immune function, making the individual more susceptible to infections and other long-term health problems. Spinal cord

injury-induced immune depression syndrome (SCI-IDS) has thus become an important topic of study. Understanding the impact of SCI on the immune system could help researchers develop therapies to enhance recovery and general health outcomes.

One possible therapeutic option is to re-establish normal communication between the nervous system and the immune system. A primary study explains that SCI can disrupt autonomic and hormonal pathways involved in immune response regulation (Rodgers et al., 2022). When these pathways are damaged, immune organs like the spleen can malfunction, resulting in a weakened immune system and higher susceptibility to infections (Rodgers et al., 2022). Researchers are therefore investigating whether targeting these disrupted pathways could help reduce immune suppression after injury (Rodgers et al., 2022).

Another important area of research is the identification of patients at high risk for the development of severe immune dysfunction. Research suggests that biomarkers such as lymphopenia (a condition characterized by drastic drops of T and B cells) and spikes of pro-inflammatory cytokines (like IL6) in SCI-IDS could help physicians identify immune suppression earlier and follow up patients more effectively (Riegger et al. 2009). Identifying high-risk patients earlier might give clinicians a chance to intervene before they develop more serious infections like pneumonia or urinary tract infections.

Concluding Remarks

Spinal cord injury (SCI) is generally considered to be a disorder of sensation and movement; however, the research reviewed in this paper shows that the implications of SCI are far beyond the nervous system. Changes in cytokine signaling after injury induce inflammatory responses that may be beneficial to tissue repair but may also contribute to long-term damage. SCI can also affect the function of the major immune organs, such as the spleen and bone marrow, which leads to immune suppression and increased risk of infection. Moreover, the degree of immune changes is modulated by factors such as the level and completeness of injury, underscoring the complex interaction between nervous and immune systems.

A major strength of the reviewed research is that it provides a consistent link between nervous system injury and immune dysfunction. Studies helped to establish the role of injury level in immune responses (Lucin et al., 2007), and other works extended these findings to clinically relevant concepts such as SCI-induced immune depression syndrome (Kopp et al., 2023). Together, these studies provide compelling evidence that immune dysfunction is an important component of SCI rather than a secondary complication.

But there are a few limitations. Much of the foundational research has been done in animal models, which are useful in identifying biological mechanisms but may not fully reflect the diversity of human spinal cord injuries. Furthermore, many studies focused on specific immune pathways or short periods of time after injury, which makes it difficult to understand how immune dysfunction develops over decades of living with SCI. Future research would benefit from more long-term human studies and a focus on how age, type of injury, and individual patient differences affect immune outcomes.

Overall, the current findings suggest that SCI should be viewed as both a neurological and immunological disorder. Continued research into the interaction between the nervous and immune systems may lead to new approaches that improve recovery, reduce infection risk, and enhance quality of life for individuals living with spinal cord injuries. Future work should explore new therapies that could reverse the effects of SCI in patients.

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