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What is the Role of Immune Cells in the Pathophysiology Post Spinal Cord Injury?

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Abstract

Introduction: Spinal cord injury triggers a host of immune responses that involve the release of Damage-associated molecular patterns (DAMPs), which in turn activate an inflammatory response. The inflammatory response following Spinal cord injuries (SCI) often becomes dysregulated and hyperactive, therefore giving way to secondary injury. This review focuses on the acute, ≤7 days, phase of SCI and discusses how various immune cells, including neutrophils, macrophages, microglia, and T cells, orchestrate SCI pathology. Elucidating these early-phase immune dynamics is very important because the degree of secondary tissue damage and the recovery outcome depend upon the nature of the initial immune response.

Methods: We synthesized primary studies dealing with immune cell behavior after SCI, focusing on neutrophils, macrophages, microglia, and T cells. Articles were identified from PubMed, MEDLINE, Embase, Cochrane, and McGill Library databases, considering studies in mouse models with experimental contusions or crush injuries. The articles were reviewed based on their investigation of immune infiltration and temporal immune responses.

Results: The acute immune response following SCI consists of rapid neutrophil infiltration within hours and a peak at 12-24 hours, which frequently correlates with the severity of the lesion. T-regulatory lymphocytes (Tregs) are recruited early on and help to modulate the inflammation, while microglia and macrophages follow and enter inflammatory states within one to three days. It was shown that while these cells promote injury, they also contribute to both injury and repair.

Conclusion: The early immune response after SCI is understudied. Gaining a more holistic understanding of it could allow us to develop immunotherapies which target and alter the inflammatory process during this critical window. Theoretically, medicines aimed at minimizing or preventing additional tissue damage and improving long-term recovery could be made possible by identifying the molecular drivers of early inflammation. According to the review, the acute period of SCI is an important topic for further exploration to guide treatments that aim to balance the early immune responses.

Keywords: spinal cord injury; acute inflammation; immune response; neutrophil infiltration; T cells; hyperinflammation; secondary injury; repair; immunomodulatory; recovery

Introduction

Spinal cord injuries (SCI) are a major public health issue, impacting 27 million individuals worldwide, with an estimated 930,000 new cases annually [1]. SCI frequently leads to permanent motor and sensory impairments which reduce the individual's quality of life. Additionally, SCI requires significant investment from healthcare systems, imposing a long-term obligation on medical professionals. Despite the severe consequences and prevalence of SCI, there is still no cure capable of preventing or reversing secondary damage after injury.

The spinal cord is a hub, controlling the motor and sensory functions of the body. The ascending sensory pathways transmit afferent information from peripheral receptors to the brain and brainstem [2]. They convey modalities of touch and proprioception through the dorsal column, and pain and temperature through the anterolateral column, two highly organized tracts within the spinal cord [2]. Descending myelinated pathways originate in the brain and brainstem, and complement the ascending pathways. They transmit motor commands to lower motor neurons located in the ventral horn of the spinal cord [3]. These neurons are organized into segmentally arranged pools that innervate specific muscles along a top-to-bottom axis [3].

Due to the highly organized nature of the spinal cord anatomy, the consequences of any given SCI greatly depend on the severity of injury, location along the spinal cord, and the specific region of the spinal cord that was injured [2]. Mild or localized injuries can cause sensory or motor deficits or weakness, while more severe, widespread injuries can lead to more major losses in sensation, dysfunction, or complete paralysis [2]. Additionally, injuries occurring at higher (rostral) levels of the spinal cord typically produce more extensive impairments than those at lower (caudal) levels [2].

SCI is typically caused by blunt-force trauma and commonly occurs in accidents involving motor vehicles, falls, or sports injuries. The severity of injuries is classified using the American Spinal Injury Association (ASIA) Impairment Scale [4] and ranges from ASIA A, defined as complete injury with no preserved motor or sensory function below the level of injury, to ASIA E, defined as normal neurological function. Grades (B–D) represent progressively greater preservation of motor and sensory strength. The spinal cord contains critical regions that are necessary for movement, such as the cauda equina, which contains spinal nerves controlling lower limbs; the ventral horn, where motor neurons originate; and tracts of white matter containing myelinated axons conveying information to and from the brain. As a result, even mild injuries can cause temporary sensory changes or partial weakness. More severe injuries can result in complete paralysis, loss of sensation, or permanent dysfunction.

At the moment of trauma, a primary injury occurs, involving compression or tearing of neural tissue and blood vessels. Injured cells immediately release damage-associated molecular patterns (DAMPs), ATP (Adenosine Triphosphate), and other alarmins, which activate resident microglia and recruit circulating neutrophils within hours post-injury. Monocytes follow shortly after, which differentiate into macrophages upon entering the spinal cord [1]. Over the next hours to days post-injury (dpi), a secondary injury cascade develops, driven by oxidative stress, excitotoxicity, ischemia, and an exacerbated inflammatory response. Although inflammation is necessary for the clearing of debris, excessive immune activation can lead to a chronic hyperinflammatory state, causing further neuronal loss and worsening overall outcomes [5]. Microglia are among the first immune cells to respond after SCI, as they are resident cells present at the injury site. They rapidly react to DAMPs, becoming activated in the process and increasing their phagocytic activity and production of inflammatory mediators. Like macrophages, microglia can shift into different states: the M2 anti-inflammatory phenotype, which helps with cleanup and healing by releasing supportive molecules, or the M1 inflammatory phenotype, which releases inflammatory agents, including Tumor Necrosis Factor alpha (TNF-α), Interleukin-1 beta (IL-1β), and Reactive Oxygen Species (ROS) that can exacerbate the damage [6]. Early after injury, microglia tend to take on the M1 state, which results in a hyperinflammatory state. However, transitioning toward the M2 state can improve debris clearance and aid in recovery.

Neutrophils recruited by the release of DAMPs and chemokines are the first circulating immune cells to arrive at the injury site, showing up within minutes to a few hours after SCI [7]. They cross the damaged blood-spinal cord barrier and demonstrate a fast, aggressive response, releasing ROS, enzymes, and pro-inflammatory cytokines. While their early activity helps clear debris and contain damage, it often amplifies tissue injury and contributes to prolonged inflammation. Their numbers peak within the first 1–3 dpi, then taper off as other immune cells take over. Circulating monocytes enter the injured spinal cord 1–3 dpi, where they differentiate into macrophages [8]. At 7 dpi, these cells, together with activated microglia, dominate the lesion environment. Macrophages also display the same M1 and M2 activation states as seen in microglia, where M1 represents a pro-inflammatory state that contributes to injury, while M2 represents a restorative state that promotes wound healing. These activation states significantly shape the injury environment. Early post-injury, monocytes often adopt a dominant M1 phenotype, contributing to the secondary wave of injury, while M2 activation is present but remains limited and insufficient to counteract the inflammatory environment. T cells infiltrate the spinal cord later in the response, peaking around day 9 post-injury. Once activated by Central Nervous System (CNS) antigens exposed during tissue disruption, $CD4^+$ and $CD8^+$ (Cluster of Differentiation) T cells release pro-inflammatory cytokines, including Interferon gamma (IFN-γ) and TNF-α, which amplify M1 activity in microglia and macrophages [9]. Some T cells also exhibit autoimmune responses against neuronal antigens, further harming surviving axons. Their sustained presence prolongs inflammation and inhibits the ability to maintain a stable repair environment, limiting functional recovery [10].

The early immune response, particularly within the first 7 dpi, is an aspect of SCI that remains under-researched, despite its critical impact on hyperinflammation in the spinal cord. In existing literature today, there is a strong emphasis on the chronic phase of SCI, with few studies investigating how the acute temporal dynamics of immune cells can impact not only inflammation but functional recovery as a whole. This paper aims to fill this gap by examining the role of neutrophils, macrophages, microglia, and T cells in the acute post-SCI phase, with the goal of discussing their contributions to SCI pathophysiology. This understanding is crucial for developing targeted immunotherapies that could improve functional recovery by modulating the early immune response. Thus, this review highlights the critical need for continued research into these biological processes following injury, with a particular focus on the role of immune cells in the acute phase after SCI.

Methods

To investigate the acute inflammation post-SCI, we conducted a synthesis of preclinical and mechanistic studies retrieved from PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, Frontiers, and the McGill Library database system. To find our sources we used a combination of the following search terms: “spinal cord injury,” “acute spinal cord injury,” “SCI mouse model,” “murine SCI,” “mouse contusion spinal cord injury,” “crush spinal cord injury,” “secondary injury cascade,” “acute

inflammation SCI," "neuroinflammation," "cellular infiltration SCI," "neutrophil infiltration," "macrophage polarization SCI," "microglia activation," "microglial states," "T cell infiltration spinal cord," "CD45+ single-cell," "Cxcl1," "Cxcl2," "chemokine expression SCI," "neutrophil recruitment," "BLT1 neutrophil axis," "astrocyte–neutrophil interaction," "regulatory T cells SCI," "flow cytometry spinal cord injury," "immune subsets SCI," "peripheral immune activation spinal cord injury," "NF-κB SCI," "inflammatory cytokines (IL-1β, IL-6, TNF-α)," "white blood cell response SCI," "immune heterogeneity," "systemic immune response spinal cord injury," and "functional recovery inflammatory cells." The studies we used investigated the impact of immune infiltration following SCI during the acute phase in mice, specifically the 1-7 dpi timeframe. The immune cells we looked at specifically include neutrophils, monocytes, macrophages, microglia, and T cells. Studies only included research on mice with experimental SCI, specifically contusions or crush injuries. All the studies were peer-reviewed, primary studies, conducted within the last 20 years. A total of 19 studies and one web article were included in this review.

Results

Neutrophils (0-7 dpi)

All the studies included in this review consistently found that in uninjured mice, there was either no detectable neutrophil infiltration into the spinal cord or very low baseline levels. Neutrophils were either completely absent or near-absent in the spinal cord of uninjured mice [11–13]. Uninjured mice showed clear fractions of neutrophils, monocytes and macrophages in peripheral blood [11].

Across studies, neutrophil infiltration rapidly increased within the first 12 h post-SCI. Flow cytometry showed neutrophil infiltration increased sharply at 12 h and remained elevated through 1 dpi [11]. Neutrophil levels experienced a significant increase to 5.8 ± 1.4% in the spinal cord at 12 h compared to the uninjured sham ($P < 0.001$), accompanied by a rise in circulating neutrophils of 77.2 ± 3.2% compared to 28.9 ± 4.8% in sham mice ($P < 0.001$) [13].

The significant early increase in neutrophils at 12 h in injured adult mice was further verified using the expression of inflammatory cytokines, with significant increases in Cxcl1 ($F(1,28)=16.54$, $p=0.0004$) and Cxcl2 ($F(1,28)=11.08$, $p=0.0024$) compared to sham injury [14].

At 1 dpi, it was consistently found that neutrophil infiltration remained elevated [11, 13, 15, 16]. Elevated neutrophils persisted from 12 h to 1 dpi in injured mice relative to naive mice ($P < 0.05$) [13]. This was further confirmed in a different study, as injured wild-type mice had extremely high neutrophil counts at 1 dpi compared to uninjured sham mice, which contained nearly 0 ($P < 0.0001$) [15]. scRNA-seq was used to further verify the presence of the neutrophils in the spinal cord at 1 dpi. This process emphasized a distinct neutrophil cluster that was not present in the uninjured mice. The cluster was characterized by transcriptional programs related to inflammation initiation, phagocytosis and chemotaxis. This cluster persisted until 3 dpi [16].

At 2 dpi, injured neutrophil levels were still elevated in both the circulating blood and the spinal cord compared to the naive mice ($P < 0.05$). Levels were beginning to trend downwards, however [13]. At 3 dpi, the continued presence of neutrophils within the spinal cord tissues was confirmed using western blot analysis, showing abundant neutrophils at 3 dpi across all mouse strains, while the uninjured mice remained absent of neutrophil infiltration [17]. A decline in neutrophils following their peak at 12 hours was also reported [11].

By 4-5 dpi, neutrophils had declined. At day 4 post injury, both infiltrating and circulating neutrophil levels were similar to those of the sham and naive mice, who did not experience an initial spike in neutrophil levels ($P <0.05$) [13]. These findings were supported by additional data, showing neutrophil levels began returning toward baseline by 5 dpi [18]. However, one study did report that neutrophils remained elevated at 7 dpi relative to the same mice prior to injury, with some variations found between strains (BALB/c < C57BL/6, $P < 0.001$) [17]. This contrasted with other studies, which reported that both infiltrating and circulating neutrophils remained at control baselines at 7 dpi ($P < 0.05$) [13, 18].

Microglia (0-7 dpi)

In uninjured mice, studies consistently reported homeostatic, non-activated microglia. Homeostatic microglia were only detected in uninjured mice using scRNA-seq, with no injury-responsive microglial subtypes identified [19]. Similarly, resident baseline microglial populations were identified in naive and sham controls [13]. Baseline microglial density in uninjured spinal cord tissue was quantified by a separate study at 85.9 ± 4.6 cells/mm² ($P < 0.01$) [20]. At 12 h post-SCI, some studies found decreased homeostatic microglia counts, while others began to detect increased density and early activation of microglia. Significantly elevated CD45^low^CD11b^high^ microglia were detected at 12 h ($P < 0.05$) [13]. Apoptotic cells positive for terminal, deoxynucleotidyl transferase dUTP nick end labeling (TUNEL-positive) were also observed at 12 h near the lesion, though no explicit microglia counts were provided [11]. At 1 dpi, homeostatic microglia transitioned into multiple reactive subclusters expressing complement, phagocytic, and antigen-presentation molecules that were not present in uninjured tissue [16]. At 1 dpi, microglial density at the lesion epicentre had decreased by ~67% to 28.8 ± 1.9 cells/mm² relative to pre-injury density due to apoptosis ($P < 0.0001$) [20].

At 3 dpi, studies found that microglia presented themselves in two activated subpopulations and

Transcriptional profiling showed the two unique groups ($P < 0.001$ vs uninjured) [19]. Subgroups were categorized as Microglia-A and Microglia-B, with gene ontology showing Microglia-A pertained to ATP synthesis, electron transport chain, and oxidative phosphorylation [19]. Microglia-B was not characterized as well in the study, however it was consistently present following SCI [19]. The microglia subclusters were associated with inflammation, complement activation, and phagocytosis [16]. At 3 dpi, there was significant accumulation of activated microglia in the grey matter regions of the spinal cord compared to the uninjured controls ($P < 0.05$) [17].

At 4 dpi, it was found that the microglia began to proliferate. Numerous $Ki67^+$ (a proliferation marker) expressing microglia were found to be present at this stage, with densities rising to 119.1 ± 15.0 cells/mm², exceeding even the uninjured baseline [20]. Microglia at 4 dpi exhibited complete loss of P2ry12 (purinergic receptor P2Y12), high CD68, and reactive morphology, particularly surrounding lesion borders [20].

At 5-7 dpi, reactive microglia became an integral component of the lesion, particularly around the perimeter. $Ki67^+$ microglia peaked at 7 dpi ($p < 0.001$), with dense clustering at the interface between infiltrating leukocytes and nascent astroglial processes [20]. The increase in microglia at this time point around lesions was further confirmed by spatial quantification ($p < 0.01$–0.001, depending on distance) [20]. Through 3–7 dpi, the sustained presence of reactive microglial clusters consistent with early scar formation was also observed [16].

Monocytes and Macrophages (0-7 dpi)

Uninjured controls consistently showed minimal monocyte/macrophage presence in the spinal cord compared to injured mice. Studies found clear fractionation of monocytes/macrophages in peripheral blood but minimal infiltration in uninjured tissue [11].

Uninjured mice contained only homeostatic monocytes and nearly no subclusters of macrophages or monocytes relative to injured mice ($P < 0.05$) [19].

At 12 h post-SCI, monocyte infiltration began. Minimal infiltration was found at 4 h, but by 12 h, monocyte/macrophage numbers increased roughly 13-fold relative to uninjured mice [11]. Parallel increases in inflammatory chemokines associated with monocyte recruitment at 12 h were found, including Ccl2 ($F(1,28)=19.80$, $p=0.0001$) and Ccl3 ($F(1,28)=41.32$, $p<0.0001$) [14]. Other studies however, contrasted these findings, showing that circulating monocytes decreased at 12 h ($P < 0.05$) [13].

At 1 dpi, monocytes differentiated into multiple activated macrophage subsets, including phagocytic macrophages positive for TYRO protein tyrosine kinase binding protein ($Tyrobp^+$) and complement component 1q subcomponent subunit A positive ($C1qa^+$) and regenerative macrophages positive for chitinase-like 3 ($Chil3^+$), $Cd163^+$ and mannose receptor C-type 1 ($Mrc1^+$) (Macro-A/B) [16]. These transcriptional changes were injury-specific and were not present in the uninjured controls [16]. M1-associated iNOS reached peak upregulation levels at 1-3 dpi, in addition to significant increases in M1 surface markers (CD86/CD16/CD32, ANOVA $p < 0.01$, post-hoc $p < 0.05$–0.001 vs uninjured) [12]. M2 markers Arg1 and CD206 were significantly elevated early but returned to baseline by 14 dpi [12]. Circulating monocytes increased significantly at 1 dpi and peaked at 4 dpi, peaking at $12.4 \pm 0.9\%$ at 4 dpi vs $5.7 \pm 1.0\%$ in naïve ($P < 0.01$) [13]. At 3 dpi, dense $CD11b^+$ macrophage clusters were found in the central grey matter that were absent in uninjured tissue [17]. Strain comparisons showed BALB/c < C57BL/6 ($P < 0.001$) [17]. At 3 dpi, a continued expression of phagocytic markers (Tyrobp, C1qa, C1qb) were documented, with increasing expression of regenerative markers (Chil3, Mrc1, Arg1) [16]. By 3 dpi, the emergence of two injury-activated macrophage subsets was documented [19].

Macrophages that were present in small numbers from 1-2 dpi became the dominant infiltrating population by 4 dpi ($P < 0.05$ vs naïve) [13]. Studies which reported systemic increases in circulating monocytes at 3 dpi ($P < 0.01$), found partial normalisation by 5–7 dpi [18].

By 7 dpi, macrophage activation peaked across models. One study reported the highest $CD11b^+$ macrophage activation at this timepoint, with BALB/c mice again showing reduced activation relative to C57BL/6 ($P < 0.001$) [17] and by 7 dpi, the M1/M2 ratio increased significantly ($p < 0.05$–0.001) due to declining M2-positive macrophages [17]. This was further confirmed through the continued observance of regenerative macrophage markers through 7 dpi [12].

T Cells (0–7 dpi)

In all studies, uninjured mice showed a low or negligible presence of T-cells in the spinal cord. Extremely low T-cell numbers were found in naïve and sham mice at all timepoints [13]. Uninjured adult mice also showed low baseline Treg levels [21].

At 6-12 h post-SCI, there was rapid recruitment of $CD4^+CD25^+FoxP3^+$ Tregs, with significant increases at 6 h, peaking at 12 h ($n=5$; $p < 0.01$) compared with uninjured and sham controls [21]. The recruited Tregs expressed significantly higher C-C motif chemokine receptor 10 (CCR10) protein and surface levels relative to sham ($p < 0.01$), while C-C motif chemokine receptor 3 (CCR3) remained unchanged [21]. At 12 h, neutralizing C-C motif chemokine ligand 28 (CCL28) or CCR10 significantly reduced Treg recruitment ($p < 0.01$) while Treg infiltration was significantly increased by recombinant CCL28 ($p < 0.01$) [21]. From 12 h to 4 dpi, circulating $CD3^+$ T cells were significantly reduced compared to naïve ($P < 0.05$) across all measured early timepoints. Spinal cord T-cell levels, however, remained extremely low and did not differ significantly from sham

[13]. At 3 dpi, T-helper 1 (Th1) related cells ($CD4^+$ IFN-γ^+) were decreased ($P < 0.01$), while Tregs were significantly elevated ($P < 0.001$) [18]. Cytokine profiling of splenocytes also showed early decreases in TNF-α, IFN-γ, interleukin-6 (IL-6), interleukin-4 (IL-4), C-X-C motif chemokine ligand 10 (CXCL10), and macrophage colony-stimulating factor (M-CSF), with M-CSF significantly decreased ($P < 0.01$) [18]. TGF-β was reduced at 3 dpi ($P < 0.05$) [18]. By 5 dpi, Tregs were found to have remained elevated ($P < 0.001$), while Th1-like cells remained decreased ($P < 0.001$) [18]. TGF-β also remained significantly reduced ($P < 0.05$) [18].

By 7 dpi, several T-cell subsets became strongly polarized. One study found that T-helper 17 (Th17)-like cells significantly increased ($P < 0.001$) compared to uninjured controls, while Th1-like cells significantly reduced ($P < 0.05$) [18]. Tregs remained significantly elevated at this time point ($P < 0.01$) [18]. CCL28 signalling shaped the cytokine environment at 7 dpi: neutralising CCL28 significantly increased IL-1β, TNF-α, and IL-6 and decreased interleukin-10 (IL-10) ($p < 0.05$–0.01), whereas recombinant CCL28 produced the opposite profile [21]. Following administration of CCL28, effector T-cell proliferation in the spinal cord at 7 dpi was significantly decreased ($p < 0.05$–0.01) [21].

Discussion

SCI is a condition that presents significant sensory and motor impairments, altering millions of lives globally. The results found in this review showed several consistent trends regarding the acute phase of immune response post-SCI all of which influence the trajectory for secondary tissue damage and determine the extent of functional recovery. The results in this review show how the different immune cells interact and how they can worsen SCI outcomes, while also possessing some beneficial function.

The findings showed that neutrophil infiltration into the spinal cord occurs very quickly following injury, and peaks as soon as 12 hours post-injury [11]. The abundance of neutrophil infiltration was also found to be correlated directly with the severity of the injury. Many studies showed that this early infiltration of neutrophils was accompanied by an increase in pro inflammatory cytokines IL-1β, IL-6, and TNF-α. This shows that neutrophils are primary contributors in the initial inflammatory cascade [14]. Neutrophils are rapidly recruited to the lesion due to chemokine gradients generated by damaged neurons and activated glial cells. Once present, they intensify inflammation by ROS', proteases, and NETs, which damage nearby neurons [5]. This direct cytotoxicity worsens the lesion and increases inflammatory signaling, creating a feed-forward loop that continues to recruit additional immune cells. Additionally, the results indicate that neutrophil infiltration is not only an early event but persists for up to 3 days post-SCI, which suggests that sustained neutrophil presence early on, may contribute to prolonged inflammation in later stages post SCI [11, 13]. However, by 4–5 dpi, neutrophil levels decrease and return to baseline, indicating that while neutrophils dominate earlier on, their influence diminishes as the acute response subsides. This clearly indicates that neutrophils play a key role in the acute inflammatory response. It also shows that they are not a significant contributor outside of the acute-subacute phase and into the intermediate/chronic phase.

It was found that microglia cells play a role in the prolonged inflammation after the initial neutrophil infiltration and inflammatory cascade. At 12 hours post-SCI, studies began to show their early activation [13]. This was represented by increased microglial density and the appearance of reactive subclusters expressing phagocytic and complement molecules [13, 16]. These molecules are necessary for debris clearance and immune response and were absent in uninjured spinal cord tissue. This demonstrates how the activation of microglial cells is a direct response to the injury. Overall, the results suggest that microglia and macrophages begin to show signs of inflammation (M1) within 1–3 dpi, with the most prominent activation occurring by day 3 [17]. By day 4, microglia show clear signs of being reactive, including increased cell growth ($Ki67^+$) and the loss of their normal markers like P2ry12 [20]. These reactive microglia then become a major part of the injury site by 5-7 dpi, clustering at the edges of the lesion where they interact with immune cells and early glial cells, forming the scar [13, 17]. The persistent microglia presence particularly around the lesion site, demonstrates microglial injury containment and prevention of further, secondary damage which facilitates the inflammatory response.

Studies also found monocytes and macrophages infiltrate the lesion within the first 12-24 hours [11]. Using flow cytometry data from several studies, it was found that the infiltrated monocyte derived macrophages and resident microglia become activated in the acute phase. It was also found that these cells later transition into inflammatory states that contribute to secondary injury [12]. This transition occurs because when both cell types initially activate, they do not yet take on a fully inflammatory state, but have a mildly reparative state. During this period (0-12 h post injury), they take on the role in clearing debris, removing apoptotic cells, and stabilizing the tissue environment; however, the highly inflammatory environment (12-24h post-injury), rich in DAMPs and cytokines, eventually drives them toward an M1 phenotype [12]. At 12 hours post injury, the infiltration of monocytes and macrophages was increased roughly 13-fold compared to uninjured tissue, as was elevated chemokine expression, particularly Ccl2 and Ccl3, which further drive their recruitment [11, 14]. In this state, they produce TNF-α, IL-1β, and nitric oxide, which kill surviving neurons and inhibit remyelination. This transition to a damaging phenotype explains how they contribute to secondary injury, and it illustrates the difficulty of balancing their

beneficial functions with their amplification of the injury. By 1 dpi, these monocyte-derived macrophages differentiated into distinct subsets, some exhibiting pro-inflammatory M1 markers (iNOS, CD86), while others expressed M2-like markers (Arg1, CD206), showing that they shift from initially protective to predominantly inflammatory states [12]. The results also showed that the elimination of microglia increased the spread of LysM+ myeloid cells by day 14, which significantly worsened locomotor recovery, demonstrating that while microglia are inflammatory, they are also essential for containing peripheral immune cell invasion [17].

The reviewed literature also showcases the involvement of adaptive immune cells during the acute phase. Although the number of T cells decreases relative to uninjured spinal cords as acute inflammation triggers apoptosis or redistribution of T cells to lymphoid organs, they remain present throughout the first week post-SCI, and their activation contributes to prolonged inflammation [22]. The T cells that do infiltrate the spinal cord may still become activated by exposed CNS antigens and contribute to inflammation through cytokine release [23]. At the earliest timepoints (6–12 hours post-injury), studies showed rapid recruitment of $CD4^+CD25^+FoxP3^+$ Tregs to the injury site, with peak Treg infiltration at 12 hours, and significant increases in CCR10 protein expression [21]. This suggests that Tregs are among the first T cell populations to be activated and play an early role in modulating the immune environment. Interestingly, other studies showed that decreasing regulatory Tregs significantly increased pro-inflammatory cytokine expression (GM-CSF, TNF-α, IL-1β, IL-6) and increased microglial activation, indicating that Tregs also play an anti-inflammatory role when overall T cell numbers decrease; demonstrating that T cells are not always bad [18]. However, there is still a lack of information on SCI, specifically regarding the functional implications of these early adaptive immunological shifts. Overall, the studies demonstrate the role of hyperacute immunological activity in influencing the development of secondary injuries, particularly inflammation caused by neutrophils and macrophages. They also highlight the complexities of early immune dynamics, as several innate and adaptive cell types undergo quick, injury-specific phenotypic and functional alterations. Even with these findings, many questions remain; the temporal coordination between neutrophils, monocytes, microglia, and lymphocytes is not yet fully defined, and the mechanisms that regulate their transitions from beneficial to pathological roles remain not fully understood. Addressing these gaps will be essential for developing targeted early-phase immunotherapies capable of minimizing tissue loss and improving functional outcomes after SCI.

Conclusions

The research conducted on the acute period ≤7 days after SCI, has been minimally studied compared to research in the chronic stages. Understanding these early cellular dynamics is critical, as this inflammatory window presents the best time for targeted immunomodulatory treatments to affect injury progression.

These findings underscore the significance of the hyperacute and early acute phase, in which the rapid infiltration and activation of immune cells have a profound impact on long-term functional outcomes. Neutrophil recruitment early on is highly related to injury severity; macrophages and microglia assume inflammatory states; and subtle changes in early adaptive immune functions significantly influence the nature of the inflammatory response. Thus, the emphasis on research into early immune events needs to be revisited since most SCI studies have focused on chronic inflammation.

Further research on the coordination between innate and adaptive immune populations in the first week post-injury, including the mechanisms that drive the switch from M2 (healing) to M1 (inflammatory) states in microglia and macrophages is required. A clearer understanding of these processes could provide insights on how to regulate the overall inflammatory response. The uncertainties on the subject that were made clear in this review should be investigated in future studies using high-resolution temporal sampling and selective targeting of early immune pathways.

Understanding the patterns of immune cells in the acute phase of SCI will be crucial for the development of next-generation immunotherapies. The molecular drivers of early inflammation could inform treatments that reduce secondary tissue loss and perhaps prevent chronic hyperinflammation to improve recovery in the long term. This review emphasizes the importance of continued research on the early immune response and supports developing treatments that target the first days after injury, a time when the potential for altering injury progression is highest.

List of Abbreviations

Abbreviation: Definition
ASIA: American Spinal Injury Association
ATP: Adenosine Triphosphate
C1qa: complement component 1q subcomponent subunit A
C1qb: complement component 1q subcomponent subunit B
CCL28: C-C motif chemokine ligand 28
CCR10: C-C motif chemokine receptor 10
CCR3: C-C motif chemokine receptor 3
CD: cluster of differentiation
Chil3: chitinase-like 3
CNS: Central Nervous System
CXCL10: C-X-C motif chemokine ligand 10
DAMPs: damage-associated molecular patterns
Dpi: Days post injury
IFN-γ: interferon gamma
IL-10: interleukin-10
IL-1β: interleukin-1 beta

IL-1β: interleukin-1 beta
IL-4: interleukin-4
IL-6: interleukin-6
M-CSF: macrophage colony-stimulating factor
Mrc1: Mannose receptor C-type 1
P2ry12: purinergic receptor P2Y12
ROS: and Reactive Oxygen Species
SCI: Spinal Cord Injury
TGF-β: transforming growth factor beta
Th1: T helper 1 cells
Th17: T helper 17 cells
TNF-α: Tumor Necrosis Factor alpha
TNF-α: tumor necrosis factor alpha
Tregs: regulatory T cells
Tregs: T regulatory lymphocytes
TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling
Tyrobp: TYRO protein tyrosine kinase binding protein

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
This manuscript is simply a review of previously published, peer-reviewed studies. It did not involve the collection of new data, nor did it involve experimenting on animals. As such, research ethics board (REB) approval and participant consent were not required.

Authors' Contributions
NSC: made contributions to the design of the study, analyzed the collected data, drafted the manuscript, and gave final approval of the version to be published.
JD: contributed to collecting the data and finding reliable sources, and gave final approval of the version to be published.
NSC & JD: both made substantial contributions to the design of the study, the collection of data, as well as interpretation and analysis of the data, revized the manuscript critically, and gave final approval of the version to be published.

Acknowledgements
The authors would like to sincerely thank Samara Leah Baum for her mentorship throughout this project. Samara provided consistent guidance through weekly meetings, offered detailed feedback, and assisted with editing and revisions at all stages of the work. Her support, insight, and constructive suggestions were valuable to the completion of this paper.

Funding
This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Alex Benedetto
Article Dates: Received Dec 30 25; Accepted Apr 11 26; Published May 31 26

Citation
Please cite this article as follows:
Cheema N.S, Dhir J. What is the role of immune cells in the pathophysiology post spinal cord injury?.
URNCST Journal. 2026 May 31: 10(5). https://urncst.com/index.php/urncst/article/view/1032
DOI Link: https://doi.org/10.26685/urncst.1032