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The multifaceted role of B cells in traumatic spinal cord injury: Antibody-dependent and antibody-independent mechanisms

Serina Rubio, Veerle Somers, Judith Fraussen *

Department of Immunology and Infection, Biomedical Research Institute, UHasselt – Hasselt University, Hasselt, Belgium

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ABSTRACT

A traumatic spinal cord injury (SCI) is caused by an acute insult to the spinal cord that inflicts severe damage to the nerve tissue and leads to impaired motor, sensory, and autonomic functions. After the initial injury, a secondary injury phase occurs, which is characterized by an excessive inflammatory response mediated by resident and infiltrating peripheral immune cells that accumulate within the spinal cord lesion. Increasing evidence supports the involvement of B cells in this secondary injury phase post-SCI. Elevated B cell numbers have been reported following experimental SCI, both within and outside of the spinal cord, as well as in human post-mortem spinal cord tissue. In the injured spinal cord, B cells have been detected at different stages of maturation and have been shown to form ectopic follicle-like structures, indicating their functional relevance post-SCI. Furthermore, enhanced B cell differentiation into antibody-secreting cells has been observed, accompanied by increased (auto)antibody levels against various central nervous system proteins. Importantly, B cell depletion and knockout mouse studies have indicated that B cells could modulate other immune cells and contribute to impaired functional recovery after traumatic SCI, highlighting the potential of targeting B cell responses in the development of more specific and personalized therapeutic strategies for SCI patients. Hence, this review provides a comprehensive overview of recent advances in understanding the role of B cells in traumatic SCI, integrating findings from both animal and human studies.

1. Introduction

Every year, more than 250,000 individuals worldwide suffer from a traumatic spinal cord injury (SCI) (World Health Organization, n.d.; World Health Organization, 2013). The insult to the spinal cord causes severe damage to the nerve tissue, leading to long-term impairment of motor, sensory, and autonomic functions (World Health Organization, n.d.). Depending on the injury level, patients may develop respiratory, bowel, bladder, or sexual dysfunction, as well as suffer from paralysis, neuropathic pain, severe infections, spasticity, and autonomic dysreflexia (National Institute of Child Health and Human Development, n.d.-a). Currently, treatment options for SCI are limited and primarily consist of stabilization and decompression surgery, general immunosuppression, rehabilitation therapy, and treatments for secondary complications (National Institute of Child Health and Human Development, n.d.-b). The extent of the neurological damage is determined using imaging techniques, such as magnetic resonance imaging (MRI), in combination with the International Standards for Neurological Classification of

Abbreviations: Ag, antigen; Ab, antibody; AIS, American Spinal Injury Association Impairment Scale; APCs, antigen-presenting cells; ASCs, antibody-secreting cells; BMS, Basso Mouse Scale; CNS, central nervous system; CRMP2, collapsing response mediator protein-2; CSF, cerebrospinal fluid; CTL, cytotoxic T cell; DC, dendritic cell; DN B cell, double negative B cell; DRG, dorsal root ganglion; ELISA, enzyme-linked immunoassay; ELISPOT, enzyme-linked immunospot; FC, flow cytometry; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GC, germinal center; GFAP, glial fibrillary acidic protein; GM1, GM1 ganglioside; HC, healthy control; HSC, hematopoietic stem cell; ICC, immunocytochemistry; Ig, immunoglobulin; IHC, immunohistochemistry; IL, interleukin; ISNSCI, International Standards for Neurological Classification of Spinal Cord Injury; (BC)KO, (B cell) knockout; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MHC, major histocompatibility complex; MIF, macrophage migration inhibitory factor; NMDA, *N*-methyl-D-aspartate; (h/d/w/m/y)pi, (hours/days/weeks/months/years) post-injury; PBMC, peripheral blood mononuclear cells; SAS, serological antigen selection; SCI, spinal cord injury; scRNA-seq, single-cell RNA sequencing; SM B cell, switched memory B cell; TBI, traumatic brain injury; Th cell, helper T cell; TLR, Toll-like receptor; TNF, tumor necrosis factor; tSNE, t-Distributed Stochastic Neighbor Embedding; UMAP, Uniform Manifold Approximation and Projection; UK, unknown; USM B cell, unswitched memory B cell; WB, western blot; WT, wild-type..

* Corresponding author at: Martelarenlaan 42, Hasselt, Belgium.
E-mail address: Judith.fraussen@uhasselt.be (J. Fraussen).

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Spinal Cord Injury (ISNCSCI) exam, which includes the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (National Institute of Neurological Disorders and Stroke, n.d.; National Institute of Child Health and Human Development, n.d.-c; Roberts et al., 2017). This exam assesses motor, sensory, and anorectal functions to categorize patients into five AIS grades. Grade A represents a complete injury; grade B a sensory incomplete injury; grades C and D motor incomplete injuries, with less than half (grade C) or at least half (grade D) of the key muscles below the neurological level having a muscle grade ≥ 3; and grade E represents normal functioning (Roberts et al., 2017). Following the primary injury phase, additional damage to the spinal cord can be inflicted during a secondary injury phase that lasts up to months after the primary insult (Ahuja et al., 2017). One key aspect of this secondary injury phase is an excessive inflammatory response. Neutrophils constitute the first immune cell population to respond as they infiltrate the lesion site within hours following the primary injury (Carlson et al., 1998; Fleming et al., 2006). During the subsequent days, microglia and monocytes/macrophages infiltrate the spinal cord lesion, followed by lymphocytes within the first weeks post-injury (Fleming et al., 2006; Popovich et al., 1997). More specifically, B cells infiltrated the injured spinal cord within the first week post-SCI in animal models of SCI, while human B cells have predominantly been detected in the spinal cord lesion starting from two weeks after the injury (Ankeny et al., 2006; Ankeny et al., 2009; Fisher et al., 2022; Kumari et al., 2025; Zrzavy et al., 2021; Schwab et al., 2023). Thus, local immune cells, as well as peripherally infiltrated immune cells, can migrate toward the spinal cord lesion and contribute to the long-lasting inflammatory reactions.

Accumulating evidence supports the involvement of B cells in this secondary inflammatory response. Following a traumatic SCI, the blood-spinal cord barrier is disrupted and central nervous system antigens can leak into the circulation (Ankeny and Popovich, 2010). These antigens can (re)activate autoreactive B cells in the secondary lymphoid organs, leading to their proliferation and differentiation into antibody-secreting cells (ASCs). The activated B cells and ASCs can then migrate toward the spinal cord lesion to exert their different inflammatory functions (Ankeny and Popovich, 2010). ASCs produce antibodies of different immunoglobulin (Ig) isotypes, which can have protective or pathological effects by activating the complement system, neutralizing toxins, bacteria, and viruses, opsonizing them for phagocytosis, or activating other effector cells of the immune system (Janeway et al., 2001). However, B cells can also exert important antibody-independent functions. B cells are antigen-presenting cells (APCs) capable of effectively inducing both $CD4^+$ helper T (Th) and $CD8^+$ cytotoxic T cell (CTL) responses through antigen presentation on major histocompatibility complex (MHC) molecules and through costimulation via expression of costimulatory molecules, such as CD80, CD86, and CD40 (Rastogi et al., 2022). Moreover, B cells can produce a variety of pro- and anti-inflammatory cytokines and chemokines that have wide-ranging effects. For example, lymphotoxin is important for the proper development and functioning of secondary lymphoid organs, interleukins (ILs) and tumor necrosis factor (TNF) are involved in the regulation of $CD4^+$ Th cell responses, and IL-10 functions as an anti-inflammatory cytokine (Shen and Fillatreau, 2015).

Over the years, both antibody-dependent and -independent B cell functions have been investigated in the context of traumatic SCI. However, the exact contribution of B cells to spinal cord pathology, as well as the therapeutic potential of targeting B cell-related processes, remain incompletely defined. Current evidence, predominantly from mouse studies, suggests a detrimental role for B cells following traumatic SCI. In this review, we summarize recent advances in understanding the role of B cells in traumatic SCI, encompassing both antibody-dependent and -independent mechanisms, providing a comprehensive overview of findings from both animal and human studies. In this way, we explore how B cell responses can contribute to the progression of secondary injury and impaired functional recovery following traumatic SCI.

2. B cell development and subsets

Human B cells ($CD19^+$) originate in the bone marrow from hematopoietic stem cells (HSCs) that undergo functional rearrangements in their Ig gene segments. Cells that successfully form and express IgM molecules on the cell surface are called immature B cells (Pieper et al., 2013; LeBien and Tedder, 2008). These cells further differentiate into transitional B cells ($IgM^+IgD^+CD24^{high}CD38^{high}$) that translocate to the periphery and develop into naive B cells ($IgM^+IgD^+CD27^-$) (LeBien and Tedder, 2008; Beckers et al., 2023; Carsetti et al., 2022). Naive B cells are mature cells that continuously recirculate between the blood, lymph, and secondary lymphoid organs in search of their cognate antigen (Carsetti et al., 2022). Upon recognition of their specific antigen in the secondary lymphoid organs, naive B cells can enter different developmental pathways (Fig. 1). Depending on the antigen structure, B cells will differentiate into ASCs and memory B cells through either T-independent or T-dependent pathways. T-independent activation results in the generation of short-lived ASCs as well as unswitched memory (USM; IgD^+CD27^+) B cells (Beckers et al., 2023; MacLennan et al., 2003). In contrast, the germinal center (GC) pathway is T-dependent and can elicit more specific and targeted responses. Somatic hypermutations occur in the Ig genes during the process of affinity maturation, after which high-affinity B cells are selected with the help of follicular dendritic cells and antigen-specific follicular Th cells. In addition, Ig isotype switching can take place. In this way, long-lived ASCs, IgM-only, and switched memory (SM; IgD^-CD27^+) B cells are formed (Beckers et al., 2023; De Silva and Klein, 2015; Fryer et al., 2022). A T-dependent but GC-extrinsic pathway also exists in which Ig isotype switching can occur, producing short-lived ASCs (Fryer et al., 2022). Both short- and long-lived ASCs are responsible for the production of different Ig isotype antibodies that can have protective as well as pathological functions. Furthermore, memory B cells create a reservoir of antigen-experienced cells that can rapidly expand and generate new ASCs in a secondary immune response, while also functioning as APCs and producing a variety of inflammatory cytokines (LeBien and Tedder, 2008). A final B cell subset, called double negative (DN) B cells, is defined as being negative for both IgD and CD27. DN B cells comprise a small fraction of B cells and their origin and development remain poorly understood. Three main DN B cell subsets have been identified in the literature and are hypothesized to originate from different developmental pathways, as reviewed in (Beckers et al., 2023). Briefly, DN1 B cells ($CD21^+CD11c^-$) are suggested to prematurely exit the GC reaction and function as precursors of SM B cells or originate from these SM B cells. DN2 ($CD21^-CD11c^+$) and DN3 ($CD21^-CD11c^-$) B cells were shown to originate from the GC-independent pathway, either from activated naive B cells or USM B cells, and further differentiate into ASCs (Beckers et al., 2023). Although it is suggested that DN B cells primarily function as precursors of ASCs and memory B cells, it is also hypothesized that these cells are involved in antibody-independent functions, including antigen presentation and pro-inflammatory cytokine production (Beckers et al., 2023).

Important differences in B cell development, subsets, and abundance have been identified between humans and mice. There are discrepancies in signaling pathways involved in early B cell development, but also in the expression of B cell surface markers and in the composition of Ig subclasses (Gordon et al., 2001; Mestas and Hughes, 2004). These species-specific differences in the B cell population are thoroughly discussed in (Garraud et al., 2012; Benitez et al., 2014; Weisel and Shlomchik, 2017). Given the differences in B cells between the two species, animal and human studies investigating B cells following traumatic SCI were discussed separately in the following sections.

3. B cells in traumatic SCI animal studies

Studies investigating the role of B cells in SCI are limited and have been performed almost exclusively in mouse models. In these studies, B cells have been investigated both systemically and within the spinal

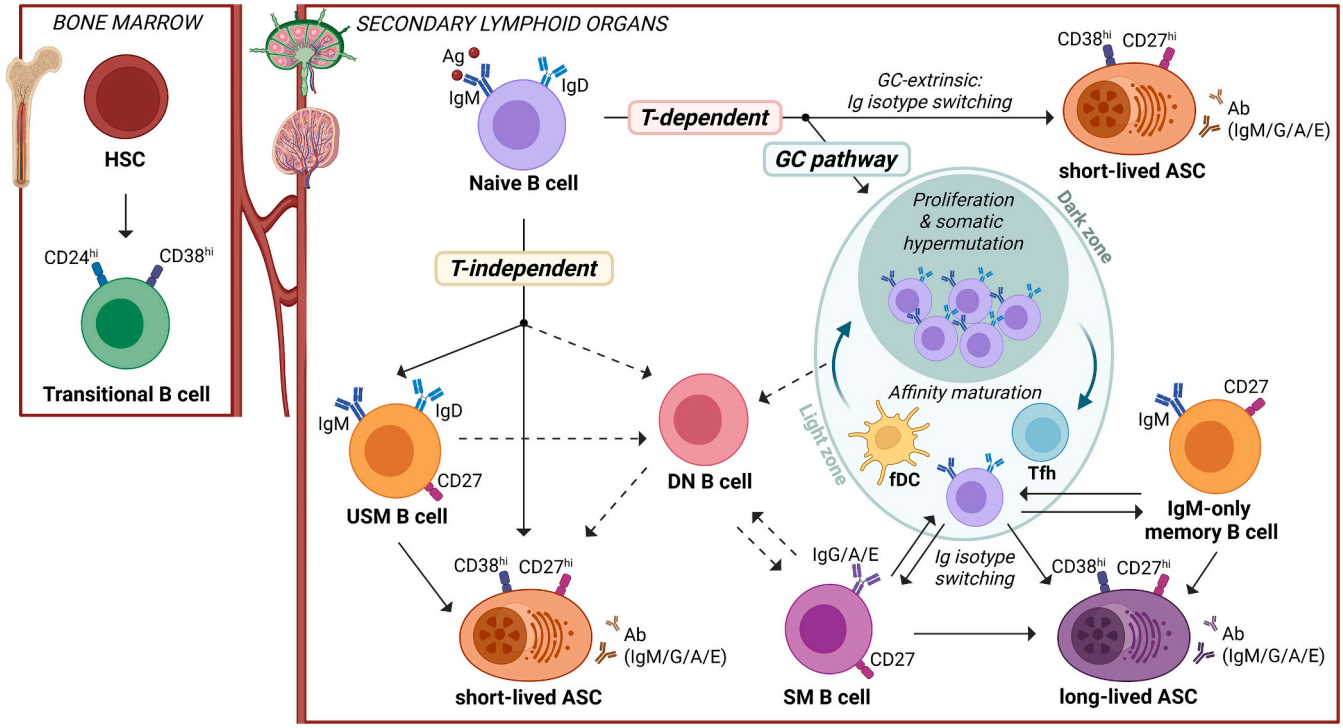

Fig. 1. B cell development. B cells ($CD19^{+}$) originate from HSCs in the bone marrow. They develop into transitional B cells ($IgM^{+}IgD^{+}CD24^{high}CD38^{high}$), translocate to the peripheral blood, and further differentiate into naive B cells ($IgM^{+}IgD^{+}CD27^{-}$). When naive B cells encounter their specific antigen in the secondary lymphoid organs (e.g., spleen and lymph nodes), they can proceed into different developmental pathways depending on the antigen structure. T-independent activation generates short-lived ASCs and USM B cells ($IgD^{+}CD27^{+}$). In contrast, the GC pathway is T-dependent and elicits more specific and targeted responses of SM B cells ($IgD^{-}CD27^{+}$), IgM-only memory B cells, and long-lived ASCs. During affinity maturation, somatic hypermutations occur in the Ig genes which leads to the generation of high-affinity B cells that are selected with the help of follicular DCs and antigen-specific follicular Th cells. In addition, Ig isotype switching can take place. A T-dependent but GC-extrinsic pathway also exists in which Ig isotype switching occurs to produce short-lived ASCs. DN B cells ($IgD^{-}CD27^{-}$) comprise a small fraction of B cells and are hypothesized to originate from different developmental pathways. DN B cells might prematurely exit the GC reaction and function as precursors of SM B cells or originate from these SM B cells. Alternatively, DN B cells might originate from the GC-independent pathway, either from activated naive B cells or USM B cells, and further differentiate into ASCs. Figure created with BioRender.com. *Ag, antigen. Ab, antibody. ASCs, antibody-secreting cells. (f)DCs, (follicular) dendritic cells. DN, double negative. GC, germinal center. HSC(s), hematopoietic stem cell(s). Ig, immunoglobulin. SM, switched memory. T(f)h cells, (follicular) helper T cells. USM, unswitched memory.*

cord, with a primary focus on antibody-dependent functions. The following sections provide an overview of studies focusing on B cells and (auto)antibodies in animal models of traumatic SCI (Table 1).

3.1. Dynamics of (auto)antibodies following SCI

In C57BL/6 mice with a T10 contusion SCI, serum IgM antibodies were reduced at 3 days post-injury compared to sham mice, whereas IgG antibody levels remained unchanged (Wu et al., 2023). In contrast, SCI induced IgM production between 7 and 14 days post-injury and IgG2a production between 14 and 42 days post-injury, while IgG1 production was reduced between 7 and 28 days post-injury in the sera of C57BL/6 mice with a T9 contusion SCI (Ankeny et al., 2006). These serum antibodies could bind to central nervous system (CNS) proteins isolated from brains and spinal cords of naive C57BL/6 mice. Moreover, injection of SCI sera in the hippocampus of uninjured mice resulted in the recruitment of microglia and astrocytes, as well as neuronal loss (Ankeny et al., 2006). Similarly, when antibodies that were isolated from sera of C57BL/6 mice with a T9 contusion SCI at 42 days post-injury were injected into the spinal cords (T12) of naive mice, they induced infiltration of $CD68^{+}$ microglia/macrophages, damaged the spinal cord tissue, and caused hindlimb paralysis with partial recovery at 7 days post-injury (Ankeny et al., 2009). These studies highlight the pathological relevance of (auto)antibodies following traumatic SCI.

Interestingly, differences in antigen-specific antibody production have been observed in C57BL/6 mice that were subjected to SCI at different neurological levels. At 14 days post-injury, a T3 transection SCI reduced circulating IgG1 antibody levels compared to sham mice, while a T9 transection SCI did not alter IgG1 antibody production (Lucin et al., 2007). Similarly, serum IgG, not IgM, antibody production was affected following a T3 crush injury, which was not observed in mice with a T9 crush injury (Oropallo et al., 2012). This highlights that antibody production post-SCI is affected by the neurological level of the injury.

3.2. Changes in B cells after experimental SCI

When analyzing B cells in the periphery, C57BL/6 mice with a T10 contusion SCI presented with reduced splenic $CD19^{+}$ B cell numbers at 3 days post-injury compared with sham mice (Wu et al., 2023). In addition, C57BL/6 mice with a T3 transection SCI displayed increased apoptosis of splenic $CD19^{+}$ B cells, as well as reduced spleen weights, at 3 days post-injury compared to sham mice (Lucin et al., 2007). At 8 days post-injury, T3 as well as T9 crush SCI reduced the proportions of B cells at different developmental stages (pro-, pre-, immature, transitional) in the bone marrow and spleen of C57BL/6 mice, which were (partially) recovered at 28 days post-injury (Oropallo et al., 2012). In contrast, $CD45R/B220^{+}$ B cell numbers were significantly increased in the spleen of C57BL/6 mice with a T9 contusion injury from 7 to 28 days post-injury, with the highest numbers seen at 14 days post-SCI (Ankeny et al., 2006). In the bone marrow, decreased immature and increased mature B cell frequencies were observed at 3 days post-injury following a T1 or T3 transection SCI (Carpenter et al., 2020; Pruss et al., 2017), consistent with the increased mature B cell numbers that were detected at 14 days post-injury following a T9 contusion injury (Ankeny et al.,

Table 1
Overview of studies focusing on B cells in animal models of traumatic SCI.

Measured outcome	Technique	Source material	Results (+ all measured time points)	Animal, injury level & type	Ref.
Antibodies					
IgM	ELISA	Serum	↓ at 3dpi	Mouse, female, T10 contusion	(Wu et al., 2023)
			Highest ↑ at 7dpi (1d, 7d, 14d, 28d, 42d)	Mouse, female,	(Ankeny et al., 2006)
		CSF	↓ at 63dpi in BCKO mice	T9 contusion	(Ankeny et al., 2009)
IgG		Serum	↑ in IgG2a and ↓ in IgG1 (1d, 7d, 14d, 28d, 42d)		(Ankeny et al., 2006)
			↓ in IgG1 at 14dpi in T3, not T9, SCI mice	Mouse, female, T3 or T9 transection	(Lucin et al., 2007)
			↓ in IgG at 28dpi in T3, not T9, SCI mice	Mouse, female, T3 or T9 crush injury	(Oropallo et al., 2012)
		CSF	↓ at 63dpi in BCKO mice	Mouse, female,	(Ankeny et al., 2009)
	IHC	SC tissue	↓ at 42dpi in BCKO mice	T9 contusion	
Cells					
B cells	FC	Splenocytes	↓ at 3dpi	Mouse, female, T10 contusion	(Wu et al., 2023)
			↑ apoptotic $CD19^+$ cells at 3dpi	Mouse, female, T3 or T9 transection	(Lucin et al., 2007)
			↓ at 8dpi (8d, 28d)	Mouse, female, T3 or T9 crush injury	(Oropallo et al., 2012)
			↓ $CD19^+$ cells at 3dpi	Mouse, female, T1 or T9 transection	(Pruss et al., 2017)
			Highest ↑ at 14dpi (1d, 7d, 14d, 28d)	Mouse, female	(Ankeny et al., 2006)
		Bone marrow	↑ at 14dpi (1d, 14d)	T9 contusion	
			↓ at 8dpi (8dpi, 28dpi)	Mouse, female, T3 or T9 crush injury	(Oropallo et al., 2012)
			↑ mature and ↓ immature B cells at 3dpi	Mouse, male & female, T3 transection	(Carpenter et al., 2020)
				Mouse, female, T1 transection	(Pruss et al., 2017)
	IHC	Spleen	↑ IgG^+ cells at 42dpi	Mouse, female	(Ankeny et al., 2006)
	scRNA-seq	SC tissue	Largest $CD45^+$ cell population at 60dpi (7d, 60d)	T9 contusion	(Fisher et al., 2022)
	IHC	SC tissue	Highest ↑ at 6wpi (2d, 6w)	Pig, male & female, T10 contusion/compression	(Kumari et al., 2025)
ASCs	ELISPOT	Splenocytes	↑ IgM^+ and $IgG2a^+$ ASCs at 14dpi	Mouse, female, T9 contusion	(Ankeny et al., 2006)
	FC		↓ $IgG1^+$ ASCs in T3, not T9, SCI mice at 42dpi	Mouse, female,	(Oropallo et al., 2012)
			↓ IgM^+ ASCs at 32dpi	T3 or T9 crush injury	
		Bone marrow	↓ $IgG1^+$ ASCs at 42dpi		
Cytokines					
Pro-inflammatory cytokines	IHC and WB	SC tissue	↓ IL-12 A, IL-1β, and TNF-α after anti-CD20 Ab injection at 24hpi	Mouse, male, T5-T8 compression	(Casili et al., 2016)
Functional outcome					
Infiltration	IHC	SC tissue	↑ $CD68^+$ microglia/ macrophages after SCI Ab injection (7d)	Serum Ab of T9 contusion female mice at 42dpi	(Ankeny et al., 2009)
			↓ $CD45^+$, $CD19^+$, $CD11\beta^+$, $CD4^+$, $CD8\beta^+$, $Iba1^+$ and $GFAP^+$ cells after anti-CD20 Ab injection at 24hpi	Mouse, male, T5-T8 compression	(Casili et al., 2016)
Ectopic follicle-like structures			Formation at 42dpi (7d, 28d, 42d)	Mouse, female,	(Ankeny et al., 2006)
			Formation at 42dpi (3d, 28d, 42d)	T9 contusion	(Fisher et al., 2022)
Recovery					
Hind limb motor function	BMS scale	*Not applicable*	Impaired after SCI Ab injection (0 to 7d)	Serum Ab of T9 contusion female mice at 42dpi	(Ankeny et al., 2009)
			Improved in BCKO mice from 42dpi (0d, 1d, 7d, 14d, 21d, 28d, 35d, 42d, 49d, 56d, 63d)	Mouse, female, T9 contusion	
			Improved after anti-CD20 Ab injection up to 6wpi (0w, 1w, 2w, 3w, 4w, 5w, 6w)	Mouse, male, T5-T8 compression	(Casili et al., 2016)
Spinal cord integrity	IHC	SC tissue	Damaged after SCI Ab injection (7d)	Serum Ab of T9 contusion female mice at 42dpi	(Ankeny et al., 2009)
			Smaller lesion volume, and tissue sparing in BCKO mice at 63dpi	Mouse, female, T9 contusion	
			Preservation after anti-CD20 Ab injection at 24hpi	Mouse, male, T5-T8 compression	(Casili et al., 2016)

Time points are depicted as hours (h), days (d), weeks (w,) months (m) or years (y) post-injury (pi). ↑, increased; ↓, decreased.
Abbreviations: Ab, antibody. ASCs, antibody-secreting cells. BCKO, B cell knockout. BMS, Basso mouse scale. CSF, cerebrospinal fluid. ELISA, enzyme-linked immunoassay. ELISPOT, enzyme-linked immunospot. FC, flow cytometry. GFAP, glial fibrillary acidic protein. Ig, immunoglobulin. IHC, immunohistochemistry. IL, interleukin. TNF-α, tumor necrosis factor-α. scRNA-seq, single-cell RNA sequencing. SC, spinal cord. SCI, spinal cord injury. WB, western blot.

2006). In the same study, ELISPOT analysis revealed increased numbers of IgM^+ and $IgG2a^+$ ASCs in the spleen of SCI mice at 14 days post-injury. At 42 days post-SCI, activated (PNA^+) germinal centers and $Ki67^+$ proliferating cells were evident, as were IgG^+ cells, in the spleens of SCI mice compared to sham mice (Ankeny et al., 2006). However, for both groups, immunohistochemistry (IHC) images of only one animal were shown. At 32 or 42 days post-injury, mice with a T3, but not T9, crush SCI displayed reduced bone marrow and splenic $IgG1^+$ ASC numbers, while splenic IgM^+ ASC numbers were reduced after both a T3 and T9 injury (Oropallo et al., 2012). As the spinal cord segments

between T4 and T9 provide sympathetic innervation of the spleen (Noble et al., 2018), SCI lesions above T4 have been associated with reduced spleen size and decreased CD19$^+$ B cell numbers in both the spleen and lymph nodes compared to T9 SCI (Pruss et al., 2017; Brommer et al., 2016). However, current evidence suggests that the altered B cell dynamics following high-thoracic SCI are not directly caused by denervation of lymphoid organs. Instead, loss of supraspinal inhibition after high SCI lesions increases sympathetic nerve activity and subsequent splenic norepinephrine levels, thereby promoting splenic atrophy and B cell apoptosis (Brommer et al., 2016). In addition, disrupted innervation of other abdominal organs, such as the adrenal glands, may further contribute to the observed splenic atrophy and B cell apoptosis through glucocorticoid accumulation in the circulation and lymphoid organs (Pruss et al., 2017; Schwab et al., 2014). These findings indicate that post-SCI B cell responses are mediated, at least in part, by injury level-dependent neuroimmune and neuroendocrine mechanisms.

When analyzing intraspinal B cells, over time, increasing numbers of B cells infiltrated the spinal cord of C57BL/6 mice following a T9 contusion injury. Interestingly, these intraspinal B cells formed ectopic follicle-like structures together with infiltrated T cells, and expressed MHC class II molecules at 42 days post-injury (Ankeny et al., 2006). Similarly, single CD45R/B220$^+$ B cells were found at 3 days post-injury in the spinal cord of C57BL/6 mice with a T9 contusion (Fisher et al., 2022). At 28 days post-SCI, these B cells started to form small clusters that developed into bigger follicle-like structures at 42 days post-injury. Further, single-cell RNA sequencing was performed on spinal cord tissue blocks, containing the lesion epicenter, of Swiss-Webster mice with and without a T9 contusion injury (Fisher et al., 2022). Within the CD45$^+$ cell population, B cells were the second largest population in the spinal cord at 7 days post-injury and the largest population at 60 days post-injury. Uniform Manifold Approximation and Projection (UMAP) analyses also revealed the presence of B cells at different maturation stages (pro-, pre-, immature, mature, activated, and antigen-presenting B cells) in the spinal cord of these contused SCI mice (Fisher et al., 2022). Pathway enrichment analysis of B cells showed the upregulation of pathways involved in the regulation of neutrophils, including degranulation or activation, at 7 days post-SCI. In contrast, IL-23-mediated signaling pathways and pathways involved in glucose metabolism and post-translational modifications were upregulated at 60 days post-injury (Fisher et al., 2022). Lastly, CD79a/B220$^+$ B cells were present in the spinal cord of Yucatan miniature pigs with a T10 contusion/compression SCI at 2 days post-injury, and were significantly increased at 6 weeks post-SCI (Kumari et al., 2025).

Thus, circulating B cell numbers appear to fluctuate after SCI, with an initial decrease shortly after the injury followed by a rapid increase thereafter. B cells can infiltrate the spinal cord and, depending on the timing post-SCI, can be found in different maturation states. In this context, they contribute to the inflammatory pathways and regulation of other immune cells, such as neutrophils.

3.3. *Effects of B cell manipulation on spinal cord integrity and functional recovery*

Because B cells were found in the spinal cord of animals with a SCI, B cell knockout (KO) and depletion studies were conducted to investigate their contribution to the secondary damage following injury. In a first study, IgH-6 B cell KO C57BL/6 mice, lacking mature B cells, with a T9 contusion SCI were used (Ankeny et al., 2009). These B cell KO mice exhibited improved functional recovery, as evidenced by increased Basso Mouse Scale (BMS) scores, up to 63 days post-injury. Additionally, they presented with smaller lesion volumes and sparing of both white and gray matter in the spinal cord. IgM and IgG antibodies were almost absent in the cerebrospinal fluid at 63 days post-injury and no IgG expression was seen in the spinal cord at 42 days post-injury in B cell KO mice compared to the wild-type (WT) mice (Ankeny et al., 2009). In a second study, CD1 mice with a T5-T8 clip compression SCI were treated with an anti-CD20 monoclonal antibody (18B12) that was intraperitoneally injected at 1 and 6 h after SCI induction (Casili et al., 2016). At 24 h post-injury, B cell-depleted SCI mice presented with increased sparing of white matter and a lower histological score compared to non-treated SCI mice. The latter was defined by histological assessment of hematoxylin and eosin staining of the spinal cord for inflammatory cell infiltration, neuronal vacuolization, and hemorrhage. However, only one image per experimental group and no individual histological scores were shown. Further, B cell depletion significantly improved functional recovery of the mice up to 6 weeks post-injury (Casili et al., 2016). At 24 h post-injury, histological and western blot analyses of spinal cord tissue showed decreased IL-12 A, IL-1β, TNF-α, and glial fibrillary acidic protein (GFAP) expression in B cell-depleted SCI mice in comparison with non-treated SCI mice. Both IL-1β and TNF-α colocalized with GFAP$^+$ astrocytes and Iba1$^+$ microglia in the spinal cord, and were decreased in B cell-depleted SCI mice as visualized using immunofluorescence. As expected, the number of CD19$^+$ B cells in the spinal cord was decreased in SCI mice treated with the anti-CD20 antibody. These mice also had reduced numbers of intraspinal CD45$^+$ leukocytes, CD11b$^+$ innate immune cells (monocytes/macrophages and natural killer cells), CD4$^+$, and CD8β$^+$ T cells (Casili et al., 2016). It must be noted that all IHC stainings were performed on spinal cord sections from the perilesional area. Taken together, these studies showed that B cells play a role in the secondary processes that occur after a SCI, not only by influencing functional recovery but also other immune cells.

4. B cells in traumatic SCI human studies

In addition to animal studies, B cells have also been investigated in the peripheral blood and post-mortem spinal cord tissue of patients with SCI. The following sections discuss human studies on traumatic SCI in which the presence and function of (auto)antibodies, ASCs, and B cells were investigated (Table 2).

4.1. *Presence of (auto)antibodies post-SCI*

Evidence for the involvement of B cells in human studies mainly comes from the presence of (auto)antibodies following traumatic SCI. A first study detected increased IgM antibody levels specific for GM_1 ganglioside (anti-GM_1), as well as anti-myelin-associated glycoprotein (MAG) antibodies ($p = 0.058$), in sera from chronic SCI patients ($n = 24$; >1 year post-injury, with a mean of 10.3 years post-injury) compared to healthy controls (HC; $n = 26$) (Hayes et al., 2002). Similar results were found for anti-GM_1 IgG antibodies in sera of SCI patients ($n = 56$) compared to HC ($n = 35$) (Davies et al., 2007). Twenty-four out of 56 patients had suffered from a SCI less than 1 year prior to sampling (i.e., between 2 and 52 weeks post-injury), and 34 out of 56 patients were in the chronic phase (i.e., >1 year post-injury). This study also indicated that patients with neuropathic pain and/or urinary tract infections had higher anti-GM_1 IgG antibody levels compared to patients without these secondary complications (Davies et al., 2007). Additionally, increased IgG antibody levels specific for myelin basic protein (MBP) were detected in sera from chronic SCI patients ($n = 12$; >10 years post-injury, with a mean of 19.55 years post-injury) compared to HC ($n = 18$) (Zajarias-Fainsod et al., 2012). In subacute SCI patients ($n = 38$; 16 ± 7 days post-injury), anti-GFAP antibodies were identified in the plasma and were increased in patients compared to HC ($n = 19$), which was not seen for chronic SCI ($n = 80$; >1 year post-injury) (Hergenroeder et al., 2016; Hergenroeder et al., 2018). These anti-GFAP antibodies were predictive for the development of neuropathic pain within 6 months after the injury and their prognostic value was significantly enhanced when measured in combination with anti-collapsing response mediator protein-2 (CRMP2) autoantibodies (Hergenroeder et al., 2018).

These studies primarily examined antibody responses against targets that had previously been identified in other CNS disorders. However,

Table 2
Overview of studies focusing on antibodies, ASCs, and B cells in traumatic SCI in humans.

Measured outcome	Technique	Results (+ all measured time points)	SCI vs HC	Clinical data SCI	Clinical data HC	Ref.
(Auto-)antibodies						
IgM	ELISA	↑ anti-GM_1 and anti-MAG IgM in serum of SCI patients more than 1ypi (mean time from injury: 10.3y)	n = 24 vs *n* = 26	Chronic SCI (AIS – A: *n* = 9, B: *n* = 6, C: *n* = 8, D: *n* = 1) with age 36.8 ± 9.8 and 79% males	Age 35.8 ± 8.2 63% males	(Hayes et al., 2002)
IgG	ELISA	↑ anti-GM_1 IgG in serum of SCI patients at different stages (less than 1ypi: 2w-52wpi and more than 1ypi) ↑ anti-GM_1 IgG in serum of SCI patients with neuropathic pain and/or urinary tract infections	n = 56 vs *n* = 35	Subacute to chronic SCI (AIS – A: *n* = 14, B: *n* = 13, C: *n* = 22, D: *n* = 7) with age 40.6 ± 11.9 and 75% males	Age 35.1 ± 9.8 52% males	(Davies et al., 2007)
	ELISA	↑ anti-MBP IgG in serum of SCI patients more than 10ypi (mean time from injury: 19.55y)	n = 12 vs *n* = 18	Chronic SCI (AIS – A: *n* = 6, B: n = 6) with age 33 ± 6 and 67% males	Age 32 ± 5	(Zajarias-Fainsod et al., 2012)
	IHC and ICC	Serum IgG from SCI patients at 10wpi binds substantia gelatinosa in the dorsal horn, and/or primary DRG neurons of Sprague Dawley rats (1w, 10w)	*n* = 55 vs *n* = 19	Subacute and intermediate SCI (AIS – A: *n* = 33, B: *n* = 4, C: n = 6, D: *n* = 12) Motor complete: age 51 (39–63) and 84% males Motor incomplete: age 59 (48–72) and 89% males	Control subjects with vertebral injuries without SC damage: Age 45 (29–58) 63% males	(Schwab et al., 2023)
	IHC	Serum IgG from SCI patients binds spinal cord tissue of Wistar rats (31d)	n = 52 vs *n* = 16	Intermediate SCI (AIS – A: *n* = 39, B: n = 4, C: *n* = 8, D: n = 1) with age 40.6 ± 2.2 and 88% males	Age 45 ± 2.8 81% males	(Arevalo-Martin et al., 2018)
	2D-WB and MS	Serum IgG from SCI patients binds GFAP, MBP and neurofilament (31d)				
	SAS	↑ antibody reactivity in SCI patients against (parts of) S100B and GAPDH (48 h, 3w)	*n* = 51 vs *n* = 49	Traumatic and pathologic SCI (AIS A – E) with age 57 ± 16 and 82% males	Age 55 ± 17 65% males	(Palmers et al., 2016)
		Identification of a panel of 3 novel antibody targets with ↑ antibody reactivity in SCI patients with AIS improvement (15d-30d) 2 novel antibodies with ↑ antibody reactivity in SCI with injury level < T4	*n* = 76	Subacute/ intermediate SCI (AIS improvers: *n* = 32, AIS non-improvers: *n* = 42; >T4: *n* = 80–81, <T4: n = 33) with age 50 (IQR: 34) and 87% males	*Not applicable*	(Pues et al., 2026)
IgA	Immunoturbidimetric assay	↑ serum IgA in high complete, not in low complete, SCI patients (15 h, 64 h, 7d, 14d, 10w)	≥T4, *n* = 20; <T4, n = 16 vs *n* = 41	High complete SCI (≥T4) with age 54 ± 19 and 80% males Low complete SCI (<T4) with age 44 ± 14 and 68.8% males	Age 49 ± 16 63.4% males	(Kopp et al., 2023)
Ig (not specified)	Capillary WB	↑ anti-GFAP Ig in plasma of SCI patients at 16dpi (16d, >1y), predictive for neuropathic pain together with anti-CRMP2 Ig	saSCI, n = 38; cSCI, n = 80 vs n = 19	Subacute SCI (AIS – A: *n* = 23, B: n = 3, C: n = 8, D: n = 4) with age 43.5 ± 17.7 and 89% males Chronic SCI (AIS – A: *n* = 28, B: *n* = 21, C: *n* = 11, D: n = 12, UK: n = 8) with age 44.1 ± 14 and 74% males	Age 35 ± 13.2 80% males	(Hergenroeder et al., 2018)
Cells						
B cells	IHC	$CD20^+$ and $CD79a^+$ B cells present in post-mortem spinal cord tissue of some SCI patients between 15dpi to 36dpi (<1d-413d)	n = 22	Acute to chronic SCI with age 33 to 80 years and 72% males	*Not applicable*	(Zrzavy et al., 2021; Schwab et al., 2023)
	High-dimensional FC	↑ IgA^+, IgM^+, naive, and SM B cells in chronic SCI patients ((sub)acute: 0d-3wpi and chronic: 6w- > 18wpi) ↑ frequency $CD74^+$ B cells and CD74 surface expression in SCI patients	n = 18 vs n = 18	≤1 month and > 1 month post-SCI (AIS – A: n = 6, B: n = 3, C: n = 3, D: n = 6) with age 56 and 89% males	Age 56 89% males	(Fraussen et al., 2022)
		Upregulation of complete MIF/CD74 axis in SCI patients	n = 51 vs *n* = 47	Acute to chronic SCI with age 57 ± 17 and 78% males	Age 56 ± 17 and 78% males	(Rubio et al., 2026)
ASCs	IHC	IgM^+ $CD138^+$ ASCs present in post-mortem spinal cord tissue of some SCI patients between 15dpi to 36dpi (<1d-413d)	n = 22	Acute to chronic SCI with age 33 to 80 years and 72% males	*Not applicable*	(Zrzavy et al., 2021; Schwab et al., 2023)
Functional outcome						
Proliferation and activation	In vitro assay	↓ B cell proliferation and activation following CD74, CD44, or MIF inhibition in primary B cell cultures	n = 10 vs *n* = 10	Subacute/intermediate SCI with age 47.6 ± 17 and 70% males	Age 48 ± 17 and 70% males	(Rubio et al., 2026)
Cytokine production	LEGENDPlex Immunoassay	↓ IL-1β, TNF-α, IL-6, and IL-10 production following CD74 or MIF inhibition in primary B cell cultures				

Time points are depicted as hours (h), days (d), weeks (w), months (m) or years (y) post-injury (pi). ↑, increased; ↓, decreased.
Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale. CRMP2, collapsing response mediator protein-2. DRG, dorsal root ganglion. ELISA, enzyme-linked immunoassay. FC, flow cytometry. GAPDH, glyceraldehyde 3-phosphate dehydrogenase. GFAP, glial fibrillary acidic protein. GM_1, GM_1 ganglioside. HC, healthy control(s). ICC, immunocytochemistry. Ig, immunoglobulin. IHC, immunohistochemistry. IL, interleukin. MAG, myelin-associated glycoprotein. MIF, macrophage migration inhibitory factor. SAS, serological antigen selection. (a/c)SCI, (acute/chronic) spinal cord injury. SM B cells, switched memory B cells. TNF, tumor necrosis factor. UK, unknown. WB, western blot.

unbiased approaches to identify antibody targets have also been used. A study published in 2018 reported that overall IgG antibody serum levels were increased in SCI patients ($n = 52$; 31 days post-injury) compared to HC ($n = 16$) (Arevalo-Martin et al., 2018). Moreover, these IgG antibodies strongly bound to spinal cord tissue isolated at 14 days post-injury from Wistar rats with a T8 contusion/short compression SCI, as shown by IHC. This study revealed that IgG antibodies colocalized with neurofilament, GFAP, and adenomatous polyposis coli. Using two-dimensional western blot and mass spectrometry, SCI antibody reactivity was seen against spinal cord proteins isolated from human pathological and healthy spinal cord tissue, primarily targeting GFAP, MBP, and neurofilament (light and intermediate) (Arevalo-Martin et al., 2018). Another group showed that IgG antibodies in the serum of traumatic SCI patients, collected at 10 weeks post-injury, bound to specific regions in spinal cord tissue, more specifically, the substantia gelatinosa in the dorsal horn, and to primary dorsal root ganglia (DRG) neurons from Sprague Dawley rats (Schwab et al., 2023). Serum IgG antibodies at 1 week post-injury did not bind to the substantia gelatinosa in the dorsal horn; however, it is not clear whether this was also true for the primary DRG neurons. Interestingly, patients that showed double immunoreactivity (against the substantia gelatinosa and DRG neurons) were treated earlier and more frequently with neuropathic pain medication (Schwab et al., 2023). Lastly, our group used serological antigen selection (SAS) to identify novel antibody targets in SCI (Palmers et al., 2016). In a first study, a cDNA phage display library generated from healthy human spinal cord tissue was screened for SCI-associated antibodies using pooled plasma samples of 10 traumatic SCI patients obtained within 48 h and 3 weeks post-injury. Some of the identified antibody targets encoded parts of known proteins, such as S100B and glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and showed (higher) antibody reactivity in SCI patients when compared with HC ($n = 49$). This was observed in both traumatic SCI patients ($n = 25$, sampled at 48 h and 3 weeks post-injury) and pathological SCI patients ($n = 26$, sampled preoperatively and 3 weeks post-surgery) (Palmers et al., 2016). More recently, both a healthy and a SCI cDNA phage display library were screened to identify novel antibody targets using plasma samples from SCI patients ($n = 11$–12) collected at 15–30 days post-injury (Pues et al., 2026). Antibodies against six novel peptide autoantigens were identified. A panel comprising three of these antigens showed potential prognostic value, with increased antibody reactivity observed in SCI patients who demonstrated AIS grade improvement (31.3%) compared to those without AIS improvement (4.8%), corresponding to a positive likelihood ratio of 6.56 (Pues et al., 2026). Furthermore, two of the six novel antibodies displayed increased reactivity in SCI patients with an injury level below T4 in comparison to patients with higher injury levels (Pues et al., 2026). The effect of injury level on antibody production has also been observed in another study that found increased serum IgA antibody levels in SCI patients with a high complete injury, and not in patients with a low complete SCI, compared to a control group (i.e., patients with a vertebral fracture without SCI) (Kopp et al., 2023). Although not as thoroughly investigated as in animal models of SCI, the level of injury also seems to affect (auto)antibodies in human SCI.

Together, the results indicate that ASCs respond to SCI by producing (auto)antibodies against various CNS antigens that remain present up to years following the injury.

4.2. Distribution of B cells and ASCs post-SCI

B cells and ASCs have been detected in human post-mortem spinal cord tissue isolated from traumatic SCI patients ($n = 22$) at different stages post-injury (Zrzavy et al., 2021; Schwab et al., 2023). In 6 out of 22 SCI patients, $CD20^+$ or $CD79a^+$ B cells were observed, whereas IgG^+ and IgM^+CD138^+ ASCs were seen in 2 out of 22 SCI patients. B cells and ASCs were mostly found around 15 days post-injury, but could still be detected up to 36 days post-injury (Zrzavy et al., 2021; Schwab et al., 2023). Although detailed clinical information was provided for all included SCI patients, it was not stated whether there were similarities in the subset of SCI patients that displayed infiltration of B cells and ASCs in the spinal cord lesion.

High-dimensional flow cytometric analysis on peripheral blood mononuclear cells (PBMC) isolated at ≤1 month and > 1 month post-injury from SCI patients ($n = 18$) and HC ($n = 18$) revealed a shift in the B cell compartment post-SCI (Fraussen et al., 2022). t-Distributed Stochastic Neighbor Embedding (tSNE) analysis showed B cell subset clustering based on Ig expression, with a highly dense IgA^+ SM B cell cluster at >1 month post-injury compared to ≤1 month post-injury and HC. This was supported by the increased frequencies of IgA^+ and SM B cells found in SCI patients at >1 month post-injury. These patients also showed increased frequencies of naive and IgM^+ B cell subsets. Furthermore, IgG^+ B cells were negatively correlated with injury severity, which was the opposite for IgM^+ B cells, meaning that patients with a more severe injury (i.e., AIS A) had fewer circulating IgG^+ B cells and more IgM^+ B cells compared to patients with a less severe injury (i.e., AIS E) (Fraussen et al., 2022).

Lastly, in silico analyses were performed on the GSE151371 dataset, comprised of chip-based RNA-sequencing data from peripheral blood of acute traumatic SCI patients ($n = 38$; median 23 h post-injury), trauma patients without CNS injury ($n = 10$; median 20 h post-injury), and HC ($n = 10$) (Kyritsis et al., 2021). In a first study, single-sample gene set enrichment analysis (ssGSEA) on the GSE151371 dataset revealed decreased levels of activated, immature, and memory B cells in the SCI group compared to the control group (HC and non-CNS trauma patients combined) (Li et al., 2022). In contrast, CIBERSORT analysis revealed decreased levels of naive B cells in SCI patients compared to HC and non-CNS trauma patients separately (Li et al., 2022). Another research group analyzed the same dataset with CIBERSORT, but excluded the trauma patients without CNS injury from the analysis (Li et al., 2024). Here, SCI patients showed increased levels of naive B cells and ASCs and decreased levels of memory B cells compared to HC (Li et al., 2024). Although the same dataset and analytical tool were used in both studies, it is unclear whether the observed differences are due to the exclusion of non-CNS trauma patients or if other parameters, not mentioned, influenced the results.

4.3. Antibody-independent function of B cells post-SCI

Next to their involvement in the production of CNS-directed autoantibodies, evidence also supports additional roles for B cells in the pathological processes post-SCI. In a high-dimensional immune profiling study, including traumatic SCI patients at ≤1 month and > 1 month post-injury, we reported that post-SCI B cell responses were characterized by increased frequencies of $CD74^+$ cells and elevated CD74 expression levels within total B cells and B cell subsets, compared to HC (Fraussen et al., 2022). CD74 serves as a surface receptor for the cytokine macrophage migration inhibitory factor (MIF), which has already been shown to be upregulated in the injured spinal cord, primarily in astrocytes and microglia, where it also regulated their function (Wang et al., 2011; Su et al., 2017; Zhou et al., 2018; Zhu et al., 2019; Zhang et al., 2019; Zhang et al., 2023). MIF binding to CD74 induces the recruitment of additional receptors, including the co-receptor CD44 and CXC-motif chemokine receptors (CXCR) 2, 4, and 7 (Jankauskas et al., 2019). In B cells, activation of this MIF/CD74 axis promotes survival, proliferation, migration, and cytokine production, as reviewed in (Rubio et al., 2024). To further investigate the role of MIF and CD74 in post-SCI B cell responses, we recently mapped the entire MIF/CD74 axis across the immune system and assessed its impact on B cell function following traumatic SCI (Rubio et al., 2026). Interestingly, we showed that not only CD74, but the complete MIF/CD74 axis, was upregulated following the injury. Plasma MIF levels were significantly increased in SCI patients compared to HC. In addition, surface expression of MIF receptors was elevated, and the frequencies of $CD74^+$, $CD44^+$, and $CXCR4^+$ B cell

subsets were increased during the subacute/intermediate phases post-SCI. Reduced intracellular MIF expression in circulating immune cells from SCI patients, compared to HC, suggested that the injured spinal cord is the main source of the elevated systemic MIF levels following SCI (Rubio et al., 2026). Importantly, blocking of CD74, CD44, or MIF in primary B cell cultures from both SCI patients and HC resulted in decreased B cell proliferation, activation, and cytokine production. These effects were more pronounced in SCI B cells, highlighting the potential of targeting the MIF/CD74 axis as a therapeutic strategy (Rubio et al., 2026). Collectively, these findings support a role for MIF/CD74-mediated B cell pathways in SCI-associated neuroinflammation and warrant further investigation into their potential for immunomodulatory intervention.

5. B cells in other CNS injuries

B cells are also involved in other CNS injuries, including traumatic brain injury (TBI) and stroke. Below, a brief discussion of B cell responses in these conditions is included to provide comparative context for B cell responses in SCI and to highlight shared and divergent immunological mechanisms across acute CNS injuries. As thorough literature review on this topic is available elsewhere (Javidi and Magnus, 2019; Maheshwari et al., 2023; Aspden et al., 2023), the following sections briefly discuss several studies that focused on B cells and (auto)antibodies in TBI and stroke.

5.1. Traumatic brain injury

Similar to SCI, TBI is characterized by primary and secondary injury mechanisms whereby infiltrating immune cells, including B cells, contribute to the neuroinflammatory processes that occur during secondary injury (Kumar and Loane, 2012; Finnie and Blumbergs, 2002).

Following experimental TBI in mice, anti-myelin oligodendrocyte glycoprotein (MOG) antibody levels were increased in sera at 1, 8, and 32 weeks post-injury (Daglas et al., 2019). Furthermore, injection of WT splenic B cells into the parenchyma of TBI mice significantly improved neurological recovery, including motor function, learning, and memory, compared to non-treated TBI mice (Sirbulescu et al., 2019). These improvements were attributable to reduced lesion sizes, preserved residual hippocampal volume, and reduced glial scarring that were observed at 35 days post-TBI (Sirbulescu et al., 2019). However, when injecting MyD88 KO- or IL-10 KO-derived murine splenic B cells into the parenchyma of TBI mice, allowing to analyze the contribution of Toll-like receptor (TLR)9 and regulatory B cell responses, respectively, the previously observed beneficial treatment effects on neurological function and lesion sizes were reversed (Sirbulescu et al., 2021). This suggests that specific B cell subsets may differentially regulate neurological recovery following TBI. Furthermore, mature naive B cells, injected into the brain parenchyma immediately prior to a controlled cortical impact injury model, were shown to primarily produce pro-inflammatory cytokines early after TBI (i.e., up to 96 h post-TBI), while anti-inflammatory cytokine production persisted longer following trauma (i.e., up to 10 days post-TBI) (Dwyer et al., 2023). Interestingly, B cell injection did not alter immune cell infiltration into the lesion site at 96 h post-injury (Dwyer et al., 2023), while B cell KO mice did exhibit increased infiltration of immune cells into the injured brain at 8 weeks post-TBI, as well as earlier and more severe neurological deficits compared to WT TBI mice (Daglas et al., 2019). These findings indicate that the migration of peripheral immune cells toward the injured brain may be regulated by peripheral B cells, again suggesting that they play a more protective role following TBI.

In patients with severe TBI, reduced IgG and IgM serum levels were detected in the first 72 h post-injury compared to HC (Wolach et al., 2001). Serum IgG levels against β-tubulin class III, a CNS protein, peaked around 21 to 23 days post-TBI and returned to normal levels at around 31 to 33 days post-injury (Skoda et al., 2006). Moreover, anti-GFAP IgG antibodies were detected in acute (within 24 h post-injury), subacute (between 4 and 10 days post-injury), and chronic (between 16 and 250 days post-injury) TBI patients, and were positively correlated with injury severity (Zhang et al., 2014; Wang et al., 2016). Besides sera, autoantibodies against CNS proteins, including MBP, have also been found in cerebrospinal fluid (CSF) samples of TBI patients, with higher levels following severe TBI (Ngankam et al., 2011). While two independent studies observed unaltered B cell numbers and frequencies up to 7 days post-TBI, another study reported increased B cell frequencies at 1 and 7 days post-injury in TBI patients compared to HC (Wolach et al., 2001; Mrakovcic-Sutic et al., 2010; Chenouard et al., 2015). Although TBI patients displayed reduced IL-10$^+$ B cell frequencies compared to HC, patients with IL-10$^+$ B cell frequencies above 3.1% were associated with a higher incidence of pneumonia, prolonged mechanical ventilation, and longer durations in the intensive care unit, compared to patients with IL-10$^+$ B cell frequencies below 3.1% (Chenouard et al., 2015). More research is needed to further clarify the role of distinct B cell subsets, including IL-10$^+$ B cells, to TBI pathology.

5.2. Stroke

A stroke results from the interruption of blood flow to the brain, either due to blockage or bleeding, leading to irreversible brain damage and neuronal cell death (Iadecola and Anrather, 2011; Moskowitz et al., 2010). More specifically, ischemic stroke is triggered by a sudden lack of blood flow due to thrombosis or embolism, followed by reperfusion of the damaged area (Iadecola and Anrather, 2011). Less frequently occurring, hemorrhagic stroke results from the rupture of blood vessels in the brain, causing intracranial bleeding (Moskowitz et al., 2010). Studies on B cell involvement in stroke have pointed toward both a protective and a damaging role in the pathology.

In a mouse model of ischemic stroke, activation of CNS antigen-specific B cells was observed in the cervical lymph nodes and spleen as early as 4 days and persisted up to 10 days following stroke induction (Ortega et al., 2015). Studies on the functional outcome following stroke showed contrasting results. In one study, B cell depleted or B cell deficient mice did not exhibit changes in functional outcome, lesion volume, or immune cell infiltration at 1 and 3 days after stroke compared to WT mice (Schuhmann et al., 2017). However, in another study, B cell KO stroke mice exhibited worsened neurological function with increased infarct sizes, mortality, and infiltration of other immune cells into the lesion compared to WT mice after 48 h (Ren et al., 2011). Interestingly, the histological and neurological deficits were reversed following adoptive B cell transfer from WT mice, which was suggested to be attributable to IL-10-producing B cells (Ren et al., 2011; Bodhankar et al., 2013). A third study showed improvement of cognitive deficits, observed 7 weeks following stroke, in B cell KO mice or following B cell depletion therapy (Doyle et al., 2015). It must be noted that neurological function primarily focused on motor function (Ren et al., 2011; Bodhankar et al., 2013), while cognitive function was defined by investigating short-term memory following ischemic stroke (Doyle et al., 2015). However, these findings also suggest that B cell functions, either beneficial or detrimental, may greatly depend on the timing following ischemic stroke and/or that specific B cell subsets, such as IL-10$^+$ B cells, may be active at different time points post-injury. These time-dependent effects on B cells might also be present following traumatic SCI, warranting further investigation. B cells were also shown to infiltrate in the infarcted region of mice with ischemic stroke and were found from around 1 week up to 12 weeks post-injury (Doyle et al., 2015). Ectopic follicle-like structures were observed around 7 weeks, as B cells clustered together with infiltrating T cells. ASCs were found within the lesion, corresponding to the increased IgG, IgA, and IgM antibodies in the brain of stroke mice compared to sham mice.

Besides animal models of stroke, evidence on B cell involvement has also been gathered in stroke patients, although limited. Oligoclonal IgG bands and increased IgG, IgA, and IgM production have been observed

in CSF of patients that suffered from an ischemic or hemorrhagic stroke (Rostrom and Link, 1981; Tsementzis et al., 1986; Pruss et al., 2012). Autoantibodies were also found to be elevated in sera of stroke patients and were directed against neuronal antigens, including neurofilament and the *N*-methyl-D-aspartate (NMDA) receptor (Bornstein et al., 2001; Dambinova et al., 2003; Kalev-Zylinska et al., 2013). Autoantibody levels were found to be positively correlated with infarct size but inversely correlated with neurological improvement or cognitive function (Kalev-Zylinska et al., 2013; Becker et al., 2016). Furthermore, B cells and IgG have been detected in infarcted lesion tissue retrieved from stroke patients with subsequent dementia-characteristics (Doyle et al., 2015). Together, these findings point to time- and context-dependent responses and functions of distinct B cell subsets following stroke.

6. Conclusions

Traumatic SCI is a severe, debilitating condition that profoundly affects the lives of patients and their relatives. Although substantial progress has been made in understanding the pathophysiology of traumatic SCI, this knowledge has yet to translate into effective therapeutic interventions. One area that warrants further investigation is the inflammatory response associated with the secondary injury phase, as it represents a potentially modifiable contributor to tissue damage and functional outcome following SCI.

This review highlights the emerging role of B cells in the pathophysiology of traumatic SCI. B cells infiltrate the injured spinal cord, as evidenced by their presence in both animal and human spinal cord tissue after traumatic SCI, and have been found at different maturation stages, depending on the timing post-SCI. Furthermore, B cells contribute to the inflammatory response, potentially via the MIF/CD74 axis, and regulation of other immune cells, but also differentiate into ASCs and produce pathological (auto)antibodies that can persist for years following the injury. Importantly, studies in B cell depleted or B cell deficient mouse models demonstrated attenuated functional deficits, decreased immune cell infiltration, and reduced tissue pathology, further underscoring the contribution of B cell responses to SCI progression.

While these findings suggest that targeting B cells may be therapeutically beneficial, broad suppression of the entire B cell compartment is unlikely to be feasible in SCI patients due to the already increased susceptibility of SCI patients to serious infections. Instead, a more detailed understanding of the aberrant post-SCI B cell responses is needed. This includes defining the contributions and pathological functions of distinct B cell subsets and the underlying molecular mechanisms and signaling pathways. In addition, the involvement of other factors, including the level of injury and interactions with other immune cell populations, requires further investigation. Such insights may facilitate the identification of more selective targets that specifically modulate pathological B cell responses while preserving protective immune functions. These targets could be exploited to inhibit the activation, migration, or other pathological functions of specific B cell subsets following traumatic SCI. Given the limited translational success of animal SCI models in predicting outcomes in humans, greater emphasis on investigating B cell responses directly in SCI patients will be essential to bridge the gap between experimental findings and clinical applications. Ultimately, the identification of selective therapeutic targets may contribute to the development of more specific and personalized immunomodulatory strategies for SCI treatment.

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CRediT authorship contribution statement

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Declaration of competing interest

All authors declare to have no competing interests.

Data availability

No data was used for the research described in the article.

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