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Review article

# The spleen as a neuroimmune interface after spinal cord injury

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ABSTRACT

Traumatic spinal cord injury (SCI) causes widespread damage to neurons, glia and endothelia located throughout the spinal parenchyma. In response to the injury, resident and blood-derived leukocytes orchestrate an intraspinal inflammatory response that propagates secondary neuropathology and also promotes tissue repair. SCI also negatively affects autonomic control over peripheral immune organs, notably the spleen. The spleen is the largest secondary lymphoid organ in mammals, with major roles in blood filtration and host defense. Splenic function is carefully regulated by neuroendocrine mechanisms that ensure that the immune responses to infection or injury are proportionate to the initiating stimulus, and can be terminated when the stimulus is cleared. After SCI, control over the viscera, including endocrine and lymphoid tissues is lost due to damage to spinal autonomic (sympathetic) circuitry. This review begins by examining the normal structure and function of the spleen including patterns of innervation and the role played by the nervous system in regulating spleen function. We then describe how after SCI, loss of proper neural control over splenic function leads to systems-wide neuropathology, immune suppression and autoimmunity. We conclude by discussing opportunities for targeting the spleen to restore immune homeostasis, reduce morbidity and mortality, and improve functional recovery after SCI.

## 1. Introduction

Traumatic spinal cord injury (SCI) triggers a robust neuro-inflammatory response involving resident glia and circulating leukocytes. Aspects of this response can both exacerbate tissue damage and promote repair (Donnelly and Popovich, 2008; Brennan and Popovich, 2018). An important, but often overlooked, organ that coordinates much of the peripheral response to antigenic challenge caused by infection or tissue trauma, including SCI, is the spleen. The spleen is the largest organ in the mammalian lymphatic system and is located in the abdominal cavity between the diaphragm and the fundus of the stomach. There is a preconception that the spleen is not a vital organ; however, it plays principal roles in both immune defense and blood filtration (Bronte and Pittet, 2013). The importance of the spleen is exemplified by the fact that spleen removal (splenectomy) doubles the risk that an individual will develop fatal thromboemboli and contract life-threatening infections.

Clinically, more than one million asplenic individuals live in the USA and are at risk for developing "overwhelming post-splenectomy infections" (OPSI) and each year, ~25,000 new splenectomies are performed, increasing the size of this "at-risk" population. Notably, people suffering OPSI have a mortality rate of ~70% (de Porto et al., 2010). Many common diseases (e.g., sickle cell, thalassemia, coeliac disease, ulcerative colitis, cirrhosis, etc.) also cause hyposplenism or compromise spleen function, placing these individuals at risk for developing OPSI (William and Corazza, 2007). When these patient populations are considered together, it is obvious that there is a huge unmet clinical need to develop new strategies to modulate spleen function (Theilacker et al., 2016). Understanding the varied mechanisms that control splenic function will facilitate the development of new and more efficient immune-modulatory therapies. Indeed, current therapies have limited efficacy and because most are injected or taken orally, they have non-specific (side) effects, which also influence non-immune cell functions. These effects are often adverse and are particularly problematic in chronic diseases (e.g., osteoporosis or psychosis induced by steroids). Thus, more precise or targeted therapies that can either boost or attenuate splenic immune function may have unique therapeutic value. Such therapies might include techniques that manipulate the autonomic nervous system, which normally exerts tonic control over spleen function. However, similar approaches may not be feasible when autonomic circuitry is damaged or destroyed. Such a scenario exists in individuals living with SCI.

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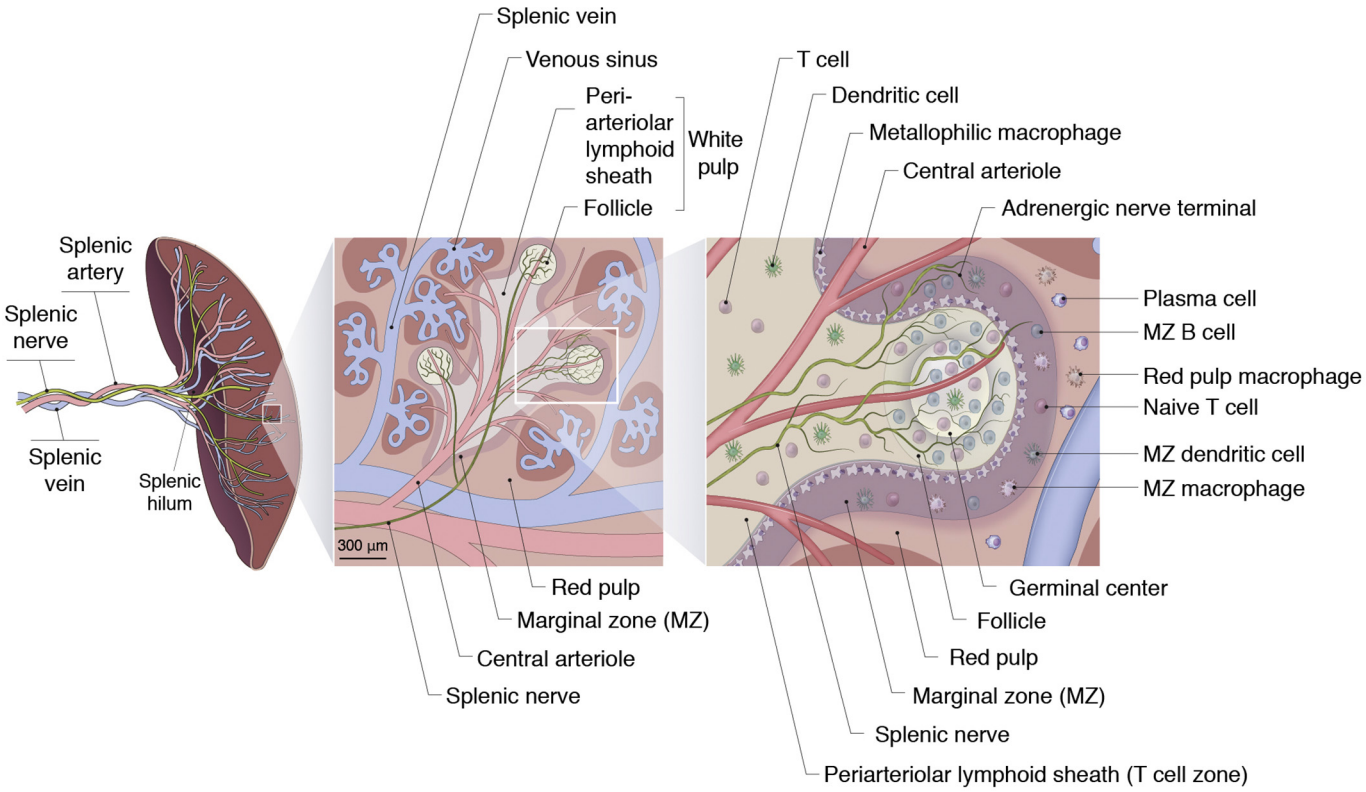


**Fig. 1.** Anatomy of the spleen. Left panel: Gross image of the spleen, showing the branching of the splenic artery and arborisation of the splenic nerve. The splenic vein directs recirculating (filtered) blood from the spleen back to the lung. Middle panel: Low power diagram showing the major zones of the spleen, including non-lymphoid red pulp, which filters blood, and the lymphoid white pulp, comprised of the periarteriolar lymphoid sheath and follicles. Right panel: Higher power diagram showing cell types specific to white pulp regions. Notice the close proximity between splenic nerve branches (green) and white pulp lymphocytes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

This review will provide an overview of normal splenic physiology, including patterns of autonomic innervation. We then describe how SCI-induced changes in splenic function contribute to a seemingly paradoxical state where chronic autoimmunity to CNS antigens develops in parallel with systemic immune suppression. Finally, the opportunities and challenges of manipulating splenic function to restore immune homeostasis after SCI are discussed.

## 2. The role of the spleen in response to immune challenge

The spleen is unique among secondary lymphoid organs because it lacks afferent lymphatic drainage. Thus, unlike lymph nodes, which receive bacteria and cell debris trafficking through lymph, the spleen processes antigens directly from the blood. It is comprised of the non-lymphoid red pulp, which primarily performs blood filtration, and the lymphoid white pulp. The white pulp has specialized subregions in distinct positions around the vasculature to allow the colocalization of antigen, antigen-presenting cells (APCs), and lymphocytes **(**Fig. 1**).** The splenic artery enters the spleen at the hilum and then branches into central arterioles that terminate in splenic sinuses. There, splenic arterial blood is dispersed into the marginal zone (MZ), which lies at the interface between white and red pulp. The slowed flow of blood in the MZ, and the extensive repertoire of pattern and scavenger receptors on MZ macrophages, enables MZ macrophages to capture dead cells, particulates and antigens from blood (e.g., bacteria) with high efficiency. The MZ outer ring contains SIGNR1$^+$MARCO$^+$ MZ macrophages that present processed antigens to MZ B cells (Aichele et al., 2003; Mebius and Kraal, 2005; MacLennan et al., 1982). The MZ inner rim is lined by CD169$^+$ metallophilic macrophages that transfer captured antigen to DCs for activation of cytotoxic (CD8$^+$) T cells (Backer et al., 2010).

Adjacent to central arterioles and surrounded by the MZ is a zone of white pulp known as the periarteriolar lymphoid sheath (PALS). Recirculating T lymphocytes and DCs follow chemoattractant gradients from the MZ and concentrate in the PALS (Bronte and Pittet, 2013). Here, T cells are activated and proliferate in response to antigen presented by resident APCs. B cells segregate to the peripheral part of the PALS and the surrounding follicles (Sprent, 1973). B cells that encounter antigen are activated by macrophages, follicular DCs and helper (CD4$^+$) T cells. Activated B cells proliferate to produce foci of antigen-specific B cells known as germinal centers (Coffey et al., 2009; Schatz et al., 1989). Most B cell clones differentiate into plasma cells, which proliferate and secrete immunoglobulins into the circulation to help neutralize the inflammatory stimulus (Mebius and Kraal, 2005). A fraction of B cells remain in B cell follicles as memory cells. At the end of an immune response, germinal center tingible body macrophages downreguate B cell responses by releasing prostaglandins (Smith et al., 1998).

Although the coordination of innate and adaptive immune responses is classically attributed to these white pulp zones, the red pulp also performs important roles in host defense. Red pulp macrophages promote the differentiation of $T_{reg}$ cells, secrete type 1 interferons, recycle erythrocyte iron to defend against bacteria (Kurotaki et al., 2015), and promote extramedullary hematopoiesis (Dutta et al., 2015). The subcapsular red pulp also houses up to half of the body's monocytes, providing an emergency monocyte reservoir that is rapidly deployed during inflammation (Bronte and Pittet, 2013; Swirski et al., 2009).

To understand how SCI adversely affects splenic immune functions, it is useful to first consider how the spleen normally responds to an inflammatory stimulus. For that purpose, lipopolysaccharide (LPS) is often used as a model inflammogen. LPS is an endotoxin found in the outer membrane of gram-negative bacteria. When LPS is injected into a healthy host organism, it binds to the LPS multi-receptor complex