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Contribution of Inflammation
to Chronic Pain Triggered by Nerve Injury

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1. Introduction

An injury to a peripheral nerve can be a slight stretch, a compression or a severe laceration. Such damage usually leads to an acute phase response characterized by nociceptive pain, inflammation and restriction of normal function. However, in about 7%-18% of the general population, pain persists, even after the injury healing, producing a state of chronic neuropathic pain. This type of hypersensitivity is debilitating and refractory to the majority of available analgesics. It adversely affects quality of life and bears a substantial cost to society. In the last two decades, compelling evidence strongly suggested that, in addition to changes in neuronal system, pathogenesis of neuropathic pain involves the interaction between the immune system and the nervous system. Inflammatory process alters local homeostasis and impairs neuronal function. In this chapter, we primarily focus on the evidence with experimental animal models obtained from our laboratory and from literature to highlight inflammatory reaction along the pain pathway (from damaged nerve to the spinal cord), and the critical role of this reaction in the development and maintenance of neuropathic pain. We also discuss the current progress and challenges of translating the inflammation related new targets into therapeutics.

2. Peripheral nerve

2.1 Infiltration of immune cells into injured peripheral nerves

Peripheral nerve injury triggers not only the activation of Schwann's cells and resident immune cells, but also the recruitment of circulating inflammatory cells. The two main cell types that enter the nerves after injury are neutrophils and macrophages. Neutrophils are the first immune cells migrating towards the injury site. Their numbers peak at 24 hours following peripheral nerve injury and decrease progressively after three days post-injury, but still remain significant for at least one week (Nadeau et al, 2011). Infiltrated neutrophils in injured nerves play an important role at the very early stages of neuropathic pain through the release of pro-inflammatory mediators, such as cytokines TNF-α, IL-1β and IL-6 and reactive oxygen species, which are involved in regulating neuronal excitability (Schafers et al., 2003). In addition, neutrophils have a significant impact on subsequent macrophage infiltration to the injured nerves by secreting chemokines/cytokines MIP-1α, MIP-1β and IL-1β (Scapini et al., 2000).

Macrophages from peripheral circulation enter the injured nerve starting about 3 days and persist for several months post-injury (Frisen et al., 1993). Infiltrated macrophages exhibit different functional phenotypes in which they promote both injury and repair. The first important characteristic of macrophages is to be able to secrete pro-inflammatory mediators including TNF-α, IL-1β, IL-6, MIP-1α, MIP-1β and MCP-1. These cytokine/chemokine expressing macrophages show high levels of MAC-1 and low levels of ED-1 antigens (personal unpublished data). Many of these immune molecules detected in damaged nerves at different time points post-injury are directly or indirectly involved in pain hypersensitivity. For instance, MCP-1 plays an important role in macrophage recruitment and the establishment of pain hypersensitivity. It has been observed that MCP-1 mRNA expression is markedly increased in the injured rat sciatic nerves in parallel with an increase of macrophage recruitment (Toews et al., 1998). However, the development of mechanical allodynia is totally abrogated in CCR2 (MCP-1 receptor) knockout mice while macrophage recruitment is attenuated (Abbadie et al., 2003). Furthermore, pro-inflammatory mediators including IL-1β, TNF-α, IL-6 and MIP-1α are directly implicated in pain hypersensitivity (Kiguchi et al., 2010; Sommer & Kress, 2004) through synergistic effects to amplify the inflammatory signals. It has been shown that direct injection of IL-1β and TNF-α into peripheral nerves causes potent mechanical and thermal hyperalgesia in rats (Zelenka et al., 2005) whereas the application of neutralizing antibodies for IL-1β or IL-1 receptor antagonist effectively attenuates tactile allodynia and thermal hyperalgesia in animal models of neuropathic pain (Kawasaki et al., 2008). The use of siRNA against CCR1 and/or CCR5 (MIP-1α receptor) also effectively prevents the induction of tactile allodynia and thermal hyperalgesia through down-regulation of IL-1β (Kiguchi et al,. 2010). Infiltrated macrophages also exhibit powerful phagocytic phenotypes. High level of ED1 antigen was found on the cell surface and membranes of cytoplasmic granules such as phagolysosomes, which indicates a close correlation with macrophage phagocytic activity (Damoiseaux et al., 1994). They engulf cellular debris such as injured Schwann cells and axotomised axons (Bruck, 1997) and promote repair process. However, whether and how these phagocytic macrophages contribute to the pain behaviour needs further investigation.

2.2 Depletion of neutrophils or monocytes/macrophages impairs neuropathic pain behavior associated with nerve injury

Systemic treatment of sciatic nerve injured mice with a monoclonal antibody against the Ly6G antigen specifically expressed by neutrophils demonstrated that depletion of neutrophils attenuates the development of neuropathic pain behaviour (Nadeau et al, 2011). Furthermore, using molecular and pharmacological approaches, partial or complete depletion of macrophages yield beneficial effects in alleviating nerve injury associated chronic pain. For instance, the depletion of circulating macrophages by liposome-encapsulated clodronate results in decreased macrophage recruitment to the injury site, alleviated thermal hyperalgesia and reduced degeneration of axons (Liu et al., 2000) as well as attenuates pain hypersensitivity in diabetic animals (Mert et al., 2009). In addition, Wallerian degeneration (WLD) in response to nerve injury is delayed in genetically deficient mice which delays macrophage recruitment (Araki et al., 2004). Hyperalgesia is also delayed in this type of mice (WLD mice) suggesting that macrophages contribute to the development of neuropathic pain following peripheral nerve injury (Myers et al., 1996).

3. Dorsal Root Ganglia (DRG)

The dorsal root ganglia (DRG) are nodules containing cell bodies of afferent sensory neurons, which lie just outside of the spinal cord, in the intraforaminal spaces of the vertebral column. The nociceptive neurons of the DRG are classified into two groups depending on nerve fiber type: myelinated Aδ-fibers which are fast conducting, or unmyelinated C-fibers which are slow conducting. Like most neurons, sensory neurons in DRG are supported by a cast of other cells. In the DRG these supportive cells are satellite glial cells (SGC), dendritic cells, macrophages, and endothelial cells.

SGCs encapsulate each neuronal cell body, and a basement lamina separates neighbouring engcapsulated neurons (Hanani, 2005). The SGCs in DRG perform many similar functions to the astrocytes of the CNS, as they perform many regulatory and immune functions. For example, SGCs regulate extracellular amounts of glutamate and aspartate (Duce & Keen, 1983). In addition, they supply the glutamate precursor glutamine (Kai-Kai & Howe, 1991), and are a reservoir of the nitric oxide precursor L-arginine (Aoki et al., 1991). In addition, like many other glia, SGCs communicate with each other using gap junctions Normal DRG are also home for a population of resident macrophages. Most of these resident macrophages contact the neuron-satellite cell complex, and there are a smaller number which reside perivascularly (Hanani, 2005). The DRG neurons are very well perfused, and the blood supply is much denser than in peripheral nerve or dorsal root. In fact, each DRG neuron soma is in close proximity to an extensive network of capillaries. The blood supply to the DRG is supplied by fenestrated capillaries which have no blood-nerve barrier, and the vessels allow large molecules to pass easily.

Sensory ganglia do not have dendrites and chemical synapses, and thus each neuron within the ganglia was thought to be an independent communication pathway. However, this turns out not to be the case, and in fact, neighboring DRG neurons have the ability to cross-excite one another. Thus after peripheral nerve injury, cross-excitation is one possible mechanism by which sensory signals can be altered in time, space, and modality to result in neuropathic pain (Devor & Wall, 1990). Inflammation, which increases the excitability of DRG neurons, enhances cross-excitation. For example this mechanism is further influenced by interactions with SGCs.

Following peripheral nerve injury or inflammation, SGCs in DRG activate, and undergo proliferation (Lu et al., 1991). This process is thought to be mediated through release of ATP from damaged neurons, which stimulate purinergic receptors on SCGs (Filippov et al., 2004). Activation of SGCs results in increased glial fibrillary acidic protein (GFAP) expression and release of pro-inflammatory cytokines, for example, TNFα and IL-1β (Ohara et al., 2009). These cytokines released by activated SGCs have excitatory actions on nociceptive neurons (Takeda et al., 2009). In spinal nerve ligation (SNL) injured rats, GFAP expression peaks at one day after nerve injury, and is still present 10 days after (Xie et al., 2009). Gap junctions in SGCs, are also increased after nerve injury (Jeon et al., 2009). These junctions seem to be involved with the generation and maintenance of neuropathic pain, as RNA interference targeting connexin 43, one of the major structural components of gap junctions in SGCs, prevents experimental neuropathic pain (Ohara et al., 2008). Gap junctions allow the redistribution of K^+ ions though SGCs. K^+ ion concentration regulation is another mechanism by which SCGs regulate the excitability of DRG neurons (Takeda et al., 2009).

Peripheral nerve injury or inflammation also recruits resident macrophages of the DRG and circulating macrophages (Hu & McLachlan, 2002). Monocyte chemoattractant protein (MCP)-1 becomes upregulated at the DRG in injured neurons following nerve injury, and this has been found to be a critical event in the recruitment of macrophages (Jeon et al., 2009). The number of macrophages in the DRG peaks at 3 to 7 days after the trigger, and increased macrophages persist for weeks (Xie et al., 2006). The increase in macrophages at the DRG can occur even without any phagocytic events (Milligan & Watkins, 2009). The activated macrophages contribute to the persistence of neuropathic pain, and respond to numerous molecules, such as neurotransmitters, growth factors, and cytokines (Schreiber et al., 2002; Xie et al., 2006).

DRG neurons increase excitability in response to a number of inflammatory compounds, and can do so in a manner that sometimes does not require changes in protein expression. For instance, perfusion of DRG *in vitro* with TNFα results in an increase of A- and C-fiber discharge, as well as increased calcitonin gene related peptide (CGRP) release from nociceptor terminals at the spinal cord (Oprée & Kress, 2000). TNFα can act on TNFR1, one of the receptor subtypes for TNFα which is expressed exclusively by neurons (Li et al., 2004). The electrophysiological effects of TNFα on DRG neurons include a profound enhancement of tetrodotoxin (TTX)-resistant Na^+ channels within a minute of application (Jin & Gereau, 2006), and an increase of vanilloid receptor 1 (TRPV1) function and expression (Hensellek et al., 2007). This increase in excitability of the DRG neurons by TNFα is thought to be mediated through p38 phosphorylation of TTX-resistant sodium channel subunits, and upregulation of TRPV1 protein expression (Jin & Gereau, 2006). Additionally other cytokines can also produce excitatory changes on DRG neurons, such as IL-1β and IL-6. DRG neurons can respond to IL-1β, sensitizing TRPV1 also (Obreja et al., 2002). Similarly, it seems IL-6 has effects on TRPV1 as well. IL-6 sensitizes the ion channel to heat, resulting in increased CGRP release from DRG neurons (Obreja et al., 2005).

Following injury to peripheral nerve, subsets of injured neurons will spontaneously ectopically discharge (Kim et al., 1993). This can result in a chronic sensitization of nociceptive neurons in both the PNS and CNS, resulting in pathological pain. While the exact mechanisms for the development of these changes are unknown, it is clear that inflammatory events at the DRG are critical (Miller et al., 2009). Such events at the DRG may include the cross-excitation of DRG neurons, activation of SGCs, recruitment and activation of macrophages, and the production of chemokines and cytokines.

4. Spinal cord

Central sensitization refers to the process through which a state of hyperexcitability is established in the central nervous system, leading to enhanced processing of nociceptive messages (Perl, 2007). Numerous mechanisms have been implicated in central sensitization, including alteration in glutamatergic neurotransmission/NMDA receptor-mediated hypersensitivity and loss of tonic inhibitory controls (disinhibition) (Basbaum et al., 2009). However, a remarkable series of findings in recent years has demonstrated a previously unrecognized role for inflammation in the initiation and maintenance of central sensitization. The involvement of non-neuronal cells, mainly astrocytes and microglia has been elucidated, to a degree that they appear now as reasonable future therapeutic targets.

4.1 Activation of spinal glial cells following peripheral nerve injury

Glia represent, by far, the most abundant cells in the nervous system, largely outnumbering neurons. Astrocytes and microglia have been shown to undergo structural and functional modifications in the spinal cord in models of chronic pain (Colburn et al., 1999; Inoue & Tsuda, 2009; Moss et al., 2007). The data supporting a crucial role for these glial cells in the pathophysiology of neuropathic pain is ample (Gosselin et al., 2010). The long-lasting changes occurring in glia include structural alterations, cell proliferation, loss of neurotransmitter and release of proinflammatory mediators among other cellular processes. Several models of chronic pain investigated so far result in such glial phenotypic changes, essentially in the spinal cord (the first synaptic relay of the nociceptive pathway). Additionally, the involvement of glia in chronic pain has been remarkably validated by the prevention and reversal of behavioral manifestations of pain following treatments with molecules bearing glia-inhibitory properties (Hua et al., 2005; Milligan et al., 2003; Raghavendra et al., 2003; Tsuda et al., 2003). This suggests that glial alteration could be a crucial mechanism accounting for the persistence of hypersensitivity. In addition to resident glial cells, blood-borne monocytes and macrophages have the ability to infiltrate the spinal cord, where they proliferate and differentiate into activated microglia (Zhang et al., 2007). Activation of different glial/immune cells occurs along a complex temporal pattern. The contribution of each cell population to the modulation of nociceptive processing in pathological conditions follows a well-organized sequence of reciprocal communication between neurons and glia and among glial cells themselves (Inoue & Tsuda, 2009; Vallejo et al., 2010; Watkins & Maier, 2002).

The events triggering astrocytic and microglial activation as well as the signals resulting from this activation producing pain hypersensitivity are currently under intense investigation. An increasing number of studies have proposed some mechanisms that seem to be consistently involved. Among them, the extracellular activating events, especially in neuropathic pain arising from peripheral damage, are very likely originating from sensory neuronal terminals reaching the spinal cord. Of special interest it's been the discovery of the critical role of several chemokines released by damaged neurons such as fractalkine (Clark et al., 2009; Milligan et al., 2004; Verge et al., 2004) and monocyte chemoatractant protein (MCP-1). The MCP-1 has raised a special interest in neuron-glia communication as its spatial profile of expression in the spinal cord dorsal horn matches that of activated microglia (Beggs & Salter, 2007; Thacker et al., 2009; Zhang & De Koninck, 2006). Peripheral nerve injury not only induces up-regulation of MCP-1 and its receptor CCR2 (Abbadie et al., 2003; Zhang & De Koninck, 2006) but also activation of spinal microglia (Zhang et al., 2007). Microgliosis in the spinal cord was prevented by spinal injection of MCP-1 neutralizing antibody or in mice lacking CCR2 (Zhang et al., 2007). Furthermore blockade of MCP-1/CCR2 signaling successfully prevents the infiltration of blood-borne monocytes into the spinal cord (Zhang et al., 2007). Taken together, these data suggest that spinal MCP-1/CCR2 signaling is critical for spinal microglial activation and the development of neuropathic pain after peripheral nerve damage.

Once activated, it is generally believed that the actions of glia in the context of neuropathic pain rely on their abilities to undergo drastic cellular changes and release of immune molecules including cytokines, chemokines and growth factors (Wieseler-Frank et al., 2005). The role of pro-inflammatory cytokines IL-6, IL-1β and TNF-α has been extensively studied. Blockers of these cytokines have been shown to reduce neuroinflammatory responses (Gomez-Nicola et al., 2008; Kiguchi et al., 2010) reduce neuronal hyperexcitability (Milligan et al., 2001) and block pain in animal models of neuropathy (Cuellar et al., 2004).

4.2 Peripheral nerve injury alters blood spinal cord barrier integrity

The blood spinal cord barrier (BSCB) constitutes a physical/biochemical barrier between the central nervous system (CNS) and the systemic circulation, which serves to protect the microenvironment of the spinal cord. However, several studies (Beggs et al., 2010; Gordh et al., 2006) have reported an important increase in BCSB permeability after peripheral nerve injury. A recent observation from our laboratory revealed that peripheral nerve injury disrupted the integrity of the BSCB and inflammatory mediators are key regulators of BSCB function. MCP-1 released by damaged neurons is an endogenous trigger for the BSCB leakage. BSCB permeability can also be impaired by circulating IL-1β. In contrast, anti-inflammatory cytokines TGF-β1 and IL-10 were able to shut down the openings of the BSCB following nerve injury. The compromised BSCB allows penetration of both inflammatory molecules (e.g., cytokine IL-1β) and immune cells (monocytes/macrophages, lymphocytes) into the spinal cord, participating in the central inflammatory response, a critical process for the development of neuropathic pain (Echeverry et al., 2011). In addition, endothelial cells have the capacity to secrete immune mediators, for example, IL-6 (Vallejo et al., 2010) and bear a series of surface molecules, such as chemokines, to modulate the entrance of immune cells which are known to have an impact on pain hypersensitivity. For a summary of the described kinetics see Fig 1.

1. Central release of MCP-1 is required for the opening of the BSCB
2. Central release of MCP-1 is also crucial for spinal microglial activation.
3. Increased BSCB permeability is not dependent on microglial activation
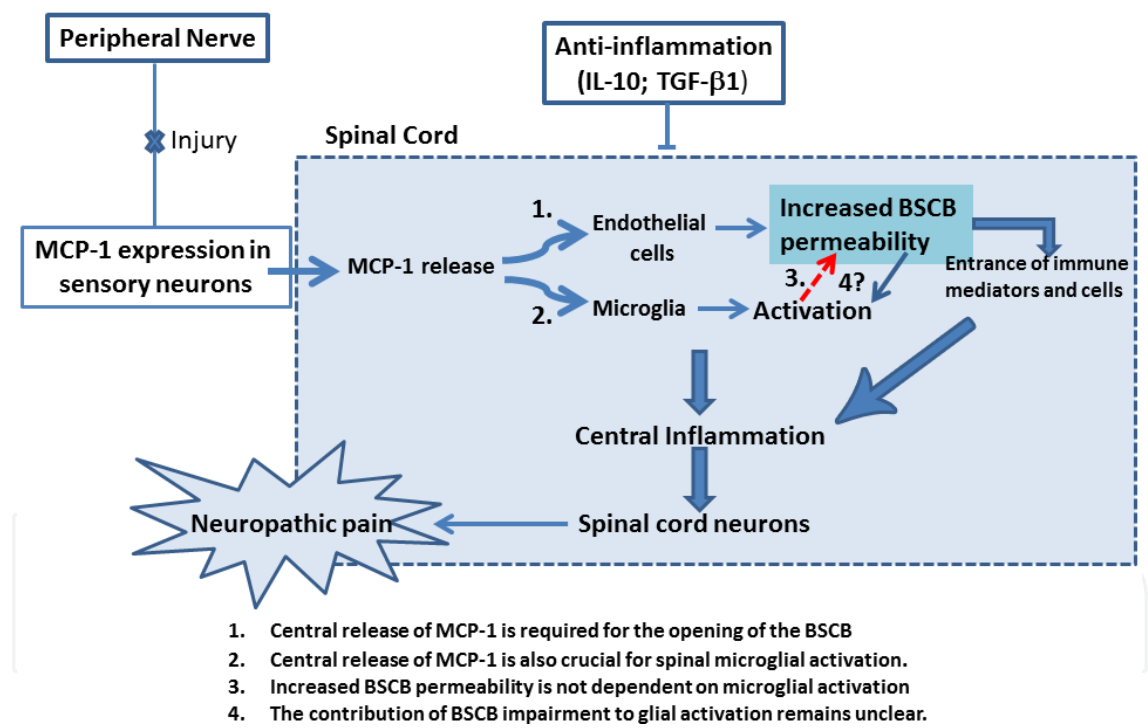4. The contribution of BSCB impairment to glial activation remains unclear.

Fig. 1. Neuronal MCP-1 released into the spinal cord not only activated its receptor CCR2 in endothelial cells (1) to impair the integrity of the BSCB, but also activated CCR2 in microglia (2) to trigger microglial activation. Microglial activation is not required for the increase of BSCB permeability (3), although due to the lack of a selective BBB/BSCB blocker without affecting the inflammatory response, it is not clear whether the opening of BSCB can promote microglial activation (4). Central inflammation resulted from the opening of BSCB and microglial activation was necessary for the development of neuropathic pain, since anti-inflammatory cytokines IL-10 and TGF-β1, which were able to shut-down the nerve injury induced BSCB disruption and microglial activation, attenuated neuropathic pain

4.3 Inhibition of the spinal inflammatory reaction can alleviate neuropathic pain

In addition to the fact that following nerve injury, many non-neuronal cells are activated and engaged in an inflammatory reaction, functional investigations using pharmacological or genetic approaches support the roles of spinal inflammation in chronic pain, especially the facilitation of neuropathic pain. Activated microglia release pain enhancing substances such as pro-inflammatory cytokines, nitric oxide, and prostaglandins, that excite spinal pain responsive neurons either directly or indirectly, and promote the release of other transmitters that can act on nociceptive neurons. Drugs that target glial activation have successfully controlled enhanced nociceptive states in animal models either by: inhibiting the synthesis of cytokines, blocking pro-inflammatory cytokine receptors or neutralizing endogenous cytokines, or disrupting pro-inflammatory cytokine signaling pathway with inhibitors of the p38MAP kinase. Anti-inflammatory molecules have been used to validate the concept in different nerve injury models associated with chronic pain. IL-10, secreted by monocytes and TH2 cells, reverses neuropathic pain behavior in animal studies (Sloane et al., 2009; Soderquist et al., 2010). Enhancement of the TGF-β1 pathway through administration of exogenous recombinant ligand (Echeverry et al., 2009) or through transgenic approaches prevents and reverses neuropathic pain induced by peripheral nerve injury (Tramullas et al., 2010). The importance of inflammation in chronic pain is also highlighted by the correlation between the pro- and anti-inflammatory balance and the outcomes of pain states in humans: Patients presenting painful neuropathies or CRPS show elevated levels pro-inflammatory cytokines (Davies et al., 2007) while patients with painless neuropathies have elevated levels of anti-inflammatory cytokines (Uceyler et al., 2007).

5. Current advances and challenges in knowledge translation

In summary, following nerve injury, the communication between the immune and the nervous systems has been enhanced, which is observed not only at the sites of damage (peripheral nerve or DRGs), but also within the spinal cord. Such inflammatory reaction can be a critical underlying mechanism in generating neuropathic pain. The role of immune/glial cells in the development and the persistence of pain after nerve injury challenge conventional concepts that focus on neural activity being solely responsible for the changes that drive neuropathic pain. This shift in our understanding provides an incredible opportunity to progress to a new therapeutic approach that will be beneficial for the millions of people suffering of neuropathic pain. However, translation of such knowledge into clinical use for human has been largely underexplored. To date, very limited evidence is available for the roles of inflammation in persistent neuropathic pain states in human (McMahon & Malcangio, 2009). Only few clinical studies have tested immunosuppressive drugs or drugs interfering with glial functions for neuropathic pain (Scholz & Woolf, 2007). The effectiveness of some anti-inflammatory compounds, such as Anakinra (Kineret®) (recombinant human IL-1 receptor antagonist), Etanercept (Enbrel®) and Infliximab (Remicade®) (TNF inhibitors), was also limited to pain associated with rheumatoid arthritis and other inflammatory conditions. Considering the fact that current treatments for neuropathic pain offer only moderated pain relief with the severe side effects of sedation, tolerance and the risk of dependence, there are enormous needs to develop new therapeutics for which we think targeting one or multiple inflammatory pathways involved in the development of neuropathic pain can be a very exciting strategy. Large sizes, high quality randomized clinical trials with different anti-inflammatory molecules are needed to

determine whether glial/immune cell mediated inflammation can be useful for the treatment of neuropathic pain.

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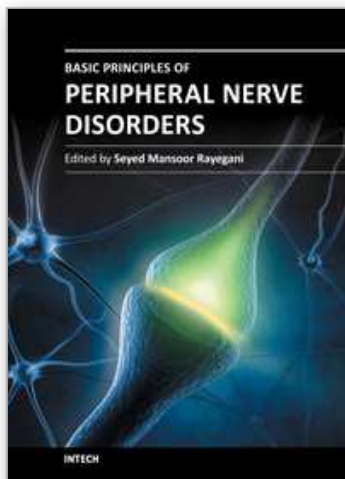
Basic Principles of Peripheral Nerve Disorders

Edited by Dr. Seyed Mansoor Rayegani

Peripheral nerve disorders are comprising one of the major clinical topics in neuromusculoskeletal disorders. Sharp nerve injuries, chronic entrapment syndromes, and peripheral neuropathic processes can be classified in this common medical topic. Different aspects of these disorders including anatomy, physiology, pathophysiology, injury mechanisms, and different diagnostic and management methods need to be addressed when discussing this topic. The goal of preparing this book was to gather such pertinent chapters to cover these aspects.

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