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Review article

Systemic inflammation in traumatic spinal cord injury

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1. Introduction

There are 17,730 new cases of spinal cord injury annually in the United States and up to 2.5 million individuals estimated to be living with chronic spinal cord injury (SCI) (Herman and Bloom, 2018; Kumar et al., 2018). There is an urgent, unmet need to improve survival, physical health and quality of life for persons with SCI, all of which are significantly worse than the able-bodied population (Gibbs et al., 2019; Herman et al., 2018). The mean age at injury is 43 years and the most prevalent etiology of injury is motor vehicle accidents, accounting for nearly half of all cases, followed by falls (National Spinal Cord Injury Statisical Center, 2019). Incomplete tetraplegia is the most common neurological status (National Spinal Cord Injury Statisical Center, 2019). Despite intense efforts, the field remains without an effective pharmacological therapy to enhance neurological recovery after SCI and the medical management of individuals with SCI remains challenging throughout their lifetime. Thus, the economic burden of care for all SCI patients exceeds $4 billion per year.

In addition to the profound motor and sensory deficits, SCI often leads to damage to multiple organ system dysfunction due to disruption of the autonomic nervous system (ANS). The ANS regulates most organ systems, including immune organs such as the spleen, lymph nodes and bone marrow (Pavlov and Tracey, 2017). After SCI, ANS disruption is associated with serious medical consequences such as autonomic dysreflexia, respiratory, bowel and bladder dysfunction, accelerated osteoporosis, and profound changes in body composition and metabolism (Bauman et al., 2012; Bauman et al., 1999a, 1999b; Bauman et al., 1999; Bauman and Cardozo, 2015; Bauman and Spungen, 2000; Gorgey et al., 2018; Spungen et al., 2003, 1995; Wecht and Bauman, 2013).

Increasingly, it is appreciated that due to ANS impairments, the immune system is also negatively changed by SCI. Infections are the leading cause of re-hospitalization and of mortality for persons with SCI, who are more than 80 times more likely to die of sepsis than uninjured persons (Cardenas et al., 2004; National Spinal Cord Injury Statisical Center, 2019; DeJong et al., 2013; DeVivo et al., 1993; Yang et al., 2015). In addition to increased infection risk, individuals with SCI have elevated systemic levels of inflammatory mediators, e.g. (Bank et al., 2015; Herman et al., 2018; Monahan et al., 2015; Papatheodorou et al., 2017; Schwab et al., 2014; Stein et al., 2013). Elevated markers of inflammation are most prevalent in persons with the greatest degree of neurological deficits and the least mobility (Morse et al., 2008; Neefkes-Zonneveld et al., 2015; Schwab et al., 2014). In the central nervous system (CNS), high levels of inflammatory mediators are directly neurotoxic, promote neurodegeneration and impede neuroplasticity (Phillips, 2017; Yong et al., 2004). *In this review, a general overview of inflammation, state-of-the-art knowledge of the prevalence, impact and potential therapeutic strategies for individuals with SCI will be provided and discussed.*

2. General overview of immunity, inflammation and the cytokine theory of disease

While a brief review of inflammation is provided here, the reader is directed to classic immunology textbooks, such as Immunobiology: The Immune System in Health and Disease, for a more complete description of innate and adaptive immunity, including inflammation and the role of individual immune cell types (Janeway et al., 2001). Briefly, the immune system is divided into the innate and adaptive arms. The innate immune system is essentially comprised of macrophages and neutrophils, (also known as inflammatory cells), which together provide control and defense against microorganisms upon first encounter, often by recognizing patterns of conserved classes of molecules displayed on the surface of an invader (Janeway et al., 2001). A canonical example of this is recognition of Gram negative bacteria via a portion of their cell wall, lipopolysaccharide (LPS) via Toll-like Receptors (TLR) on the surface of macrophages. Cells of the innate immune system, such as macrophages, then activate potent antigen presenting cells called dendritic cells, which then migrate to lymph nodes to activate lymphocytes of the adaptive immune system. Only lymphocytes that recognize the specific antigen that a dendritic cell is presenting on its surface will

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become activated, initiating clonal expansion of the lymphocyte population into effector populations (Janeway et al., 2001).

Inflammation is described as the host immune system's response to a foreign object, microorganism, or other environmental irritant (Care, 2010). Inflammation may occur acutely within minutes, as is often the case in response to traumatic injury, and last for days, or chronically, as is in the case of autoimmune diseases, which can last for months or years (Pahwa and Jialal, 2019). Most biomedical researchers are familiar with the definitive clinical hallmarks of inflammation as *rubor* (redness), *calor* (heat), *dolor* (pain), *tumor* (swelling). Systemic inflammation is defined as a multi-organ process triggered by systemic damage that typically involves inflammation in endothelial cells, plasma, circulating white blood cells (leukocytes), connective tissue, as well as vital organs (Zotova et al., 2016).

For decades, scientists have investigated the cellular and molecular basis of inflammation with a significant breakthrough in the 1980s with the discovery of cytokines. Cytokines are small proteins are produced by immune cells in response to infection, trauma or injury (Tracey, 2007; Janeway et al., 2001). Cytokines produced locally at the site of infection, trauma or injury interact as ligands of specific receptors on the surface of the same or neighboring cell types and trigger biological responses (Janeway et al., 2001). Responses by innate and adaptive immune cells range from killing microorganisms and infected cells to producing additional pro- and anti-inflammatory cytokines and other immune mediators to secreting factors that promote wound healing and tissue repair. Macrophages, which are critical phagocytic cells of the innate immune system, produce multiple inflammatory cytokines in response to infection, injury or trauma, that include interleukins, tumor necrosis factors, and other structurally unrelated inflammatory mediators. Other types of white blood cells, such as Natural Killer (NK) cells, T cells, and B cells, can also produce cytokines in response to infection, injury or trauma. Over the past fifty years, it has become increasingly clear that many of the clinical hallmarks of inflammation are in fact due to biological effects of cytokines and other factors derived from immune cells, rather than from invading microorganisms, leading to the cytokine theory of disease (Tracey, 2007).

While cytokine responses are essential for host immunity and tissue repair, high acute or even lower but sustained levels of inflammation contribute to a host of clinical symptoms and syndromes, with negative effects on emotional and physical health. Some of the negative health effects promoted by chronic systemic inflammation include: (1) infection susceptibility via induction of suppressive immune cell phenotypes, (2) accelerated atherogenesis, (3) elevated risk of cardiovascular disease and stroke, (4) depression, and (5) ongoing tissue damage. Independent of SCI, there are multiple potential sources of inflammatory mediators in humans, including adipose tissue, local and circulating immune cells, and other organs such as the liver. For example, C Reactive Protein (CRP), a marker of systemic inflammation used clinically to stratify risk of cardiovascular disease, is primarily produced in the liver in response to inflammatory cytokines, but can also be produced by adipose tissue, macrophages, endothelial cells, lymphocytes and smooth muscle cells (Sproston and Ashworth, 2018). Baseline CRP levels are influenced by factors such as age, gender, body mass index (BMI), smoking status, estrogen levels, and genetic polymorphisms (Sproston and Ashworth, 2018). While levels across populations vary, baseline CRP levels are typically classified as: < 1 (low), 1-3 (moderate), and > 3 mg/L (high). CRP levels > 10mg/L may indicate an acute infection or trauma (Ridker et al., 2003). In a recent study of more than 6000 able-bodied adults, elevated levels of CRP correlated with the number of physical or mental unhealthy days (Wilkins et al., 2018). Inflammatory cytokines are thought to play a critical role in the aging process "inflamm-aging" by promoting accumulation of chronic diseases (Francheschi et al., 2006). Many studies have demonstrated that inflammation is increased with obesity or a sedentary lifestyle and that conversely, physical activity reduces CRP and other markers of inflammation.

2.1. Anti-cytokine therapies

The successful translation of the cytokine theory of disease into the clinic has led to an incredibly successful class of biological therapeutics, such as Infliximab, Anakinra, or Sarilumab, which block the effects of TNF-alpha, interleukin (IL)-1, and IL-6 respectively, to treat inflammation in a multitude of clinical settings, including rheumatoid arthritis, Crohn's disease, psoriasis, arthritis and lupus (Dinarello et al., 2012; Kopf et al., 2010). More recent investigation of endogenous mechanisms regulating inflammation led to the discovery by Tracey and colleagues of the cholinergic "*inflammatory reflex*", which is mediated by the vagus nerve of the parasympathetic nervous system (Borovikova et al., 2000; Tracey, 2007, 2002). In a first-in-man clinical trial, electrical stimulation of the vagus nerve was able to reduce systemic inflammatory cytokine levels and clinical symptoms in individuals with rheumatoid arthritis who were refractory to other therapeutic interventions (Koopman et al., 2016). This opened up a potentially new avenue of bioelectronic anti-inflammatory strategies. Upstream of inflammatory cytokine expression is activation of Toll-Like Receptors (TLR), which are innate pattern recognition receptors critical for maintaining immunity against pathogens and their activation promotes production of inflammatory mediators (Foster and Medzhitov, 2009). TLR modulating therapeutics are in current clinical trials for indications such as autoimmune disease and chronic inflammation (Gao et al., 2008). Of course, many other common therapeutic interventions such as non-steroidal anti-inflammatory drugs (NSAIDs), steroids or statins, also reduce levels of inflammatory mediators.

2.2. Physical activity reduces inflammation

Another anti-inflammatory therapeutic strategy that has been successful across clinical populations is consistent physical activity, which promotes both emotional and physical health. Data indicate that even light-moderate intensity activities such as walking reduce risk of comorbidities that promote coronary heart disease, prompting the American Heart Association to recommend walking at least 30 minutes per day to reduce risk of coronary heart disease and stroke (Williams and Thompson, 2013). Mechanisms underlying the health benefits of walking and other physical activities include reducing systemic inflammation and mobilizing as well as promoting effective immune cell function (Chang et al., 2019; Garber et al., 2011; Gleeson et al., 2011, 2006; Pavlov and Tracey, 2012; Walsh et al., 2011).

Being sedentary promotes inflammation, while physical activity reduces body fat, a potent source of inflammatory mediators, and reduces multiple markers of inflammation (Garber et al., 2011; Martin et al., 2009; Vieira et al., 2009; Williams and Thompson, 2013). Increased large muscle group physical activity may reduce inflammation by building muscle, reducing adiposity, and through direct action on molecular pathways, such as gene regulation of circulating leukocytes (Gjevestad et al., 2015; Neefkes-Zonneveld et al., 2015). Gene expression of the TLR signaling pathway is higher in sedentary individuals and one of the most consistent biological effects of physical activity across populations, including the elderly, is that physical activity reduces expression of CRP, TLR and other inflammatory genes (Beavers et al., 2015, 2010; Bianchi, 2018; Gleeson et al., 2011, 2006; Vieira et al., 2009). In addition to metabolic benefits, across clinical populations regular physical activity also decreases pain, depression, anxiety and stress (Americans et al., 2018; Association, 2016; Garber et al., 2011). Flynn and colleagues recently discussed that the concept of "inflamm-aging" must be considered in light of physical activity level, as decreased physical activity is often associated with increased aging and the converse appears to be true (Figaro et al., 2006; Flynn et al., 2019; Jefferis et al., 2014; Sousa et al., 2016). Individuals with SCI, who often have profoundly reduced physical activity, are often considered to be in a state of accelerated aging, manifested by many clinical signs including altered carbohydrate and lipid metabolism (Bauman and Spungen,

1994; Nash, 1994a). In order to understand which anti-inflammatory therapeutic interventions (pharmacological, physical activity, or other) may be most useful or appropriate for testing in the SCI population, we will next consider the published literature demonstrating elevated systemic inflammation after SCI.

2.3. Anatomical origins of systemic inflammation in SCI: Autonomic dysfunction

As mentioned above, in persons with SCI, impaired autonomic regulation of organ systems below the injury level is associated with complex secondary medical consequences, ranging from autonomic dysreflexia to adverse changes in metabolism (Wecht and Bauman, 2013). Disrupted descending ANS control following SCI triggers impairments in many critical organ systems including the heart, peripheral and cerebral vasculature, lung, bowel, bladder, sudomotor and thermoregulatory centers (Bauman and Spungen, 2000; Krassioukov et al., 2012). A causal relationship has been described and proposed between SCI level-dependent changes in autonomic and immune system function that range from chronic inflammation to immunosuppression (Brommer et al., 2016; Failli et al., 2012; Kopp et al., 2017; Prüss et al., 2017; Riegger et al., 2009, 2007; Schnell et al., 1999). In particular, persons with SCI rostral to thoracic level 6 (T6), where sympathetic nervous system (SNS) fibers exit the spinal cord and innervate immune organs, have the greatest inflammation and infection susceptibility (Campagnolo et al., 2000; Failli et al., 2012; Hughson and Shoemaker, 2015; Schwab et al., 2014). This is particularly important in light of the fact that the most common level of injury is cervical and incomplete tetraplegia is the most common neurological status(National Spinal Cord Injury Statistical Center, 2019). After SCI, cardiometabolic and other organ systems may also be influenced by autonomic dysfunction. Deconditioning, due to the reduced physical activity with paralysis, also contributes to autonomic downregulation, which may potentially further promote inflammation (Wecht et al., 2001). Better 24-hour heart rate variability was reported in more active persons with SCI and vagal (parasympathetic) recovery after a maximal exercise bout was enhanced in endurance trained persons with paraplegia compared to their sedentary counterparts (Rosado-Rivera et al., 2011; Wecht et al., 2006). Thus, bioelectronic approaches to reducing inflammation in SCI, such as vagus nerve stimulation, may need to be considered in the context of additional therapeutic approaches such as physical activity.

Krassouikov and Claydon characterized the severity of autonomic injury in persons with SCI using supine plasma noradrenaline levels (Claydon and Krassioukov, 2008a, 2008b, 2006). Injuries were defined as "autonomically complete" by Claydon and colleagues if plasma noradrenaline levels are below 0.56 $nmol/L^{-1}$ (Claydon and Krassioukov, 2008b). Immune cells are regulated by noradrenaline and changes in catecholamines may modulate inflammation directly and indirectly (Chang et al., 2019; Pavlov and Tracey, 2017, 2015, 2012). Understanding the relationship between the autonomic nervous system and immune system function, and identifying therapeutic modalities that improve both, is thus highly desirable for persons with chronic SCI.

3. Published literature demonstrating elevated systemic inflammation in individuals with SCI

3.1. Inflammation in acute SCI

The topic of acute intraspinal inflammation after SCI has been intensely investigated in pre-clinical models and reviewed in many excellent publications, and thus it will only be briefly mentioned here (*for example, see Special Issue Experimental Neurology 2014, Vol 258, Neuroimmunology of Spinal Cord Injury*). Wound healing is required after SCI and in animal models and over minutes to days after traumatic SCI, resident microglia, as well as neutrophils, macrophages and lymphocytes recruited from the periphery, are activated. These cells and reactive astrocytes release reactive oxygen species, pro-inflammatory cytokines and chemokines, creating a fibrin-rich clot and glial scar that amplifies the inflammatory response and inhibits axonal regeneration (Burnside and Bradbury, 2014; Tran et al., 2018). Locally produced inflammatory cytokines exacerbate neuronal loss and induce secondary damage after SCI (Bethea et al., 1998; Horn et al., 2008; Kigerl et al., 2009; Klusman and Schwab, 1997; Schnell et al., 1999; Streit et al., 1998).

In human SCI, a limited number of immune parameters have been studied in relatively small cohorts. A study of cadavers showed that intraspinal activated microglia/macrophages were observable within one hour after SCI, present in large numbers within zero to three days, peaked in number at 5-10 days and persisted for months after injury (Fleming et al., 2006). The same study demonstrated that neutrophils were present in the spinal cord within hours of injury, while CD4+ and CD8+ T cells were present weeks after SCI. Discrete subsets of activated macrophages promote axon retraction or regeneration in acute SCI (Kigerl et al., 2009). Based on the concept of a monocyte/macrophage population that is beneficial to the spinal cord after injury, a phase II clinical trial of autologous macrophages delivered into the caudal lesion boundary within 14 days of initial SCI was recently performed, but did not demonstrate differences in any of its primary outcomes (Lammertse et al., 2012).

Due to its known deleterious effects such as neurotoxicity, acute inflammation after SCI has long been considered an important therapeutic target. Steroids are widely used in clinical settings as potent anti-inflammatory drugs. Glucocorticoids have been shown to be anti-inflammatory, anti-oxidant, and neuroprotective in the mammalian CNS and in pre-clinical models of SCI, *e.g.*(Genovese et al., 2009; Genovese et al., 2007a; Genovese et al., 2007b; Glezer and Rivest, 2004; Karsy and Hawryluk, 2017). Steroid use (methylprednisolone) in acute SCI was the topic of three national clinical trials (NASCIS I-III) (Ahuja et al., 2017; Badhiwala et al., 2018; Bracken and Holford, 2002, 1993; Bracken et al., 1998; Coleman et al., 2000; Lyons et al., 1990; Bracken et al., 1984, 1985). Unfortunately, the trials did not report consistent improvements in neurological recovery and did report serious adverse events such as increased bleeding. The current acute management guidelines for adults with traumatic SCI state that: "*No clinical evidence exists to definitively recommend the use of any neuroprotective pharmacological agent, including steroids, in the treatment of acute spinal cord injury in order to improve functional recovery*"(Wing, 2008). Despite disappointing results of the NASCIS trials, the concept of targeting inflammation acutely after SCI to reduce neurotoxicity from inflammation remains appealing.

Identification of specific elevated inflammatory mediators have thus been of intense interest as potential therapeutic targets and also as biomarkers of injury severity (Kwon et al., 2019). In a groundbreaking study, Kwon and colleagues identified a panel of biomarkers (S-100β, GFAP and IL-8) elevated in CSF within 24 hours of SCI that was predictive of segmental motor recovery at six months after SCI (Kwon et al., 2010). This study also showed that levels of inflammatory mediators in blood mirrored those in CSF, albeit at concentrations at least 10-fold lower. Within the first 72 hours after SCI, elevated levels of several inflammatory mediators (IL-6, IL-8, IL-16, MCP-1 and IP-10) were proportional to injury severity, and highest in American Spinal Injury Association Scale (AIS) A participants. Subsequently, Kwon and colleagues studied proteins related to structural damage of neurons in individuals with acute SCI and found that levels of S-100β, neuron specific enolase and neurofilament-H were higher in those with clinically motor complete, as compared to incomplete, injuries (Pouw et al., 2014). Acute cerebrospinal fluid (CSF) inflammatory and neuronal structural biomarkers were as good as MRI for indicating AIS grade six months later (Dalkilic et al., 2018). Biomarker studies in acute SCI are ongoing by Kwon and other colleagues, including both microRNA and proteomic profiling in cerebrospinal fluid (CSF) and sera (Streijger et al., 2017; Tigchelaar et al., 2019; Wu et al., 2016).

3.2. Inflammation in chronic SCI

Far less is known from pre-clinical models about the time course, extent and impact of intraspinal or systemic inflammation in the chronic phase of SCI or how it relates to acute inflammation. In rodent models of SCI, elevated numbers of MHCII+ microglia/macrophages have been observed six weeks after SCI (Popovich et al., 1993; Rosenberg et al., 2005). Large numbers of T cells have been observed in the spinal cord up to 60 days after injury, and infiltrating dendritic cells were observed in mice 60 days after SCI (Sroga et al., 2003). In rodent models of SCI, signs of inflammation persist 6 weeks after injury and in the case of one study, more than 25 weeks after injury (Schwab et al., 2014). In a cadaver study, inflammatory cells were detected in human spinal cord tissue for years after the initial injury (Fleming et al., 2006).

Systemic inflammation is common in individuals with chronic SCI (Nash et al., 2018, 2016; Noller et al., 2017). Due to its clinical utility, several studies have demonstrated elevated levels of CRP in individuals with chronic SCI (Davies et al., 2007; Frost et al., 2005; Nash et al., 2016; Ridker et al., 2003). A recent meta-analysis of data from more than 250 persons with SCI concluded that the mean CRP level was 4.8mg/dL; 76% of individuals included in the analysis had moderate-high risk of cardiovascular dysmetabolic syndrome (Nash et al., 2016). A new SCI cardiometabolic clinical practice guideline recommends that CRP and other inflammatory mediators be studied further for their ability to predict and influence risk of persons with SCI developing cardiometabolic diseases (Nash et al., 2018). As mentioned, individuals with SCI at levels rostral to T6 have the most inflammation; CRP levels are highest in persons with SCI who are motorized wheelchair users (Morse et al., 2008; Neefkes-Zonneveld et al., 2015; Schwab et al., 2014).

Circulating plasma levels of a limited number of other inflammatory cytokines and adipokines have also been shown to be significantly elevated in individuals with chronic SCI (Farkas et al., 2018; Farkas and Gater, 2018; Hayes et al., 2002; Segal et al., 1997). In a study examining the relationship of cytokine levels to pressure ulcers in chronic SCI, circulating plasma levels of IL-6, IL-2R, and ICAM-1 were significantly elevated in all chronic SCI participants as compared to uninjured controls and cytokine levels were higher in individuals with slow resolving pressure ulcers (Segal et al., 1997). . In a later study implicating the IL-2 pathway, individuals with chronic SCI had higher levels of IL-2 and TNFα, as well as anti-GM1 ganglioside antibodies, than uninjured individuals. The majority of participants with SCI in that study did not have higher circulating levels of IL-4, IL-10 or white blood cells (Hayes et al., 2002). Participants with chronic SCI were shown to have higher levels of CRP, but not IL-6 or TNF-α, than uninjured controls (Frost et al., 2005). Davies et al reported on a larger number of participants with chronic SCI (N = 56) that serum levels of IL-6, TNF-α, IL-1RA, and anti-GM1 antibodies were significantly elevated as compared to uninjured controls, but not IL-2, IL-4, or IL-10 (Davies et al., 2007). Individuals with the highest levels of IL-6 or IL-1RA had neuropathic pain, urinary tract infections (UTI), or pressure ulcers. Bloom and colleagues discovered that two inflammatory proteins that are present constitutively at high amounts in both neuronal and immune cell types, MIF and HMGB1, which is also an endogenous ligand of the innate immune TLR receptor TLR4, are elevated in individuals with chronic SCI, regardless of injury severity, level, or time from injury (Papatheodorou et al., 2017; Stein et al., 2013).

Recent technical advances have provided the opportunity to examine genome wide changes in inflammation and other immune related mediators. Two functional genomics studies have examined this question in individuals with chronic SCI (Herman and Bloom, 2018; Saltzman et al., 2013). The first study of white blood cell (leukocyte) gene expression was performed by Battaglino, Morse and colleagues in males who were uninjured or with chronic SCI (N = 7, 13) and showed elevated expression of BCMA, BAFF and APRIL, which are autoimmune-promoting cytokines (Saltzman et al., 2013). This is consistent with prior data and laboratory signs of autoimmunity in SCI (Schwab et al., 2014). Bloom and colleagues performed a more recent, larger functional genomics study in chronic SCI, analyzing data from 31 individuals with SCI and 26 uninjured individuals (males and females in both groups)(Herman et al., 2018). This study identified profound changes in whole blood gene expression in chronic SCI, including a dramatic reduction in Natural Killer (NK) cell genes and upregulation of inflammatory genes. Of the 2226 genes that were differentially expressed in chronic SCI, more than one thousand genes were elevated. TLR-related signaling genes, which promote inflammation and can drive infection susceptibility when chronically elevated (Iwasaki and Medzhitov, 2004; Jialal et al., 2014), were strongly upregulated in individuals with higher cord level lesions. There were no statistically significant differences in samples obtained six months apart from individuals with SCI, supporting the notion that the changes in gene expression observed reflect a chronic inflammatory state (Herman et al., 2018; Herman and Bloom, 2018). Validating the potential impact of this approach to identify pharmacological strategies to reduce inflammation, Bloom and colleagues discovered genes elevated in persons with chronic SCI that are targets of FDA-approved drugs, such as JAK2, the beta adrenergic receptor, and other genes targeted by drugs or compounds being tested in clinical trials (Herman et al., 2018; Herman and Bloom, 2018). Neither of these first functional genomics studies in chronic SCI measured body composition, physical activity, mobility mode, and autonomic injury severity, all of which may contribute to or correlate with systemic inflammation.

4. How systemic inflammation may impact various aspects of living with SCI

4.1. Systemic inflammation influences intraspinal events

Systemic inflammation, either by endogenous or exogenous mediators, may promote intraspinal inflammation (Kigerl and Popovich, 2009; Schwab et al., 2014). Acutely after SCI, the blood-spinal cord barrier is breached and increased vascular permeability persists at 28 days post injury and also at eight weeks after injury (Herrera et al., 2010; Popovich et al., 1996; Schnell, 1999). Studies of the mechanisms underlying the chronic autoimmune disease, lupus, have shown that stress or infection can cause breaches in the blood brain barrier, allowing for high molecular weight mediators, such as antibodies, to gain access to the CNS, where they are neurotoxic and can alter neuronal function (Degiorgio et al., 2001; Faust et al., 2010; Kowal et al., 2004). A similar scenario is thus also possible for circulating inflammatory mediators in chronic SCI, where environmental conditions promoting breach of the vascular permeability barrier, such as infection, are common. Cytokines and chemokines elevated in the plasma may therefore be able to gain access to, and act upon, neurons within the CNS in chronic SCI.

In both the acute and chronic phase, pre-clinical evidence supports the concept that systemic inflammation negatively modulates functional recovery and systemic anti-inflammatory interventions promote functional improvements. For example, minocycline is neuroprotective in SCI and yielded improved locomotor function in mice six weeks after SCI (Arnold and Hagg, 2011; Teng et al., 2004). In a mouse model of SCI, inhibition of Regulatory T cell function with anti-CD25 antibodies promoted locomotor recovery(Arnold and Hagg, 2011). Acute intermittent hypoxia (AIH) is a relatively new strategy to induce neuroplasticity and systemic inflammation may influence responsiveness to AIH after SCI. In a series of elegant studies, Mitchell and colleagues demonstrated that administration of the exogenous TLR2/4 ligand, lipopolysaccharide (LPS), which is a portion of a Gram negative bacterial cell wall, triggered systemic and intraspinal inflammation that blocked phrenic nerve long-term facilitation induced by mild AIH and that this effect of LPS could be abrogated by NSAIDs (Huxtable et al., 2013; Vinit et al., 2011). Administration of A2A antagonists overcome LPS-induced

constraints on AIH motor facilitation in rats (Hoffman et al., 2010; Navarrete-Opazo et al., 2017). This is in contrast to the phrenic long-term facilitation triggered by more severe AIH, which Mitchell and colleagues showed to be adenosine-dependent and inflammation-independent (Agosto-Marlin et al., 2016). A recent clinical trial with a cross-over design aimed to test effects of a single dose of ibuprofen 90 minutes before AIH did not show an effect (Lynch et al., 2017). However, the study did not measure markers of inflammation before or after the NSAID, making the result difficult to interpret. In a rat model of chronic SCI (cervical dorsolateral quadrant lesion), Fouad and colleagues showed that systemic administration of LPS triggered intraspinal inflammation (Torres-Espin et al., 2018). In that study, animals that received LPS together with *high intensity* rehabilitation training had better neurological recovery, which suggested to the authors that "mild neuroinflammation may be used to enhance the efficacy of rehabilitative training after chronic spinal cord injury." (Torres-Espin et al., 2018) In contrast, the authors also noted that LPS given *alone* or in combination with *low intensity* task-specific training had worse recovery of reaching and grasping, suggesting that effects of inflammation may be distinct in this preclinical model when combined with or without high intensity rehabilitation interventions (Torres-Espin et al., 2018). As in acute SCI, persistent systemic inflammation in chronic SCI may exert a negative influence and may partially explain why some persons experience less benefits than others from an experimental intervention or standard of care rehabilitation protocol (Schwab et al., 2014; Torres-Espin et al., 2018) The number of rehabilitation clinical trials to enhance functional abilities in persons with chronic SCI is rapidly increasing.

In addition to neurological recovery, inflammation may impact many clinically significant medical consequences of SCI, including neuropathic pain, which affects the majority of individuals living with SCI (National Spinal Cord Injury Statistical Center, 2019; Gibbs et al., 2019). Walters and colleagues discovered that after SCI, primary nociceptors are hyperexcitable (Bedi et al., 2011, 2010). As reviewed recently by Walters, primary nociceptors are sensitive to inflammatory mediators and anti-inflammatory therapies that target cyclooxygenase II, IL-6, IL-10 or TNF-alpha have been shown to reduce pain in pre-clinical models. As mentioned above, minocycline is neuroprotective and promotes recovery in pre-clinical models of SCI. In a separate study, minocycline also decreased neuropathic pain in rodents four weeks after SCI (Hains and Waxman, 2006). Detloff and colleagues have shown macrophages infiltrate the dorsal root ganglia (DRG) where they promote pain after SCI and that exercise decreases both macrophage infiltration and hypersensitivity (e.g.(Chhaya et al., 2019; Detloff et al., 2016, 2014, 2013, 2008). An observational cohort study to identify inflammatory and other biomarkers of pain in individuals with chronic SCI is currently being conducted (NCT00913471).

Newly injured individuals with SCI are at increased risk for developing rapid obesity concurrent with accelerated atherogenesis, type II diabetes mellitus, and other medical consequences that promote stroke and cardiovascular disease (Bauman et al., 1999a; Bauman and Spungen, 2008, 2000, 1994; Davies et al., 2007; Frost et al., 2005; Gater, 2007; Gater et al., 2019; Hayes et al., 2002; Pavlov and Tracey, 2012; Stein et al., 2013). Spungen and colleagues showed that individuals with SCI gain an average of 10kg in total fat mass, including abdominal fat, within the first two years after injury (Bauman et al., 2012; Emmons et al., 2011; Farkas and Gater, 2018) They also showed that individuals with SCI lose 3.2% of lean body tissue per decade (Bauman et al., 2012). The prevalence of obesity is estimated to be 40–60% in the SCI population (Gater, 2007; Rajan et al., 2008; Shojaei et al., 2017). As mentioned, above, fat tissue itself is a potent source of inflammatory cytokines and elevated circulating LPS, or "metabolic endotoxemia," in obesity is increasingly appreciated as a factor promoting chronic systemic inflammation (Bianchi, 2018; Cani et al., 2012; Chang et al., 2019). Whether individuals with SCI have elevated levels of circulating LPS is presently unknown. As mentioned earlier, systemic inflammation in chronic SCI correlates inversely with mobility status (Morse et al., 2008; Neefkes-Zonneveld et al., 2015; Schwab et al., 2014) and it may promote the medical consequences which are higher in persons who are non-ambulatory, such as elevated risk of type II diabetes, accelerated atherogenesis, cardiovascular disease and stroke. Thus, fat reduction in individuals with SCI is considered an important strategy to reduce inflammation (Bauman and Spungen, 2008, 2000; Bianchi, 2018; Cirnigliaro et al., 2015). *Given the evidence of elevated inflammation in SCI, there is clear rationale for launching studies to better understand how inflammation negatively influences responsiveness to rehabilitation interventions and to identify strategies that decrease inflammation to promote general health and wellness.*

5. Potential strategies to reduce systemic inflammation in SCI

5.1. Pharmacological approaches to reduce inflammation

The systemic immune system is extremely druggable and as mentioned above, anti-inflammatory/anti-cytokine biological agents and drugs are a billion dollar industry (Kopf et al., 2010). Coupled with a series of recent human studies demonstrating elevated inflammation acutely after SCI (*e.g.* Dalkilic et al., 2018; Kwon et al., 2019, 2010; Streijger et al., 2017; Tigchelaar et al., 2019; Wu et al., 2016), this supports the rationale for ongoing clinical trials that aim to dampen inflammation via pharmacological therapy in acute SCI. A recent phase II clinical trial of minocycline was feasible and demonstrated encouraging results particularly for individuals with cervical motor incomplete injuries (Casha et al., 2012). An analysis of inflammatory biomarkers in that trial indicated that heme oxygenase and neurofilament heavy chain were reduced in CSF of minocycline-treated patients (Casha et al., 2018). A phase III study of minocycline in acute SCI is listed as recruiting (NCT01828203). A phase I study of ibuprofen and indomethacin in acute SCI was recently completed, with results to be reported (Kopp et al., 2016). Table 1 shows examples of clinical trials or studies investigating how inflammation may change in response to various interventions in SCI or if inflammatory mediators may serve as biomarkers of neurological recovery in SCI, curated from www.clinicaltrials.gov.

As mentioned above, in a functional genomics study in chronic SCI, pro-inflammatory genes were among the most upregulated differentially expressed genes, including JAK2, a protein tyrosine Janus kinase family member. JAK2 is the target of several FDA-approved drugs and there are more than 60 studies of various conditions and diseases targeting the JAK pathway listed on clinicaltrials.gov. In Herman et al., 2018, the beta-2 adrenergic receptor, the target of several FDA-approved drugs, was also identified as elevated in individuals with chronic SCI (Herman et al., 2018; Herman and Bloom, 2018). TLR signaling pathways were highly enriched among genes upregulated in participants with SCI rostral to T5 (Herman et al., 2018). TLR modulating agents are listed in more than 200 clinical trials, including some for sepsis, which is associated with infections and is a major cause of mortality for persons with SCI (National Spinal Cord Injury Statistical Center, 2019; Gao et al., 2008). Adrenomedullin, a vasodilator that is increased in sepsis, was also upregulated in participants with SCI rostral to T5, see Supplementary Table 1 in (Herman 2018). A recent phase I clinical trial of anti-adrenomedullin antibodies was performed, with the hopes of developing them as a therapeutic agent in sepsis (Geven et al., 2018).

5.2. Dietary changes may reduce inflammation and be beneficial after SCI

As mentioned earlier, fat and obesity are associated with systemic inflammation, independent of SCI. Ditor and colleagues have spent the last several years developing and testing an anti-inflammatory diet in individuals with chronic SCI (Allison et al., 2018, 2016; Allison et al., 2017b, 2017a; Allison and Ditor, 2015; Bailey et al., 2018). In small

Table 1
Examples of clinical trials or studies investigating how inflammation may change in response to various interventions in SCI or if inflammatory mediators may serve as biomarkers of neurological recovery in SCI, curated from www.clinicaltrials.gov.

Title	NCT identifier
A. Search Terms "Inflammation" AND "spinal cord injuries"	
A Pilot Nutrition Program for Spinal Cord Injury and MS	NCT03977922
Aquatic Specific Physiotherapy on Incomplete Spinal Cord Injuries	NCT03962218
Single Exercise Session or Meal vs Control in SCI: Case Series	NCT03955523
Clinical Study of an Autologous Stem Cell Product in Patients With a (Sub)Acute Spinal Cord Injury	NCT03935724
Effect of Preventional Drug Therapy on Pain Regulation Mechanisms Among SCI	NCT03748290
Postprandial Lipid Tracer and Exercise in Spinal Cord Injury	NCT03691532
Health Promotion and Cardiovascular Risk Reduction Among People With Spinal Cord Injury	NCT03689023
Ketogenic Diet to Improve Neuro-recovery	NCT03509571
The Neuroinflammatory Response and Biomarkers in Acute Traumatic Spinal Cord Injury	NCT03505463
Adipose Stem Cells for Traumatic Spinal Cord Injury	NCT03308565
B. Search Terms "biomarkers" AND "spinal cord injuries"	
Canadian-American Spinal Cord Perfusion Pressure and Biomarker Study	NCT03911492
Effects of Remote Ischemic Conditioning on Hand Use in Individuals With Spinal Cord Injury	NCT03851302
The Neuroinflammatory Response and Biomarkers in Acute Traumatic Spinal Cord Injury	NCT03505463
Biomarkers of Spontaneous Recovery From Traumatic Spinal Cord Injury	NCT02731027
Prognostic Value of Biochemical Markers in Cerebrospinal Fluid for Functional Outcome of Spinal Cord Injured Patients	NCT01861808
Molecular Markers of Neuroplasticity During Exercise in People With Incomplete Spinal Cord Injury	NCT01538693
Detection of Peripheral Blood Biomarkers in Intermediate Phase Spinal Cord Injury: Correlation With Neurological and Functional Outcomes, and Comparison to Other Central and Peripheral Neurological Conditions	NCT01516385
The Canadian Multicentre CSF Monitoring and Biomarker Study	NCT01279811
S-100B and Neuron-specific Enolase (NSE) in Spinal Trauma	NCT00980434

group sample sizes, they have seen positive effects on multiple outcome measures related to pain, cognitive function, mood, and nutrition. Ketogenic diets have been explored for their anti-inflammatory effects in epilepsy, cancer and in other indications (Wright and Simone, 2016; Yu et al., 2013). Tetzlaff and colleagues have shown in pre-clinical studies of SCI that a ketogenic diet improves motor function (Streijger et al., 2013). Based in part on the rationale that it should attenuate neuroinflammation, neurological effects of a ketogenic diet are now being studied in a clinical trial of individuals with acute SCI (NCT03509571).

5.3. Regular physical activity may reduce inflammation and is beneficial for persons with SCI

As highlighted by Nash and others since the 1990s, exercise is an excellent strategy to modulate the immune system in individuals with SCI, depending on autonomic innervation and other factors (Nash, 2005, 2000, 1994a, 1994b; Noller et al., 2017). For cardiometabolic health benefits, adults with a SCI are recommended to engage in at least 30 minutes of moderate to vigorous intensity aerobic exercise three times per week (Martin Ginis et al., 2017; van der Scheer et al., 2017). While there is less data available for tetraplegia than paraplegia, physical activity has multiple health benefits for individuals with SCI (Bresnahan et al., 2019; Gorgey et al., 2012; Hicks et al., 2011; van der Scheer et al., 2017). Most studies have measured effects after an acute bout of exercise. Traditionally, physical activity and exercise modalities studied in persons with chronic SCI include: arm crank ergometer exercise, wheelchair training on motorized treadmill, functional electrical stimulation (FES) cycling, wheelchair competition sports, and body-weight supported treadmill training, with some studies using stratification by mobility or activity level (Neefkes-Zonneveld et al., 2015; van der Scheer et al., 2017). Several studies in individuals with chronic SCI showed an inverse correlation between physical activity levels and CRP, again with the caveat that most of the data is from small sample group sizes of persons with paraplegia, rather than tetraplegia, the population in most need of immune system boosting (Koury et al., 2013; Neefkes-Zonneveld et al., 2015). Reductions in inflammatory cytokines after consistent physical activity in persons with SCI has also been shown (Bochkezanian et al., 2015; Nash, 2005, 1994b; Neefkes-Zonneveld et al., 2015; Noller et al., 2017). The most widely studied cytokine in this context is IL-6, which has been shown to be reduced in individuals with SCI who engaged in exercise such as FES cycling, but again, the caveat is that most reports have been of small sample group sizes and studied after acute bouts of exercise rather than effects of prolonged exercise training programs designed for improving cardiovascular fitness (Neefkes-Zonneveld et al., 2015; van der Scheer et al., 2017).

5.4. Potential modes of physical activity for individuals with chronic SCI

While evidence-based physical activity guidelines exist, there are many barriers for persons with SCI to achieve consistent physical activity and there is a need to launch larger prospective studies to determine anti-inflammatory effects of consistent exercise in the chronic SCI population (Barclay et al., 2016; Blauwet, 2019; Cowan et al., 2013). Persons with acute and chronic SCI are often unable to perform upright overground or lower extremity exercise and/or do not have regular access to adaptive sports equipment. Exoskeletons have not yet been widely incorporated into clinical or home use, as the potential health benefits of exoskeletal assisted walking (EAW) are only now beginning to be reported. The biomedical and rehabilitation community is in the early stages of examining the therapeutic potential of these devices. Exoskeletons may be used as assistive devices that enhance mobility, with potential to increase community integration. However, at this stage in the development and technology of these devices, mobility is limited compared with the wheelchair. Preliminary data suggest that exoskeletons are most likely to be used as a form of upright, over ground physical exercise that provides a stimulus for remaining innervated musculoskeletal tissues above the lesion and in individuals with intact neural sparing below the level of injury.

Demonstration of quantifiable health benefits such as reduced body fat and inflammation would provide evidence for more third-party reimbursement for these devices. Encouraging data show that EAW in persons with chronic SCI provides opportunities for overground walking and is metabolically challenging, yielding several health benefits similar to walking in able-bodied populations (Asselin et al., 2016; Evans et al., 2015; Fineberg et al., 2013; Kozlowski et al., 2015). Spungen and colleagues found that EAW provides mechanical loading and exertion (heart rate, oxygen demand) similar to walking in other populations (Asselin et al., 2015; Yang et al., 2015). Importantly, two groups have now found that EAW led to significant improvements in body composition and total body weight loss (Karelis et al., 2017;

Spungen et al., 2013). An ongoing study by Bloom and Spungen to determine if there is a correlation between decreased body fat and inflammatory mediators in individuals with chronic SCI who perform consistent exoskeletal assisted walking (NCT02314221, NCT02658656).

For the general population, telehealth approaches to delivering physical activity is a highly successful commercial industry. Home-based physical activity delivered via a real-time telemedicine portal is intuitively applicable to persons living with reduced mobility due to SCI, to modify the common environmental barriers to achieving the anti-inflammatory and other benefits of regular physical activity. To address these and other barriers, telehealth approaches are being increasingly studied in the context of SCI, including voice only, video and voice, web-based live and stored video content. Encouraging results have been obtained across physical health measures, (i.e., assessment/management of pressure ulcers, catheterization, wound care, and rehabilitation of hand function), as well as psychological health. A study measured the effects of a home-based exercise program in persons with chronic SCI, including outcome measures of metabolism, body composition, physical activity, energy intake, resting metabolic rate, heart rate and blood pressure, aerobic capacity, immune function, and adipose gene expression, with positive effects thus far reported on health-related quality of life (Nightingale et al., 2018, 2016). Sweet and colleagues are conducting a randomized controlled trial of an 8-week telerehabilitation program for individuals with paraplegia to measure changes in psychosocial variables related to exercise participation and quality of life, with positive preliminary results reported (Chemtob et al., 2019; Sweet et al., 2017). A recent small qualitative study showed that individuals with tetraplegia liked the concept of a physical activity program delivered via a telemedicine platform and made concrete suggestions about desired features of such a program (Pekmezaris et al., 2019). Backus and colleagues are currently conducting a comparative effectiveness study of in-person or telemedicine-based supervision of an exercise program for individuals with multiple sclerosis (NCT03468868), which may inform future development of similar studies for individuals with SCI.

6. Summary/Conclusions

In summary, there is substantial evidence demonstrating systemic inflammation in individuals with acute or chronic spinal cord injury. An open question is how acute inflammatory events contribute to chronic inflammation in SCI. This question is being addressed in several ongoing prospective longitudinal studies that recruit individuals with acute SCI and then follow them into the chronic phase, (e.g. NCT02731027, NCT01279811). Independent of SCI, inflammation negatively impacts the nervous system and promotes many of the common medical consequences of living with SCI. Identifying therapeutic modalities that target inflammation and may therefore improve functional recovery and/or multiple medical consequences of SCI is therefore of interest. Outside of SCI medicine, there are many anti-inflammatory pharmacological and non-pharmacological therapies that are in use or under investigation in the clinic. Interesting data from diet and physical activity studies, which are anti-inflammatory and have multi-modal health effects therapeutic strategies across populations, suggest that these types of strategies may also reduce inflammation and be beneficial in individuals with SCI. Larger prospective randomized clinical trials must be performed in individuals with acute or chronic SCI to identify whether these modalities, alone or combined with pharmacological anti-inflammatory therapies, should be introduced broadly into the medical management of SCI.

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