NEUROSCIENCE

NEUROSCIENCE FOREFRONT REVIEW

S. David, R. López-Vales / Neuroscience 466 (2021) 273–297

Bioactive Lipid Mediators in the Initiation and Resolution of Inflammation after Spinal Cord Injury

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Abstract—Neuroinflammation is a prominent feature of the response to CNS trauma. It is also an important hallmark of various neurodegenerative diseases in which inflammation contributes to the progression of pathology. Inflammation in the CNS can contribute to secondary damage and is therefore an excellent therapeutic target for a range of neurological conditions. Inflammation in the nervous system is complex and varies in its fine details in different conditions. It involves a wide variety of secreted factors such as chemokines and cytokines, cell adhesion molecules, and different cell types that include resident cell of the CNS, as well as immune cells recruited from the peripheral circulation. Added to this complexity is the fact that some aspects of inflammation are beneficial, while other aspects can induce secondary damage in the acute, subacute and chronic phases. Understanding these aspects of the inflammatory profile is essential for developing effective therapies. Bioactive lipids constitute a large group of molecules that modulate the initiation and the resolution of inflammation. Dysregulation of these bioactive lipid pathways can lead to excessive acute inflammation, and failure to resolve this by specialized pro-resolution lipid mediators can lead to the development of chronic inflammation. The focus of this review is to discuss the effects of bioactive lipids in spinal cord trauma and their potential for therapies.

Key words: spinal cord injury, inflammation, bioactive lipids, omega-3 fatty acids, prostaglandins, phospholipase A_2.

INTRODUCTION

Spinal cord injury (SCI) is a devastating condition that leads to loss of motor, sensory and autonomic control below the level of lesion. This loss is permanent because of the limited capacity of the CNS for repair. The worldwide incidence of traumatic spinal cord injury (SCI) is 10.5 cases per 100,000 population. The estimated new cases annually are about 768,500 globally (Kumar et al., 2018). The incidence of SCI is lower in low to middle income countries (8.72 per 100,000 persons) as compared to high-income countries (13.69 per 100,000 persons) (Kumar et al., 2018), with road traffic accidents, followed by falls, being the leading causes of SCI. The incidence is highly variable even in European countries ranging from 5.5 cases per million in Norway to 195.4 cases per million in Ireland (Jazayeri et al., 2015). Its incidence also varies in North and South America. The incidence rate in Canada is estimated to be 53 cases per million (published in 2012), and 40 cases per million in the US, compared to 17.3 cases per million in Brazil (between 1986 and 2007) (Jazayeri et al., 2015). According to the National Spinal Cord Injury Statistical Center (NSCISC; https://www.nscisc.uab.edu/Public_Pages/Database) in the US, the average age of SCI patients has risen from 29 years to the current 42 years over the past 50 years, with 80% of cases being males (Frontera and Mollett, 2017). Data also collected by the NSCISC indicate that 46% of cases are partial tetraplegia, followed by an equal number (20%) of partial and complete paraplegia, and 14% with complete tetraplegia. The severity of the clinical outcome and life-long nature of disabilities have a direct bearing on the economic burden to the individual and the health care system. In the US, acute surgical intervention (decompression, vertebral stabilization) costs up to $ 50,000 per patient, and medical costs alone total up to $30,000. Long-term medical costs vary considerably depending on the co-morbidities, which range from urinary tract infections (48%), pneumonia (34%), decubitus ulcers (pressure sores) (20%) and depression (27%) (Dryden et al., 2004). The estimated life-time economic burden per person with SCI in Canada ranges from $1.5 million for incomplete paraplegia to

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https://doi.org/10.1016/j.neuroscience.2021.04.026
0306-4522/

double that for complete tetraplegia (Krueger et al., 2013). With improved acute and chronic medical care, life expectancy of SCI patients has improved, depending on the level and severity of the injury and the age at which the injury is sustained. All of this highlights some of the economic costs of medical care to which is the added loss of productivity, and the life-long social and emotional toll on the individual and their families. There is therefore an urgent need to find treatments to reduce functional loss after SCI.

The damage to the spinal cord and functional disability are due to both the physical damage caused by the primary injury, and secondary damage that occurs subsequent to trauma. The incidence and severity of the primary injury can be reduced by safe driving habits and attention to safety in the workplace and in sports and recreation but cannot be completely prevented. Although preventing and reversing primary damage remains of utmost importance, there is still an important need to limit the extent of secondary damage in order to aid in maximizing functional recovery. A wide range of factors can contribute to secondary damage. These include oxidative damage, ischemia, the effects of proinflammatory cytokines, glutamate, apoptosis of glia (e.g., oligodendrocytes) and neurons, and multiple detrimental effects of inflammation. There are overlapping boundaries between the effects mediated by these and other mechanisms that drive secondary damage. It is becoming increasingly clear that inflammation in the CNS after injury has both detrimental and beneficial effects. An understanding of the mechanisms that drive these two opposing aspects of inflammation is needed to develop effective therapeutic strategies.

In this review, we will focus our attention specifically on the role of bioactive lipids in triggering the initiation and resolution of inflammation after SCI. Bioactive lipids are a large family of versatile mediators of inflammation that deserve special attention. They include prostaglandins and related eicosanoids known to be important regulators of inflammation. Several enzymes are needed to convert fatty acids associated with cell membranes to eicosanoids and other bioactive lipid mediators. The first enzyme in this process is phospholipase A_2 (PLA_2), which hydrolyzes the ester bond at the *sn*-2 position of membrane glycerophospholipids to release arachidonic acid (AA) as well as other fatty acids, and lysophospholipids. Several downstream synthetic enzymes are needed for the generation of prostaglandins and other eicosanoids from AA. These bioactive molecules mediate their effects via binding to a family of G-protein coupled receptors. The eicosanoids generated from AA, an omega-6 polyunsaturated fatty acid (n-6 PUFA), are generally proinflammatory, although some, such as prostaglandin J2, are anti-inflammatory. On the other hand, omega-3 fatty acids (n-3 PUFA) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) give rise to a wide range of bioactive lipid mediators that actively resolve inflammation (Serhan et al., 2015). The fatty acid composition of membrane phospholipids, their regional variability, and localization to different immune and CNS cell types, and their changes after SCI, are factors that impact on the inflammatory response and determine the initiation and resolution of inflammation. Here, we take a renewed look at the growing literature on bioactive lipid mediators of inflammation to evaluate the current knowledge, reconcile conflicting data, and summarize future perspectives. We will first begin by discussing some of the key aspects of the inflammatory response after SCI.

INFLAMMATION IN SPINAL CORD INJURY

Over 3700 papers on inflammation in SCI were published in the last 40 years, with 8 papers published in 1980 and rising to 353 papers in 2020 alone. This increase in interest has come with a growing understanding of the complexity of the inflammatory response after SCI. Evidence that the inflammatory response is detrimental after SCI came from early preclinical studies with steroids (Braughler and Hall, 1984; Hall and Braughler, 1982) that led to the clinical testing of methylprednisolone (MP) in three large National Acute Spinal Cord Injury Studies (NASCIS) studies done in the 1990's (Bracken et al., 1990, 1992, 1997). Steroids have multiple effects including a role in reducing inflammation. These led to the clinical use of MP for treatment within 8 h of SCI, however, the results of these studies were criticized for the statistical analyses used, post-hoc analysis of a subset of patients, selection bias, and lack of placebo controls (Hurlbert et al., 2013). A recent systematic review of the clinical literature made by an international group of clinical specialists found that high dose of MP (30 mg/kg) given within 8 h of SCI showed evidence of a small improvement in motor scores compared with the control group (Fehlings et al., 2017). The small effect may reflect the fact that although some aspects of the inflammatory response are detrimental, other aspects are beneficial, and that this treatment is directed only at the acute inflammatory response occurring within hours after injury, while inflammation can continue for months after SCI. A better understanding of various aspects of the inflammatory response over time after injury is needed to develop more effective therapeutic approaches to minimize the detrimental aspects and enhance the resolving aspects of the inflammatory response after SCI. We will focus next on myeloid cells and immune cells that play a role in the inflammatory response after SCI.

Microglia

The early inflammatory response after SCI involves mainly microglia, neutrophils and monocyte-derived macrophages (MDMs) (Beck et al., 2010; Donnelly and Popovich, 2008; Sroga et al., 2003), and at later phases also includes T cell and B cell responses (Ankeny et al., 2009, 2006; Beck et al., 2010; Donnelly and Popovich, 2008) (Fig. 1). Microglia, the resident macrophages of the CNS, are the first cells to respond within minutes after CNS injury. Microglia, under resting conditions, referred to as 'homeostatic' microglia, have extensive branching

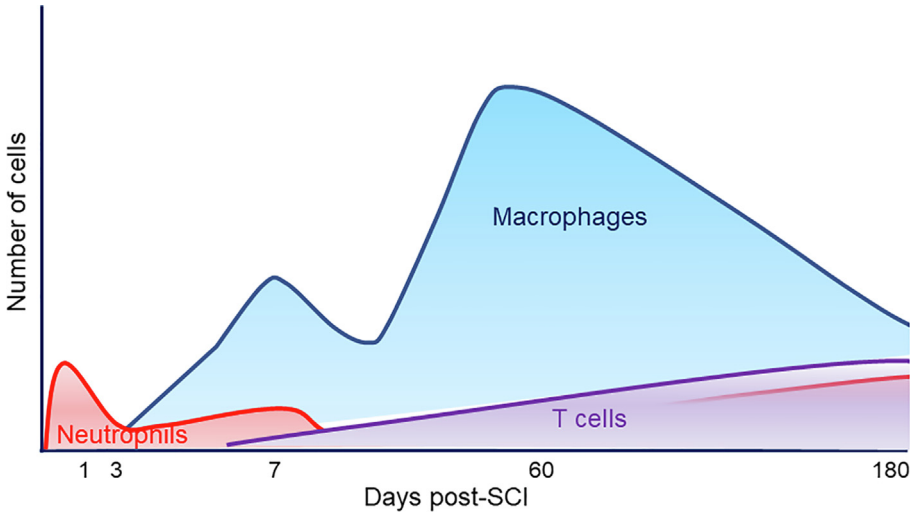

Fig. 1. Diagram illustrating changes in the number of different immune cell populations that infiltrate into the spinal cord after contusion injury. Note that neutrophils are the first cells to enter the CNS within 6–12 h after injury. MDMs from the periphery enter the spinal cord after about 3 days and peak in number around 7 days. Some reports indicate a subsequent peak weeks later after SCI. These peaks may include both infiltrating MDMs and activated phagocytic microglia. MDMs persist in the CNS for prolonged periods indicating chronic inflammation. Lymphocytes also enter the CNS after about 1 week and persist at low levels. Adapted from (Beck et al., 2010) and (Donnelly and Popovich, 2008).

processes that contact-inhibit adjacent microglia to maintain their own individual cellular domain (Davalos et al., 2005). These processes are highly motile and perform surveillance functions to monitor the environment. Two-photon microscopy imaging of GFP-labeled microglia show that they respond within 10–15 min after small stab wounds of the cerebral cortex (Davalos et al., 2005; Haynes et al., 2006; Nimmerjahn et al., 2005). They do so by extending their processes towards the edge of the lesion and form a dense wall along the lesion perimeter. Some microglia near the vicinity migrate their cell bodies towards the lesion (Dibaj et al., 2010; Nimmerjahn et al., 2005). Microglial process extension is mediated by ATP released from damaged cells and signaling via $P2Y_{12}$ G-protein coupled receptors (Davalos et al., 2005; Haynes et al., 2006). The size of the lesion enlarges if this early microglial process extension towards the lesion is blocked pharmacologically or the microglia are removed by laser ablation (Hines et al., 2009) indicating that this early microglial response is protective. Such protective effects of microglia immediately after injury are also detected with larger brain lesions. Depletion of microglia using the CSF-1R inhibitor (PLX3397) prior to induction of cerebral ischemia resulted in much larger lesion size. However, depletion of microglia after induction of cerebral ischemia had no effect (Szalay et al., 2016). These acute, protective effects of microglia are in part due to their ability to maintain calcium homeostasis and prevent calcium-mediated excitotoxicity (Szalay et al., 2016). Similarly, after spinal cord contusion injury in adult mice, microglia are deployed along the edge of the lesion and help in organizing an astrocytic scar that prevents the entry and infiltration of peripheral immune cells into the injured spinal cord (Bellver-Landete et al., 2019). This response is protective as depletion of microglia with the CSF-1R inhibitor causes expansion of the lesion, and results in increased neuronal and functional loss (Bellver-Landete et al., 2019). Recent studies have also shown that microglia from neonatal brain express fibronectin and various peptidase inhibitors that reduce the astrocytic scar and promote axon regeneration after SCI (Li et al., 2020). Furthermore, transplantation of neonatal microglia or adult microglial treated with peptidase inhibitors is beneficial for axon regeneration (Li et al., 2020). Taken together, these studies emphasize a protective and beneficial response of microglia to CNS injury. At later subacute and chronic states activated microglia may produce factors such as superoxide, NO and glutamate and other factors that are detrimental to neuronal and glial viability (Brown and Vilalta, 2015). Recent single cell analysis using a suite of techniques to assess populations of microglia from the developing and adult brain and from CNS injury and disease states have revealed substantial heterogeneity of microglial subtypes (Masuda et al., 2019). Microglial clusters differ in different states of CNS insults with unique clusters in nerve injury versus demyelination states (Masuda et al., 2019). Understanding the functional role of different microglial clusters will reveal how they modulate inflammation.

Proteomics analysis of the extracellular proteome of the injured spinal cord, and transcriptomics analysis of injured tissue reveled extracellular alarmins that can trigger inflammation via toll-like receptors (TLRs) dominated by IL-1 and NFκB signaling (Didangelos et al., 2016). This pathway can amplify inflammation that worsens pathology and impairs repair after SCI. Recent work has also shown that extracellular ADP acts on the P2Y12 receptors to activate NF-κB and the NLRP3 inflammasome complex to enhance microglial inflammation involving IL-1β and IL-6 responses (Suzuki et al., 2020). This and other signaling mechanisms such as 'damage-associated molecular patterns' (DAMPs), which are released from damaged tissue, and include messenger RNA (mRNA), single stranded RNA, heat shock proteins (Hsp), and small breakdown fragments of extracellular matrix molecules (ECM) (Piccinini and Midwood, 2010; Zindel and Kubes, 2020) all of which contribute to the early inflammatory response after CNS injury (Heiman et al., 2014). DAMPs bind to TLRs on microglia, astrocytes as well as other CNS cells to rapidly activate and release chemokine and cytokines that promote inflammation and recruit peripheral immune cells to the site of CNS injury (Heiman et al., 2014; Li et al., 2021). Different TLRs exist and have differing specificities for dif-

ferent species of DAMPs (Piccinini and Midwood, 2010; Zindel and Kubes, 2020). See further discussion of MDMs in a later section below.

Neutrophils

In general neutrophils play a vital role in fighting infections via releasing cytotoxic granules containing bactericidal agents (myeloperoxidase (MPO), defensins, lysozyme, serine proteases, etc.) and also neutrophil extracellular traps (NETs) which are extracellular DNA material that trap pathogens (Phillipson and Kubes, 2019). They are therefore the first line of defense to prevent infections after penetrating wounds and essential for the multiple traumas associated with motor vehicle accidents in humans. However, the factors produced by neutrophils to neutralize pathogens can also cause secondary damage to CNS tissue. Hence there is a need for timely removal of neutrophils. Neutrophils are the first cells to infiltrate the injured spinal cord, reach peak numbers by as early as 6–12 h and reduce markedly in a few days but with low residual levels detected for weeks, which vary in number in different species and strains (Beck et al., 2010; Fleming et al., 2006; Kigerl et al., 2006; Sroga et al., 2003; Stirling et al., 2009) (Fig. 1). They have a short lifespan which can be up to 5–6 days (Filep and Ariel, 2020). Injury and other insults induce rapid mobilization of neutrophils from the bone marrow, resulting in increased numbers in the circulation and in the affected tissues (Brennan et al., 2019; Kolaczkowska and Kubes, 2013). This mobilization out of bone marrow is mediated by the chemokine CXCR2. Recent work shows that this mobilization is negatively regulated by the complement activation product C3a/C3aR1 and its downstream partner phosphatase and tensin homolog (PTEN) (Brennan et al., 2019). Lack of this signaling in *C3ar1*$^{-/-}$ mice increases neutrophil mobilization from the bone marrow and subsequent infiltration into the injured spinal cord leading to impaired locomotor recovery (Brennan et al., 2019). Depletion of neutrophils in spinal cord injured *C3ar1*$^{-/-}$ mice improved functional recovery to wildtype levels (Brennan et al., 2019). Earlier studies also reported that reducing neutrophil infiltration into the injured spinal cord by blocking integrins or other methods, partially reduces the severity of tissue damage and improves locomotor function (Fleming et al., 2008; Gris et al., 2004; Taoka et al., 1997). However, the effects in these studies cannot be solely attributed to neutrophils because macrophage numbers were also reduced. In contrast to these studies, selective depletion of neutrophils with anti-Ly6G/Gr-1 monoclonal antibody was reported to worsen histological and functional outcome after SCI (Stirling et al., 2009). A subsequent study was not able to replicate this effect (Lee et al., 2011). This study found no improvement when either neutrophils or macrophages were selectively depleted with Ly6G/Gr-1 antibody or clodronate, respectively (Lee et al., 2011). Clodronate, a bisphosphonate, which is packed in liposomes is taken up by macrophages and results in intracellular accumulation that leads to cell death and depletion of macrophages. Partial recovery of locomotor control, and reduction in oxidative stress markers was obtained when both cell types were depleted simultaneously (Lee et al., 2011). A recent study blocking the entry of mature neutrophils into the injured CNS with systemic treatment anti-CXCR2 (a receptor expressed on mature neutrophils) has shed important insights (Sas et al., 2020). Such treatment in mice after optic nerve injury and intraocular injection of zymosan enhanced retinal ganglion cell (RGC) survival and optic nerve regeneration. This treatment was accompanied by a delay in the entry of neutrophils and other leukocytes into the vitreous fluid in the eye. Interestingly, a major new subpopulation of neutrophils was detected in the vitreous fluid that has an immature phenotype (Ly6G^{lo}CD14^{hi}) with ring-shaped nuclei, expresses markers of alternative activation, similar to M2 macrophages, and expresses growth factors (Sas et al., 2020). Intraocular transplantation of such alternatively activated neutrophils promoted RGC survival and optic nerve regeneration. Transplantation of such neutrophils also enhanced regeneration of dorsal root axons after SCI. Although the extent of such growth is small (about 1.5 mm in the optic nerve, and about 200 μm after SCI) (Sas et al., 2020), nevertheless, these studies reveal important differences in the infiltration and function of immature, alternatively activated subpopulation of neutrophils that have pro-repair properties. Earlier experiments with neutrophil depletion after SCI will therefore need to be re-evaluated. Neutrophils have a very short lifespan and undergo apoptosis and are phagocytosed through a process called efferocytosis. The phagocytosis of apoptotic neutrophils can lead to reprograming of macrophages from a pro-inflammatory to an anti-inflammatory state and produce specialized pro-resolving bioactive lipid mediators, such as resolvin D1 (RvD1) and Maresin 1 (MaR1) that resolve inflammation (Filep and Ariel, 2020). Given the beneficial effects of neutrophils, it would be preferable to modulate their responses than preventing their entry completely.

Monocyte-derived macrophages

MDMs and microglia differ in their ontogeny (Ginhoux et al., 2010; Schulz et al., 2012), and expression of transcripts and proteins some of which can be used to distinguish between microglia and MDM (David et al., 2018). This includes the following for microglia, Tmem119, P2ry12, siglec-H, Sall1, FCRLS, and others; and CD45^{hi} and LysM for peripheral myeloid cells (David et al., 2018; Greenhalgh et al., 2016). However, several caveats limit the full use of these markers as discussed in other reports (David et al., 2018). Such markers have been used with caution to distinguish these two myeloid cell populations (Greenhalgh and David, 2014; Greenhalgh et al., 2016). Genetic approaches such as the *Cx3cr1creER::R26-TdT* mice have also been used to distinguish microglia from MDMs (Bellver-Landete et al., 2019).

MDM are recruited in a CCR2 dependent manner (Greenhalgh et al., 2018; Shechter et al., 2009) into the injured spinal cord after 3 days, peaking in numbers by 7 days and persisting for months (Fig. 1) (Beck et al., 2010; Fleming et al., 2006; Greenhalgh and David, 2014; Kigerl et al., 2006; Mawhinney et al., 2012; Sroga

et al., 2003). Although microglia and MDMs are interspersed within the injury site for the first week after SCI, at later time points MDMs are mostly concentrated in the core of the lesion while microglia are located at its edges (Zhu et al., 2015). It has long been suspected that reducing the macrophage response and numbers after SCI is beneficial. This was based on macrophage depletion studies with clodronate (Popovich et al., 1999) and other interventions (Fleming et al., 2008; Gris et al., 2004; Stirling et al., 2004; Wells et al., 2003) that succeeded in reducing macrophage numbers and improved recovery. The antibody blocking and minocycline (an antibiotic with anti-inflammatory and other effects) experiments are, however, not selective for macrophages, and the clodronate effects on locomotor recovery are minimal as it improves only the BMS subscore (Popovich et al., 1999). As noted above, another study showed that depleting macrophages with clodronate had no effect on locomotor recovery but reducing both neutrophil and macrophages simultaneously improved outcome after SCI (Lee et al., 2011). However, another study depleting macrophages with clodronate showed reduced fibrotic scaring and improved axon growth (Zhu et al., 2015). Taken together these studies suggest that depleting MDMs may have some beneficial effects after SCI. Blocking CX3CR1 signaling in infiltrating MDMs is protective and results in improved function and tissue damage after SCI (Donnelly et al., 2011). Earlier work has shown that macrophages allowed to phagocytose peripheral nerve material *in vitro* before transplantation into the CNS promote axon regeneration and repair in the injured spinal cord and optic nerve (Rapalino et al., 1998; Schwartz and Yoles, 2006). Phagocytosis of myelin was subsequently shown to shift macrophages from a proinflammatory to an anti-inflammatory, pro-repair phenotype (Kroner et al., 2014).

The characterization of macrophage phenotypes has undergone tremendous changes in the past two decades. Macrophages were described as varying in phenotype from proinflammatory, cytotoxic M1 cells to anti-inflammatory, pro-repair M2 cells (Gordon and Taylor, 2005; Martinez et al., 2008). While macrophages with both phenotypes are present in the injured spinal cord, the M1 phenotype predominates (Kigerl et al., 2009; Kroner et al., 2014). This was shown to be due to TNF preventing the myelin phagocytosis-induced conversion of M1 cells to M2 cells, and the effects of iron-loading by phagocytosis of red blood cells (RBCs) inducing the conversion of M2 macrophages to M1 cells (Kroner et al., 2014). Therefore, TNF in the proinflammatory environment of the injured spinal cord and the phagocytosis of RBCs due to hemorrhage at sites of SCI contribute to macrophages acquiring a predominantly pro-inflammatory phenotype (Kroner et al., 2014). M1 and M2 macrophages may also enter the injured spinal cord via different routes (Shechter et al., 2013). Small subpopulations of macrophages with pro-repair properties have been found in the injured spinal cord injury (Francos-Quijorna et al., 2016, 2017; Rathore et al., 2011; Shechter et al., 2009). It should be noted, however, that the M1 and M2 phenotypes were identified based on *in vitro* studies (Gordon and Taylor, 2005; Martinez et al., 2008) in which the conditions for activation are well-defined. In contrast, *in vivo*, macrophages and microglia at sites of CNS injury are influenced simultaneously by many factors, both pro and anti-inflammatory. As a result, their phenotype will not be as clearly polarized to either a classic M1 or M2 phenotype but have multidimensional phenotypes that vary considerably but can be skewed towards a pro- or anti-inflammation state depending on the prevailing conditions of the cellular microenvironment after injury (David et al., 2015). Thus, the bimodal classification of microglia and macrophages is being replaced by recognition of the multidimensional states the identity of which is being made possible by high throughput single-cell analyses (Hammond et al., 2019; Masuda et al., 2019; Mrdjen et al., 2018).

As mentioned above, phagocytosis of apoptotic neutrophils induces a shift in macrophage phenotype from pro -inflammatory to resolution-phase macrophages (Filep and Ariel, 2020). We also reported another unexpected beneficial role of macrophages that infiltrate into the CNS after trauma (Greenhalgh et al., 2018). Microglia respond within minutes after injury and begin to phagocytose damaged CNS cells and myelin. If this response is not curbed it could lead to chronic microglia-mediated inflammation. Our recent work suggests that MDMs from the peripheral circulation, which infiltrate into the injured spinal cord at about 3 days after injury, switch-off microglial activation and take over the phagocytic functions from microglia (Greenhalgh et al., 2018). MDMs that infiltrate the injured CNS may thus prevent microglial-mediated chronic inflammation that can be detrimental. The mechanism underlying such microglia-macrophage interactions will be discussed later in the section on prostaglandins.

Other studies have reported that infiltrating macrophages are beneficial and blocking CCR2-dependent infiltration of macrophages with CCR2 antibodies worsens locomotor recovery after SCI (Greenhalgh et al., 2018; Shechter et al., 2009) and stroke (Wattananit et al., 2016). There is another potential benefit of infiltrating macrophages taking over the phagocytic functions from microglia. Under normal conditions, microglia monitor the CNS environment for any perturbations via their extensively branched motile processes. This surveillance function will be compromised if they retract their processes as would happen when they become phagocytic and acquire an ameboid shape (Kreutzberg, 1996). Therefore, the entry of MDMs (professional phagocytes) into the injured CNS would prevent microglia from being co-opted for phagocytic function, and thus help retain the important surveillance function of microglia. Our recent work shows that MDMs and microglia communicate with each other and differentially regulate cytokine expression and phagocytic function in each other. Of note, microglia-mediated phagocytosis and inflammation are suppressed by peripheral macrophages (Greenhalgh et al., 2020). Taken together, the evidence from the literature suggests that there are different subpopulations of macrophages and microglia in the injured CNS that can play

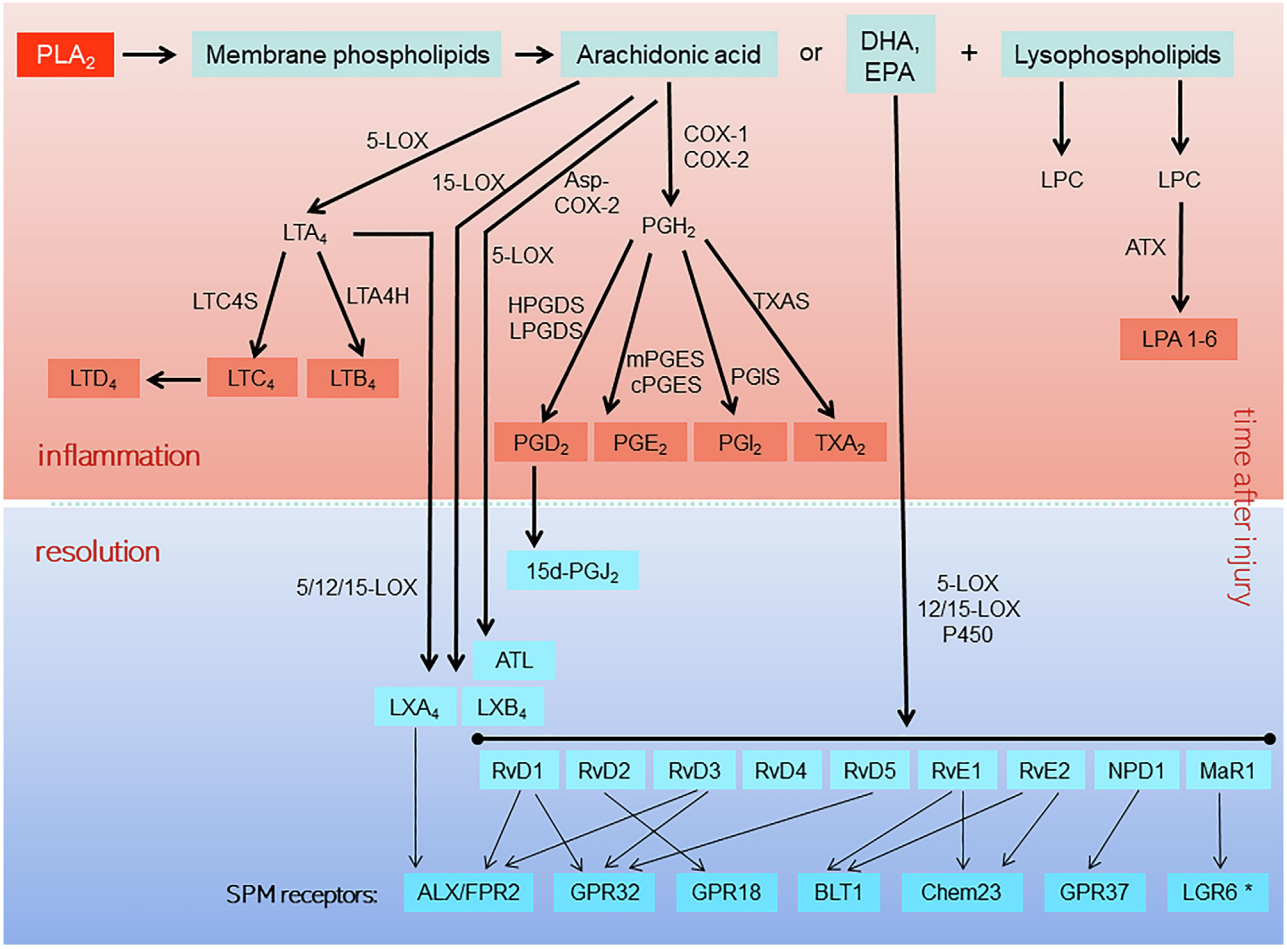

Fig. 2. Diagram illustrating how bioactive lipid mediators of inflammation are generated from the actions of PLA_2 on membrane phospholipids to give rise to AA, DHA or EPA. PGs, leukotrienes, and other eicosanoids are derived from omega-6 PUFA, AA, and SPMs derived from omega-3 PUFAs, DHA and EPA. The top half of the diagram (in reddish-brown) shows bioactive lipids generated from AA that are pro-inflammatory, while the lower half (in blue) shows bioactive lipids generated from DHA and EPA that are pro-resolution lipids. Also note the pro-resolution lipids, LXA4, LXB4 and ATL, generated from AA. For the sake of simplicity only SPM receptors are shown. *Note that MaR1 can also bind intracellularly to RORα. Note also that RvE3 and MaR2 are not shown, which have unidentified receptors.

either protective or detrimental roles depending on reciprocal interactions and the influence of factors in the local microenvironment.

BIOACTIVE MEDIATORS OF INFLAMMATION

Membrane lipids are a rich source of lipids that give rise to the large and diverse family of bioactive lipids that modulate various aspects of the inflammatory response, including effects on a range of immune cell responses and vascular changes. The first key enzyme involved in the breakdown of membrane phospholipids is PLA_2. This large family of enzymes catalyze the hydrolysis of the ester bond at the *sn*-2 position of membrane glycerophospholipids leading to the release of free fatty acids, such as AA, DHA and EPA and the formation of lysophospholipids (Dennis et al., 2011) (Fig. 2). These four bioactive lipids serve as precursors for a large number of potent lipid mediators that include prostaglandins, leukotrienes and thromboxanes, and an expanding list of Specialized Resolution Mediators (SPMs) (Fig. 2). These lipid mediators play roles in the initiation, progression, and resolution of inflammation in injury and disease. The change from mediating inflammation to resolution of inflammation requires lipid mediator class switching from the production of prostaglandins from AA to resolution mediators from DHA and EPA and also lipoxins derived from AA (Fig. 3) (Buckley et al., 2014; Serhan et al., 2015). The sequential timing of the expression of these mediators is crucial for the initiation and effective resolution of inflammation and the prevention of chronic inflammation. Both acute and chronic inflammation can produce secondary tissue damage in the CNS, which has detrimental consequences due to the limited capacity of the CNS to regenerate.

We will begin with a discussion on the PLA_2 enzymes which are responsible for the release of fatty acids (AA, DHA, EPA, etc.) that serve as substrates for the generation of a variety of bioactive lipid mediators. This will be followed by separate sections on various eicosanoids (prostaglandins and leukotrienes), LPAs and SPMs.

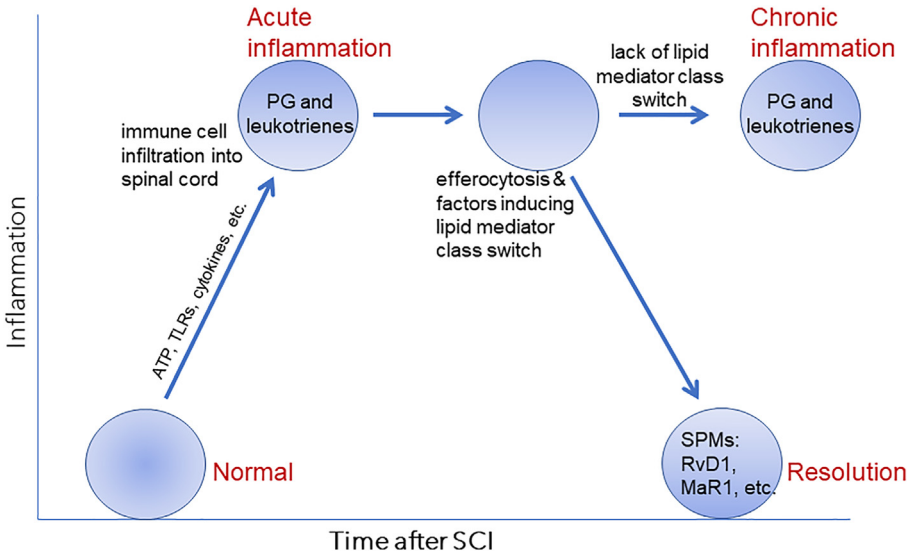

Fig. 3. Schematic diagram showing the class switch in bioactive lipids derived from omega-6 fatty acid AA (PG and leukotrienes) that induce the acute inflammatory response, to omega-3 fatty acids DHA and EPA (SPMs) that trigger resolution of inflammation. Absence of this switch is thought to give rise to chronic inflammation.

Phospholipase A_2

Mammalian PLA_2s belong to a superfamily of over 30 enzymes that are arranged into 6 main subgroups, each with several isoforms that differ in their structural, biochemical and functional characteristics. These subgroups include secreted PLA_2 ($sPLA_2$), cytosolic PLA_2 ($cPLA_2$), Ca^{2+}-independent PLA_2 ($iPLA_2$), platelet-activating factor acetylhydrolases (PAF-AH-PLA_2), lysosomal PLA_2 ($LPLA_2$), and α/ß hydrolase (ABHD) (Dennis et al., 2011). Various members within subgroups are also called by different group designations. We will focus here mainly on $sPLA_2$ group IIA, $cPLA_2$ group IVA, and $iPLA_2$ group VIA as these are the main PLA_2s studied in the context of SCI and other neurological disorders. Note that in mammals there are 6 $cPLA_2$s, 9 $iPLA_2$s and 11 $sPLA_2$s. The role of different PLA_2 in SCI will depend on the cell types that express them and the time after injury when they are expressed. The secreted $sPLA_2$s act on cell membranes extracellularly and other extracellular targets, while $cPLA_2$ and $iPLA_2$ are localized intracellularly and act on the cell membrane and lipid bilayers of intracellular organelles. The main physiological functions of PLA_2s are membrane remodeling and repair (removing harmful oxidized fatty acids) (Kita et al., 2019). They also play a role in maintaining the balance between saturated and unsaturated fatty acids at the *sn*-1 and *sn*-2 positions. Under pathophysiological conditions, the increased expression of PLA_2 gives rise to release of higher levels of AA and other fatty acids as well as lysophospholipids, and mediate inflammatory responses in arthritis, cardiovascular disease, neurological conditions, and a wide variety of disorders (Dennis et al., 2011).

PLA2s in spinal cord injury. Studying the role of PLA_2s in SCI or any neurological condition is challenging because of the large number of PLA_2s. To help to narrow down the PLA_2s to study, we first assessed changes in the mRNA expression of 14 members of the PLA_2 family. Of these only three ($cPLA_2$GIVA, $iPLA_2$GVIA and $sPLA_2$GIIA) showed increases in expression after SCI (Lopez-Vales et al., 2011a). This was further confirmed by Western blotting and cell type distribution in tissue sections of the injured spinal cord. Our studies on the functional role of these PLAs were aided tremendously by the availability of selective inhibitors, as well as pan-inhibitors, to these three members of the PLA_2 family.

We found that treating mice immediately after SCI with a highly selective inhibitor $sPLA_2$ (GK115), which does not display any inhibition of $cPLA_2$ or $iPLA_2$, significantly improved locomotor recovery (Lopez-Vales et al., 2011a). Inhibiting $sPLA_2$ also reduced secondary damage after SCI as indicated by increased sparing of tissue, myelin and motor neurons adjacent to the lesion epicenter. These experiments were done on BALB/c mice which express $sPLA_2$GIIA. In contrast, this inhibitor did not have any effects on C57Bl/6 mice, which have a naturally occurring null mutation of $sPLA_2$GIIA (Kennedy et al., 1995), thus confirming the role of $sPLA_2$GIIA in SCI. $sPLA_2$GIIA is mainly expressed by oligodendrocytes and astrocytes after SCI. Loss of oligodendrocytes led to myelin loss after injury (Lopez-Vales et al., 2011a). In other work, direct injection of bee venom $sPLA_2$GIII into the rat spinal cord induced demyelination, loss of oligodendrocytes and axonal damage as well as functional loss (Liu et al., 2006; Titsworth et al., 2007). $sPLA_2$GIII is also found in mammals including humans and has structural similarity to the bee venom form (Valentin et al., 2000), but unlike other more typical $sPLA_2$s ($sPLA_2$GIIA and V), no inhibitors are available to $sPLA_2$GIII (Murakami et al., 2019) to directly test its role in SCI. Nevertheless, our work with the $sPLA_2$GIIA inhibitor indicates that this isoform of $sPLA_2$ plays a detrimental role in SCI.

Expression of two intracellular PLA_2s, $cPLA_2$GIVA and $iPLA_2$GVIA, are also increased after SCI in mice. The $cPLA_2$GIVA has a calcium-dependent lipid binding domain which is required for translocation to the membrane, while $iPLA_2$s are calcium-independent (Kita et al., 2019). $cPLA_2$GIVA is expressed mainly in ventral horn neurons, while $iPLA_2$GVIA is expressed mainly in oligodendrocytes. An $iPLA_2$GVIA inhibitor (FKGK11) which blocks 95% of $iPLA_2$ activity but also moderately inhibits $cPLA_2$ (17%) and $sPLA_2$GIIA (28%) had a small but significant improvement in the finer aspects of locomotor control (i.e., the Basso Mouse Scale subscore). Surprisingly, the highly selective $cPLA_2$GIVA inhibitor

(AX059) (> 95% inhibition), which does not have any inhibitory activity against iPLA$_2$GVIA and sPLA$_2$GII/V, had a detrimental effect on locomotor recovery and exacerbated tissue damage after SCI (Lopez-Vales et al., 2011a). The selectivity of the inhibitors used in our studies between different PLA$_2$ isoforms was determined by *ex vivo* assays, and details of their selectively and potency are detailed in our publication (Lopez-Vales et al., 2011a). The effect of the cPLA$_2$GIVA was further confirmed with the cPLA$_2$ null mouse (Lopez-Vales et al., 2011a). In addition, AX059 treatment and cPLA$_2$GIVA null mice also showed cavitation after SCI, which it is an unusual feature after SCI in mice but not in rats. Another study, however, found that cPLA$_2$ null mice showed improved recovery after SCI and did not lead to tissue cavitation (Liu et al., 2014). The reasons for the difference between the two studies is not known but may have to do with differences in the gut microbiota in the two animal colonies influencing the immune response. Gut microbiota have been reported to alter inflammatory responses in the CNS in the mouse model of SCI (Kigerl et al., 2016, 2018). Another explanation could be related with the technology (including the background strains) used to generate these two lines of cPLA$_2$GIVA knockout mice. These studies also reported improvement after SCI using a small molecule inhibitor of intracellular PLA$_2$ (AACOCF3) or mepacrine (Liu et al., 2014, 2006). AACOCF3 has also shown efficacy in lumbar spinal canal stenosis (Khan et al., 2015). Mepacrine has a broad range of targets and so is not selective for cPLA$_2$ *in vivo*, while AACOCF3 although referred to as an inhibitor of cytosolic PLA$_2$, is not selective for calcium dependent PLA$_2$ (cPLA$_2$) as it also blocks iPLA$_2$ (Ackermann et al., 1995; van Tienhoven et al., 2002). AACOCF3 has also shown to be an inhibitor of CoA-independent transacylase and 5-lipoxygenase (Fonteh, 2002). We have also shown that although AACOCF3 is effective in reducing the severity of EAE (Kalyvas and David, 2004), treatments with selective PLA$_2$ inhibitors showed that blocking iPLA$_2$ but not cPLA$_2$ reduced EAE disease severity when treatments were started after onset of symptoms (Kalyvas et al., 2009). Nevertheless, the studies with AACOCF3 in SCI clearly show that PLA$_2$s, regardless of the precise isoform, play a detrimental role (Liu et al., 2014, 2006). Blocking iPLA$_2$ with the same inhibitor (FKGK11) is more effective in EAE than it is after SCI, indicating that PLA$_2$s play differing roles in different neurological conditions. Furthermore, iPLA$_2$ and cPLA$_2$ are both involved in Wallerian degeneration after peripheral nerve injury, playing a role in the breakdown and clearance of myelin and damaged axons, and thus help promote axon regeneration (Lopez-Vales et al., 2008).

Our findings of the potential protective effects of cPLA$_2$ after SCI was surprising since PLA$_2$s in general play a role in promoting inflammation and have detrimental effects. There is, however, some similarity between our observed protective effects of cPLA$_2$ in SCI and the protective effect of cPLA$_2$ in colonic inflammation. In the colon, cPLA$_2$GIVA mobilizes prostaglandin E2 to protect against colonic inflammation (Murakami et al., 2019). The protective effects of cPLA$_2$ in such inflammation was also detected in the exacerbation of dextran sulfate sodium-induced colitis in cPLA$_2$-GIVA null mice (Murase et al., 2016). Furthermore, patients with gene mutations of cPLA$_2$GIVA with decreased cPLA$_2$ activity have multiple gut ulcers (Adler et al., 2008). The protective effects of cPLA$_2$ in the colon may be mediated via the EP4 receptor (Murakami et al., 2019). Interestingly, experiments using a pan-PLA$_2$ inhibitor (AX115) that blocks all three forms of PLA$_2$ (cPLA$_2$-GIVA, iPLA$_2$GVIA and sPLA$_2$GIIA) to about the 50% level (Lopez-Vales et al., 2011a) induces remarkable improvement in locomotor recovery as well as significant sparing of tissue, myelin and neurons. This effect was better than that seen with the sPLA$_2$ and iPLA$_2$ selective inhibitors used in the same study (Lopez-Vales et al., 2011a). On the other hand, a very potent inhibitor that blocks all three PLA$_2$s to about the 90% level was detrimental in all measures analyzed after SCI (Lopez-Vales et al., 2011a). This potent pan-inhibitor (FKGK2) worsened locomotor recovery and histological outcome even more than blocking cPLA$_2$ alone. This may be due to blocking the essential, normal physiological roles of PLA$_2$s in membrane repair and turnover. The less potent pan-inhibitor (AX115) which only blocks 50% of the enzyme activity may permit the normal physiological functions to continue. Similar reasons may also underlie the beneficial effects of AACOCF3 in SCI (Liu et al., 2014). These findings suggest that in some cases PLA$_2$ inhibitors that have less selectivity and lower potency may be more effective as therapeutic agents.

A lipidomic analysis of CNS tissue from EAE mice treated with inhibitors to cPLA$_2$GIVA (AX059) and iPLA$_2$ (FKGK11) showed that the potent cPLA2 inhibitor blocked the release of fatty acids from four species of phospholipids, and prevented production of PGE$_2$, thromboxane B$_2$ (TXB$_2$), 11-HETE and 15-HETE that promote inflammation (Kalyvas et al., 2009). The iPLA2 inhibitor (FKGK11), prevented the hydrolysis of 13 of the 18-fatty acid/phospholipid combinations detected in vehicle-treated EAE mice (Kalyvas et al., 2009). Interestingly, the iPLA2 inhibitor still permitted the hydrolysis of 65% of the EPA from cardiolipin, and 80% of the EPA from lysophosphatidylcholine (Kalyvas et al., 2009). The loss of 80% of the fatty acids from lysophosphatidylcholine (LPC) would render it unable to demyelinate, as LPC (lysolecithin) is a potent demyelinating agent when injected into the CNS and is widely used to study demyelination and remyelination in the CNS (Moyon et al., 2017; Ousman and David, 2000, 2001; Plemel et al., 2018). This inactivation of LPC to demyelinate may underlie, in part, the significant beneficial effects of the iPLA$_2$ inhibitor in EAE (Kalyvas et al., 2009). Furthermore, the EPA that is released can give rise to E-series resolvins, which are specialized pro-resolution mediators (SPM) that actively resolve inflammation (Ariel and Serhan, 2007). This will be discussed in a later section.

Tissue localization of phospholipids and eicosanoids in the spinal cord

A major step in understanding the biology of bioactive lipids is the development of imaging techniques to localize fatty acids and eicosanoids in histological

sections by Imaging Mass Spectrometry (IMS) incorporating matrix-assisted laser desorption/ionization (MALDI), along with quantification by liquid chromatography–electrospray ionization–tandem mass spectrometry (LC–ESI–MS/MS) of liquid extracts of the spinal cord (Hanada et al., 2012). MALDI-MS spectral analysis of the normal spinal cord showed 150 mass peaks of phosphatidylcholine (PC), 14 of which belong to abundant PC species (Hanada et al., 2012). The most abundant PC species (diacyl-16:0/18:1) was found by IMS analysis to be uniformly distributed in normal spinal cord gray matter, while PCs with oleic acid (18:1), i.e., PC (diacyl-18:0/18:1) and PC (diacyl-18:1/18:1), were localized to spinal cord white matter. Oleic acid containing PCs are known to be enriched in CNS myelin (Hankin et al., 2007). In contrast, DHA-containing species, i.e., PC (diacyl-16:0/22:6), PC (diacyl-18:0/22:6), and PC (diacyl-18:1/22:6), are localized to gray matter in the normal spinal cord, particularly high in large ventral horn neurons (Hanada et al., 2012). There is, therefore, much regional differences in the spinal cord grey and white matter localization of membrane phospholipids with different fatty acid composition.

The IMS imaging technique was used to assess changes in fatty acid distribution in the injured spinal cord (contusion injury at T10 level) at 12 h, 1 day, 1, 2 and 8 weeks (Hanada et al., 2012). This study revealed that SCI induces irreversible loss of DHA-containing PCs at the lesion epicenter starting at 1d post-injury and progressing up to 8w (Hanada et al., 2012). As DHA containing PCs are localized to neurons, this loss of DHA-containing PCs might reflect the loss of neurons at the lesion epicenter (Ghasemlou et al., 2010; Kerr et al., 2008; Lopez-Vales et al., 2011a). In contrast, there is a transient increase in AA-containing PCs (PC (diacyl 16.0/20.4 and diacyl-18.0/20.4) at the lesion epicenter at 1w post-injury, which resolves to normal levels by 8w (Hanada et al., 2012). The pattern of localization and timing of increase in AA-containing PCs corresponds with increased immune cell influx (Hanada et al., 2012). There is also evidence linking increased AA-PCs with microglial activation in the dorsal horn after sciatic nerve injury (Banno et al., 2017). Interestingly, this indicates that injury can induce rapid changes in the fatty acid composition of PCs in CNS glia. Furthermore, LPC (LPC18.0) generated by the hydrolysis of AA from PC (diacyl-18.0/20.4) by PLA_2 is enriched at the site of immune cell invasion at 1 and 2 weeks after SCI. LPC is localized to the border region between infiltrating immune cells and CNS tissue (Hanada et al., 2012). As mentioned above, LPC is a potent demyelinating agent and therefore likely to contribute to demyelination seen after SCI (Ghasemlou et al., 2010; Kerr et al., 2008; Lopez-Vales et al., 2011a). The localization of LPC at the lesion border also suggests that infiltrating immune cells are responsible for producing AA that result in the formation of prostaglandins (PGs). Other reports have also found accumulation of AA and lysophospholipids at the lesion epicenter and adjacent regions after SCI (Girod et al., 2011). Increase in AA containing PCs is seen in regions with reactive microglia and astrocytes after peripheral nerve injury (Xu et al., 2016) and PGE_2 contributes to signaling between microglia and neurons to mediate pain related behaviors (Zhao et al., 2007). Quantitative imaging of PGs in tissue sections has been limited (Duncan et al., 2018; Girod et al., 2011). These results suggest that at the site of injury, AA and PGs are generated by infiltrating immune cells as well as resident cells of the CNS.

Prostaglandins and other eicosanoids in spinal cord injury

Eicosanoids are a large family of signaling molecules derived from AA and other polyunsaturated fatty acids (PUFAs) via enzymatic and non-enzymatic oxidation. These include prostaglandins, leukotrienes, thromboxane derived from omega-6 fatty acids (AA) but also SPMs derived from omega-3 fatty acids (EPA and DHA). SPMs include resolvins of the D and E series, protectins, maresins and others. In this section we will focus on the AA derived lipid mediators (prostaglandins and leukotrienes) and their receptors. The omega-3 derived SPMs will be discussed separately in the next section.

AA released from membrane glycerophospholipids by PLA_2 gets converted to a variety of prostaglandins (e.g., PGE_2, PGD_2, PGI_2, and PGJ_2) via cyclooxygenase 1 and 2 (COX-1 and 2) to prostaglandin H2 (PGH_2) and then via various PG synthases (PGSs) (Fig. 2). Thromboxane A_2 and B_2 (TxA_2 and TxB_2) are generated from PGH_2 via thromboxane synthase, while the lipoxygenase enzyme (5-LOX) catalyzes the conversion of AA to leukotriene A4 (LTA_4), which is then converted by LTA_4 hydrolase to LTB_4, and via LTC_4 synthase to LTC_4. LTD_4 and LTE_4 are metabolic degradation products of LTC_4 (Fig. 2). These eicosanoids act via G-protein coupled receptors – the respective PGs bind to DP1 and DP2 receptors, EP1-EP4 receptors, FP and IP receptors, and thromboxane to TP receptors. Leukotrienes C4, D4 and E4 are cysteinyl LT (cystLT) and bind G-protein coupled cystLT1 and cystLT2 receptors (Hata and Breyer, 2004). Leukotriene B4 binds to LTB_4 receptor 1 (BLT1) and mediates neutrophil chemotaxis (Ford-Hutchinson et al., 1980). These eicosanoid receptors mediate their effects on a variety of systems to effect pro- and anti-inflammatory responses by regulating the levels of intracellular cAMP, mobilize Ca^{2+} and phosphoinositol turnover (Hata and Breyer, 2004). The contribution and role of these lipid mediators in SCI will depend on the cellular localization and timing of expression of these eicosanoids and their receptors.

Assessing the expression of these lipid mediators in the injured spinal cord is therefore a good starting point to understand their potential role in CNS injury. Changes in the levels of 5 eicosanoids ($PGF_{2\alpha}$, PGE_2, PGD_2, 6-keto-$PGF_{1\alpha}$ and TXB_2) 1 day, 1, 2, and 8 weeks after SCI was quantified by LC-ESI-MS/MS (Hanada et al., 2012). PGE_2 increased at 1 day, peaked at 1 week and returned to almost normal levels by 2 weeks and beyond. TXB_2 and PGD_2 showed 2 peaks – at 1 and 8 weeks. The first peak at 1 week suggests that PGE_2, PFD_2 and TXB_2 may be produced by infiltrating immune cells that also peak at this time after SCI. The second

peak at 8w may indicate production by chronically reactive microglia and/or astrocytes. $PGF_{1\alpha}$ showed a gradual and very low-level increase starting at 1-week post-SCI suggesting it may not play a significant role in SCI. As the earliest increase in PGE_2 and PGD_2 is detected at 1d after injury (Hanada et al., 2012), which is before the influx of peripheral macrophages, it is likely that these PGs may be produced by activated microglia, astrocytes or neutrophils at this time.

Earlier studies reported that PGE_2 and TXB_2 levels are elevated as early as 2–4 h after SCI in rats and reduced but still at higher than normal levels at least after 72 h (the longest time assessed) (Resnick et al., 2001a). As expected, inhibition of COX-2 reduced PGE_2 and TXB_2 levels after SCI (Resnick et al., 2001b). PGE_2 levels in the CSF are also elevated in dogs with naturally occurring SCI (Russell et al., 2016). A significant increase in LTC_4, TXB_2, and 6-keto-prostaglandin $F_{I1\alpha}$ is also detected 1 to 7 days after experimental SCI in dogs (Nishisho et al., 1996). Similar increases also occur in the early phase after SCI in humans with values returning to normal levels at 6 months (Nishisho et al., 1996). A study of chronic SCI in adult rats found elevated levels of PGE_2 (>80 pg/ml) and LTB_4 (10 pg/ml) at 9 months after SCI, and undetected in the uninjured spinal cord (Dulin et al., 2013). These values, however, are 15-fold lower than the increase of 1215 pg/ml of PGE_2 at 4 h in rats (Resnick et al., 2001a), indicating that eicosanoids likely have their major effects early (hours-days) after SCI. Nevertheless, a dual COX/5-LOX inhibitor (Licofelone) treatment of chronic SCI rats (8 months post-SCI) reversed changes in oxidative and inflammatory metabolites as well as reduced mechanical but not thermal allodynia (Dulin et al., 2013), indicating that even low-level increase in eicosanoids at chronic time points can mediate adverse neurological effects. Intrathecal administration of PGE_2 and PGD_2 induces hyperalgesia, while application of PGE_2 and $PGF_{2\alpha}$ causes allodynia (Vanegas and Schaible, 2001). Four weeks after SCI in rats, PGE_2 mediates microglia-neuron signaling that underlie pain behaviors mediated via EP2 receptors (Zhao et al., 2007). PGE_2 also mediates activation of spinal cord microglia in models of neuropathic pain and blocking EP1 receptors attenuates microglial activation and mechanical allodynia (Kunori et al., 2011). Interestingly, ATP-induced migration of microglia *in vitro* is blocked by PGE_2 via the EP2 receptor (Kunori et al., 2011). Pre-treatment with a COX-2 inhibitor (NS-398), 15 minutes before SCI in adult rats was also reported to reduce tissue damage and improve locomotor recovery (Hains et al., 2001). NS-398 also enhanced functional and histological outcomes when administered 30 min after SCI (Lopez-Vales et al., 2006) but this could reflect blocking the effects of many downstream eicosanoids.

Prostaglandin E_2. As mentioned earlier in the PLA_2 section, we found that the pan-PLA_2 inhibitor AX115 which blocks about 50% of the activity of $cPLA_2$, $iPLA_2$ and $sPLA_2$ was most effective in promoting locomotor recovery after SCI (Lopez-Vales et al., 2011a). In an effort to examine the potential mechanisms of action of this pan-PLA_2 inhibitor, we found that treatment with AX115 increased expression of $cPLA_2$GIVA (60%), COX2 and microsomal PGE synthase 1 (mPGES1) (>2-fold) at 3 and 7 days post-SCI, and a 50% increase in expression of the E-prostanoid 1 (EP1) receptor at 7 days post-injury (Lopez-Vales et al., 2011a). In this study, treatment with the EP1 receptor antagonist SC51089 significantly reduced the beneficial effects of AX115 on locomotor recovery. These findings suggest that the pan-PLA_2 inhibitor AX115 is likely to mediate protection after SCI via upregulation of $cPLA_2$ and PGE_2 that acts via the EP1 receptor. This is surprising as the EP1 receptor is known to mediate pro-inflammatory responses and neurotoxic effects e.g., in models of NMDA toxicity and middle cerebral artery occlusion (Ahmad et al., 2006). However, opposite results were obtained with intracerebral hemorrhage (ICH) in EP1 knockout mice (Singh et al., 2013), and little or no effect seen after traumatic brain injury (TBI) after pharmacological blocking of the EP1 receptor (SC51089) and EP1 knockout mice (Glushakov et al., 2014). In the intracerebral hemorrhage study, EP1 receptor knockout mice ($EP1^{-/-}$) mice showed worse outcome after ICH, including large lesion volume, greater neuronal loss, worse neurological deficits (Singh et al., 2013). The commonality between ICH and SCI in which EP1 appears to be neuroprotective is hemorrhage, which leads to marked increase in iron deposition and iron-mediated toxicity. For reasons that are not fully understood at present, under such conditions of iron-mediated oxidative stress, activating the EP1 receptor has protective effects. More work is needed to understand the mechanisms underlying these beneficial effects of PGE_2-EP1 in SCI.

In other studies, we reported on a novel role for PGE_2 and the EP2 receptor in regulating microglia-macrophage interactions that control microglial activation (i.e., phagocytosis and expression of inflammatory genes) (Greenhalgh et al., 2018). Despite the presence of microglia in the CNS, MDMs from the circulation rapidly enter the injured spinal cord by 3 days after SCI (Beck et al., 2010; Greenhalgh and David, 2014; Sroga et al., 2003; Thawer et al., 2013). In order to assess the relative contribution of these two cell types to phagocytose and clear tissue debris, we used the LysM-eGFP knock-in mice in which peripheral myeloid cells are tagged with the eGFP, while microglia are not (Faust et al., 2000; Greenhalgh and David, 2014; Mawhinney et al., 2012). In the first 2 days after SCI, resident microglia become aligned along degenerating axons in the dorsal white matter and appear to phagocytose damaged axons (Greenhalgh and David, 2014). In contrast, when eGFP + MDMs enter the spinal cord starting at 3 days after injury, they appear to displace microglia and rapidly deploy along damaged axons (Greenhalgh and David, 2014). The number of microglia associated with degenerating axons assessed at 1, 3 and 7 days after SCI decreased, while the number of eGFP + infiltrating macrophages associated with damaged axons increased during this period (Greenhalgh and David, 2014). When the phagocytic ability of microglia harvested at 1 and 3 days after SCI (i.e., before and after entry of MDMs into the spinal cord) was probed *in vitro* using pH-rhodo labeled myelin, microglia were found to

lose their ability to phagocytose after MDMs enter the spinal cord. Additionally, co-culture experiments showed that in the presence of bone marrow-derived macrophages (BMDMs), microglia lose their ability to phagocytose myelin and reduced expression of inflammatory and cell death pathway genes (Greenhalgh et al., 2018). There is evidence that PGE_2 via EP2 receptors inhibit microglial phagocytic activity (Nagano et al., 2010; Shie et al., 2005). We therefore assessed if this mechanism might underlie the inhibitory effects of macrophages on microglia. The ability of macrophages to reduce phagocytosis by microglia was lost when macrophages from *mpges*$^{-/-}$ mice (which cannot produce PGE_2) were used in co-culture experiments (Greenhalgh et al., 2018). The inhibitory effects on myelin phagocytosis by macrophages on microglia could also be mimicked by a PGE_2 agonist (Butaprost), or blocked by an EP2 receptor antagonist, (PF-0441894) (Greenhalgh et al., 2018). We also assessed the role of the EP2 receptor on myelin phagocytosis by microglia *in vivo* by injecting ph-rhodo-labeled myelin along with either vehicle or EP2 antagonist PF-0441894 into the adult mouse corpus callosum. Three days later, in vehicle injected mice, the area containing ph-rhodo labeled myelin was populated mainly by infiltrating CD11b+, TMEM119-negative MDMs, while in animals injected with the EP2 antagonist, the area containing ph-rhodo labeled myelin contained large numbers of TMEM119+ microglia (TMEM119 is a microglial marker) (Greenhalgh et al., 2018). These findings confirm that PGE_2 produced by macrophages acts via EP2 receptors on microglia to suppress phagocytic activity. In a broader sense, these findings suggest that when circulating macrophages enter the spinal cord a few days after injury, they take over the phagocytic functions from resident microglia, which have already been recruited to respond to injury. The entry of macrophages from the circulation may, therefore, permit microglia to remain process-bearing and perform their normal surveillance function and leave phagocytosis to the professional phagocytes (MDMs). Note that activated phagocytic microglia retract their processes and acquire an ameboid shape, one that would not be conducive to surveillance functions. Macrophage-microglial interactions via PGE_2-EP2 also reduce the expression of pro-inflammatory cytokines. Recent work has shown that macrophage migration inhibitory factor (MIF), a proinflammatory cytokine, induces expression of COX2, mPGES-1 and PGE_2 in SCI (Zhang et al., 2019). Furthermore, MIF-induced expression of PGE_2 by astrocytes reduced TNFα and increased IL-1β and IL-6 production by LPS-stimulated macrophages (Zhang et al., 2019). These finding suggest that bioactive lipid mediators are involved in interactions involving microglia, astrocytes and infiltrating macrophages to regulate inflammation after SCI.

Prostaglandin E_1 is a potent vasodilator that increases blood flow and reduces platelet aggregation. It is widely used for a variety of clinical disorders such as atherosclerosis and peripheral artery disease, as well as injected into the corpus cavernosum of the penis for erectile dysfunction including in patients with SCI (Lombardi et al., 2015). Viagra (a specific and potent inhibitor of cGMP-specific phosphodiesterase type 5) has now replaced it for the latter use. PGE_1 has been approved for clinical use for the past 40 years. PGE_1 has also been found to be effective in SCI. Continuous intravenous administration of PGE_1 (0.5 μg/kg/min) via the jugular vein starting 30 min after spinal cord compression injury (20 g weight for 20 min) in rats and lasting for 3 h post-compression improved locomotor recovery (stride length and base of support), reduced hemorrhage area, reduced neutrophil influx (myeloperoxidase activity) and TNF expression (Naruo et al., 2003). PGE_1 packaged in liposomes (Lipo PGE_1; 10 μg/kg) administered intravenously 5 min prior to a 20 g compression of the rat spinal cord for 40 min improved spinal cord blood flow monitored by a laser doppler system for 30 min post-compression (Hamamoto et al., 2010). Spinal cord blood flow was restored to 90% of precompression levels in rats treated with PGE_1, while untreated SCI control rats recovered blood flow to 60% (Hamamoto et al., 2010). In other experiments, PGE_1 was packaged in nanoparticles (Nano PGE_1) to increase retention and improve delivery as compared to Lipo PGE_1 (Takenaga et al., 2010). In a model of spinal cord contusion injury in rats, a single injection of 5 μg/kg of Nano PGE1 was significantly more effective than Lipo PGE_1 in improving locomotor function (BBB score), reduce lesion size and myelin loss (Takenaga et al., 2010). A PGE_1 analog Limaprost was also reported to improve outcome after spinal cord compression injury in rats (Umemura et al., 2010). Adult rats were infused intravenously (30 ng/kg/h) starting 30 min before injury and continued for 3 h post-compression injury produced by 20 g weight for 20 min to the lower thoracic region. Limaprost treatment reduced TNF and increased IGF-1 expression after SCI. It also reduced neutrophil entry (MPO activity) and caspase-3 levels, and decreased neuronal apoptosis (TUNEL labeling), and improved locomotor recovery measured by the inclined plane test and the Tarlov score (Umemura et al., 2010). Such studies indicate that PGE_1 has anti-inflammatory and beneficial effects that promote recovery after SCI.

Prostaglandin D_2. PGD_2 is expressed in activated mast cells and is involved in type 1 acute allergic responses (Hata and Breyer, 2004). It is also expressed in antigen presenting dendritic cells and Th2 T cells, and is involved in antigen-specific autoimmune responses (Hata and Breyer, 2004). Its expression is controlled by two synthases – lipocalin-type prostaglandin D synthase (L-PGDS) and hematopoietic-type prostaglandin D synthase (HPGDS) (Fig. 2). In the CNS, L-PGDS is one of the most abundant proteins in the cerebrospinal fluid (CSF) and is expressed by meningeal cells, cells of the choroid plexus, and by oligodendrocytes. PGD_2 produced by L-PGDS is involved in regulating sleep (Cherasse et al., 2018). In contrast, HPGDS is expressed by immune cells of hematopoietic origin. In the early postnatal CNS, it is expressed by ameboid microglia in the subventricular zone, leptomeningeal cells and in cells in deep cortical layers. After postnatal day 10–15 it is expressed in microglia (Mohri et al., 2003). The mRNA levels peak at postnatal day 10 and reduced threefold thereafter (Mohri et al.,

2003). In CNS pathology, HPGDS expression is upregulated in microglia surrounding senile plaques in Alzheimer's disease (Mohri et al., 2007). PGD_2 mediates its effects via two GPCRs, DP1 and DP2 (also known as 'chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2)' (Hata and Breyer, 2004). *In situ* hybridization studies showed that the DP1 receptor is localized to microglia and reactive astrocytes within senile plaques, indicating that PGD_2 exerts its effects via both autocrine and paracrine mechanisms (Mohri et al., 2007). In transgenic mouse models of Alzheimer's disease, HPGDS and DP1 were localized by immunocytochemistry to microglia and astrocytes in the plaques (Mohri et al., 2007). The role of DP1 was also assessed in the *twitcher* mutant mouse (C57BL/6J-*GALCtwi*:*GALCtwi/twi*) which has a deficiency of galactosylceramidase, and is an animal model of globoid cell leukodystrophy or Krabbe's disease (Duchen et al., 1980). This is a demyelinating disease in which early developmental myelination occurs normally but oligodendrocyte apoptosis starts at postnatal day 30, resulting in demyelination (Taniike et al., 1999). Double mutants of HPGDS null × *twitcher* or DP1 null × *twitcher* mice, or twitcher mice treated with a small molecule inhibitor of HPGDS (HQL-79; 4-benzhydryloxy-1-[3-(1*H*-tetrazol-5-yl)-propyl]piperidine) showed marked reduction of demyelination, astrogliosis, spasticity and twitching (Taniike et al., 1999). Furthermore, oligodendrocyte apoptosis was also reduced about threefold in HPGDS null mice (Taniike et al., 1999). These results suggest that PGD_2 expressed by microglia play a key role in microglia-astrocyte interactions via the DP1 receptor, which result in astrocyte reactivity, oligodendrocyte apoptosis, leading to demyelination in *twitcher* mice.

We studied the changes in expression of HPGDS and LPGDS after SCI, and the role of PGD_2 in SCI using HPGDS null mice and the HPGDS small molecule inhibitor HQL-79 (Redensek et al., 2011). The mRNA levels of HPGDS increased twofold at 3 d post-SCI, and up about eightfold by 7 d and reduced to about fivefold at day 28. It was expressed mainly in CD11b+ macrophages/microglia in the injured spinal cord (Redensek et al., 2011). LPGDS was expressed in oligodendrocytes, and there was no change in mRNA or protein expression after SCI (Redensek et al., 2011). PGD_2 levels in the injured spinal cord assayed by enzyme-linked immunoassay showed a threefold increase in PGD_2 at 14 d in wildtype mice but no change in HPGDS null mice, indicating that HPGDS is necessary for the upregulation of PGD_2 after SCI (Redensek et al., 2011). Both HPGDS null mice and wildtype mice treated with HQL-79 showed significant improvement in locomotor recovery, sparing of myelin and neurons, as well as greater serotonergic innervation of the ventral horn compared to controls (Redensek et al., 2011). HPGDS null mice also showed increased expression of IL-6 and TGFβ after SCI. Interestingly the expression of the antioxidant metallothionein III which can be regulated by IL-6 was increased 15–20-fold between 1 and 3 days after SCI (Redensek et al., 2011). These results suggest that PGD_2 may promote detrimental effects after SCI. In contrast to traumatic injury models, PGD_2 produced via HPGDS was reported to be protective in transient focal cerebral ischemia (Liu et al., 2009). The DP1 receptor has also been reported to protect the brain in ischemia–reperfusion damage (Saleem et al., 2007) and the DP2 receptor protects neonatal mouse brain from hypoxic ischemic injury (Taniguchi et al., 2007). More work is needed to understand why PGD_2 can have such opposite effects in different types of neurological injury, i.e., trauma, Alzheimer's disease, demyelinating disease, and ischemic injury.

15d-Prostaglandin J_2. $15dPGJ_2$ is derived from PGD_2 in a series of non-enzymatic dehydration steps (Fig. 2). It has anti-inflammatory, and protective effects in various neurological disorders, such as stroke, EAE and SCI (Diab et al., 2002; Kerr et al., 2008; Pereira et al., 2006). 15d-PGJ_2 is a high affinity natural ligand for peroxisome proliferator-activated receptor-γ (PPARγ) (Forman et al., 1995) and also binds and regulates the function of other targets such as nuclear factor κB (NF-κB) via which it has effects on inflammation and cell death (Giri et al., 2004; Straus et al., 2000). PPARγ is a transcription factor belonging to the nuclear receptor superfamily (Kota et al., 2005). Rosiglitazone, and pioglitazone are potent synthetic agonists of PPARγ that have been found to be effective in reducing inflammation and improving outcomes after SCI (McTigue et al., 2007; Park et al., 2007) and in models of neuropathic and inflammatory pain (Churi et al., 2008; Park et al., 2007; Taylor et al., 2002). 15d-PGJ_2 and rosiglitazone have been shown to reduce nerve injury induced allodynia. A single intrathecal injection of 15d-PGJ_2 or rosiglitazone dose-dependently reduced mechanical and cold hypersensitivity after sciatic nerve transection in rats (Churi et al., 2008). These effects were also blocked by treatment with a PPARγ antagonist (bisphenol A diglycidyl ether).

Studies testing the effects of PPARγ agonists in SCI have also shown variable results. In one study, pioglitazone given intraperitoneally (1 and 10 mg/kg) to rats starting 15 min after contusion injury and then every 12 h for 7 d (McTigue et al., 2007) showed a small improvement in locomotor recovery. In this study, although there was no significant improvement in the main BBB locomotor score, improvements were found in finer aspects of locomotor control (e.g., stepping, toe clearance, and paw position). In a replication study in the same publication, the main BBB score was improved only at day 7 post-injury, not at later time points (McTigue et al., 2007). Pioglitazone treated SCI rats, however, showed some sparing of white and grey matter, and of motor neurons rostral and caudal to the lesion epicenter. In another study, pioglitazone (1.5 mg/kg; at 5 min and daily for 2 d) improved the main BBB locomotor scores between 7 and 42 d (Park et al., 2007). This treatment also reduced thermal hyperalgesia, reduced neuronal and myelin loss, astrogliosis and microgliosis, as well as expression of proinflammatory cytokines (IL-1β, IL-6 and MCP-1) and increased expression of neuroprotective genes including heat shock protein (HSP) 27 and 70, glutathione peroxidase and catalase (Park et al., 2007). Overall, this work suggests that PPARγ agonists improve

outcome after SCI. These SCI studies only tested the effects of PPARγ agonist (McTigue et al., 2007; Park et al., 2007).

To extend the above work, we assessed the effects of 15d-PGJ_2 in SCI. This work showed that 15d-PGJ2 itself can act to improve sensory and motor outcome after SCI independent of PPARγ via reducing activation of NF-κB, enhancing SOCS1 and reducing JAK2 activation (Kerr et al., 2008). NF-κB and the JAK/STAT pathways are essential for coordinating multiple inflammatory responses, which may mediate secondary degenerative changes after SCI. 15dPGJ_2 inhibits IκB kinase (IKK) which phosphorylates IκB and frees NF-κB to enter the nucleus and activate inflammatory genes; it also inhibits NF-κB binding to DNA (Straus et al., 2000). 15d-PGJ_2 is also more effective than synthetic PPARγ ligands in inhibiting iNOS expression (Ricote et al., 1998) suggesting it may have PPARγ-independent activity. We treated adult mice with 15d-PGJ_2 (200 μg/kg; intraperitoneally) daily for 2 weeks starting 1 h after SCI. This treatment showed greater recovery of sensory and locomotor function as compared to vehicle treated SCI controls (Kerr et al., 2008). Sensory function was assessed using a range of calibrated von Frey hairs (bending force 0.12–1.4 g) to monitor hindlimb withdrawal reflexes. 15d-PGJ_2 treatment significantly improved sensory responsiveness to such mechanical stimulation starting as early as day 5 post-SCI. Significant improvement in locomotor recovery (BMS score) was evident from day 6 onwards (Kerr et al., 2008). Higher dose of 15d-PGJ_2 at 1 mg/kg was detrimental. Such dual dose-dependent protective and detrimental effects of 15dPGJ_2 have been reported by others (Yagami et al., 2018). 15d-PGJ_2 also improved survival of ventral horn motor neurons and increased serotonergic innervation of the ventral horn, and reduced demyelination. It also reduced microglia/macrophage activation, and NF-κB activation in the first 3 days post-SCI. As PPARγ is not detected in the injured spinal cord during this early time, the early effects of 15d-PGJ_2 after SCI appears to be mediated by PPARγ-independent mechanisms (Kerr et al., 2008). 15d-PGJ_2 also increased SOCS1 expression in the injured spinal cord and significantly attenuated levels of phospho-JAK2, thereby reducing pro-inflammatory cytokine expression (Kerr et al., 2008). These findings suggest that in SCI, 15d-PGJ_2 may act independently of PPARγ via regulating NF-κB activation and SOCS1-JAK2 signaling to induce resolution of inflammation and reduce secondary damage after SCI. In other SCI work, a much lower dose of 15d-PGJ_2 (30 μg/kg) was effective in reducing neutrophil infiltration, inflammatory cytokine expression, NF-κB activation, oxidative damage and apoptosis, which resulted in improved locomotor function (Genovese et al., 2008a). Previous studies have also reported that PPARγ agonists can mediate anti-inflammatory effects independent of PPARγ via directly modulating NF-κB activation (Rossi et al., 2000) and SOCS1-JAK2 signaling (Park et al., 2003). Therefore, the effects of PPARγ antagonist needs to interpreted with caution. Nevertheless, these *in vivo* data suggest that 15d-PGJ_2 mediates reduction of inflammation after SCI.

Other eicosanoids. Leukotriene B_4 is a strong chemoattractant of neutrophils. Its effects are mediated via the specific, high affinity LTB_4 receptor 1 (BLT1), which is mainly expressed by neutrophils (Ford-Hutchinson et al., 1980; Yokomizo et al., 1997). The role of BLT1 in SCI was assessed in BLT1 knockout mice, and in wildtype mice treated pharmacologically with a LTB_4 receptor antagonist (ONO-4057) (Saiwai et al., 2010). Inhibition or lack of BLT1 reduced neutrophil influx, reduced expression of chemokines and cytokines (IL-1β, IL-6, TNFα, CXCL1 and CXCL2) in the injured spinal cord, and reduced neuronal and myelin loss, with a modest but statistically significant improvement in locomotor recovery (Saiwai et al., 2010). Other studies assessed the effects of Montelukast a leukotriene receptor (Cys-LT) antagonist, and Zileuton a 5-LO inhibitor. Both these studies were reported to improve outcome (locomotor recovery, reduction in inflammatory markers, lipid peroxidation and tissue damage) when evaluated within 7 or 10-days post-SCI (Ersahin et al., 2012; Genovese et al., 2008b). Longer survival times need to be tested to characterize the full extent of recovery.

Lysophosphatidic acid

Lysophosphatidic acid (LPA) is one of the simplest lipids composed of a glycerol backbone connected to a phosphate head group and are commonly ester-linked to an acyl chain of varied length and saturation (Aoki et al., 2008). The generic term LPA (mono-acyl-*sn*-glycerol-3-phosphate) often refers to 18:1 oleoyl-LPA (1-acyl-2-hydroxy-sn-glycero-3-phosphate), reflecting its widespread use. However, many other chemical forms of LPA with different acyl chain lengths, saturation, and position also exist (Yung et al., 2015). LPA is generated from phospholipids by two major metabolic routes. In the first pathway, LPA is produced from lysophospholipids, such as LPC, generated by the action of PLA_2 and PLA_1, which are then converted to LPA via autotaxin (ATX) (Fig. 2). This seems to be the main pathway responsible for LPA production, at least in the blood, since conditional knockout mice for ATX display a ~60% reduction in LPA levels in plasma (Katsifa et al., 2015). In the second pathway, phosphatidic acid (PA) is first generated from phospholipids or diacylgycerol by the action of phospholipases D (PLD) and then deacylated by PLA_1 or PLA_2 (Aoki et al., 2008).

LPA acts as an intracellular and extracellular messenger and regulates a wide range of cellular responses, including cellular proliferation, apoptosis, cell migration, cytokine and chemokine secretion, smooth muscle contraction, platelet aggregation, axon elongation and guidance, among others (Aoki et al., 2008). All these actions are mediated by signaling through 6 different G protein-coupled receptors, with the protein products named LPA1 to LPA6 and with gene names LPAR1 to LPAR6 in humans and *Lpar1* to *Lpar6* in other species (Birgbauer, 2020). Despite the importance of LPA and its receptors in regulating many important physiological functions, it is now known that they are involved in diseases, such as cancer, autoimmune disease,

cardiovascular diseases, and neurological conditions (Yung et al., 2014, 2015). In this review we will focus on the role of LPA in CNS trauma.

Involvement of LPA in SCI. LPA levels increase very rapidly in the spinal cord following contusion injury in mice. Its expression peaks at day 3 post-injury, when it reaches ~10-fold and remains at significantly high levels for up to at least 2 weeks after lesion (Santos-Nogueira et al., 2015). The increase in LPA is not unique to SCI, as increases in LPA are also detected in the brain and CSF after traumatic brain injury (TBI) in mice and humans, respectively (Crack et al., 2014). The most abundant LPA species after SCI is 18:1 LPA, whereas in TBI the 18:0 LPA is the most predominant form, while 18:1 LPA is almost undetectable (Crack et al., 2014; Santos-Nogueira et al., 2015).

The increase of LPA levels in the CNS parenchyma has deleterious effects. This is clear from experiments demonstrating that intraspinal injection of LPA leads to inflammation and demyelination (Santos-Nogueira et al., 2015). Moreover, the administration of the B3 antibody, which is able to bind LPA and other lysophospholipids and, thus, expected to reduce their bioavailability, ameliorates functional deficits and tissue damage after TBI and SCI (Crack et al., 2014; Goldshmit et al., 2012; Santos-Nogueira et al., 2015). As different LPA species have differing affinities for different LPA receptors, the divergent LPA species found in SCI and TBI, suggest that LPA signaling could differ in the two types of neurotrauma. The nervous system is one of the major loci for LPA receptor expression. All 6 LPA receptors are expressed constitutively in the CNS (Santos-Nogueira et al., 2015). However, only the contribution of LPA1 and LPA2 in SCI has been studied so far (Lopez-Serrano et al., 2019; Santos-Nogueira et al., 2015).

LPA1 is the most abundant LPA receptor in the CNS. It is expressed in oligodendrocytes, microglial cells, astrocytes, ependymal cells and neurons (Yung et al., 2015). Mice lacking LPA1 (ma*Lpar1*) show reduced cortical thickness because of increased apoptosis and reduced proliferation of neural progenitor cells due to early and aberrant differentiation of these progenitors (Matas-Rico et al., 2008). These mice also display decreased neurogenesis in the hippocampus (Matas-Rico et al., 2008). However, the most understood involvement of LPA1 in neurological conditions is related to the development of neuropathic pain (Inoue et al., 2004). Recent reports have addressed the role of LPA1 in neurotrauma. Although *Lpar1* transcripts do not increase in the spinal cord following contusion injury in mice, the use of LPA1 knockout mice (ma*Lpar1* mice) and pharmacological antagonist (AM095) revealed that LPA-LPA1 signaling leads to demyelination and functional impairment in SCI. Even though LPA1 is expressed in oligodendrocytes, the demyelinating effects of LPA are unlikely to be mediated by LPA1 signaling in oligodendrocytes, since pharmacological blockade of LPA1 does not attenuate oligodendrocyte cell death after LPA exposure (Santos-Nogueira et al., 2015). Indeed, the demyelinating actions triggered by LPA1 are likely to be mediated by microglia, as conditioned medium of cultured microglia stimulated with LPA promote massive oligodendrocyte cell death. This effect is partially prevented by pharmacological blockade or gene deletion of LPA1 in LPA-stimulated microglia (Santos-Nogueira et al., 2015).

LPA1 signaling also contributes to secondary damage after cerebral ischemia as blocking with AM095 or silencing with shRNA treatment attenuates microglial activation and tissue damage (Gaire et al., 2019) further confirming the deleterious role of LPA1 in CNS injuries. Interestingly, a recent transcriptomic analysis revealed that *Lpar1* is the most downregulated gene in sprouting vs quiescent corticospinal neurons after unilateral pyramidotomy, in mice (Fink et al., 2017). Furthermore, pharmacological blockade of LPA1 with AM095 results in a 10-fold increase in the sprouting of corticospinal axon arbors after unilateral pyramidotomy and improves functional recovery (Fink et al., 2017). Therefore, these studies provide clear evidence that LPA-LPA1 signaling, apart from contributing to tissue damage, is also an intrinsic axon growth modulator that prevents sprouting and plasticity of undamaged axons after CNS injury.

The other LPA receptor that is known to contribute detrimentally to SCI is LPA2. LPA2 transcripts are markedly upregulated in the mouse spinal cord after contusion, peaking at day 3 (Lopez-Serrano et al., 2019). LPA2 in the CNS is expressed mainly in oligodendrocytes, neurons, and microglia. The suppression of LPA-LPA2 signaling reduces demyelination after intraspinal injection of LPA and after SCI, indicating a key deleterious role of LPA2 in SCI pathology (Lopez-Serrano et al., 2019). Like LPA1, the demyelinating actions of LPA2 after neurotrauma are likely to be mediated by microglial cells. *In vitro* studies suggest that LPA-LPA2 signaling in microglia induces the release of purines, which in turn, activate P2X7 in oligodendrocytes, which is responsible for triggering cell death (Lopez-Serrano et al., 2019). However, the mechanism that underlies the pathological effects of LPA2 in SCI *in vivo* remains unknown. The demyelinating actions of LPA2 after SCI cannot be extrapolated to all demyelinating disorders, since LPA2, for instance, is protective in EAE (Schmitz et al., 2017). Interestingly, the beneficial effects of LPA2 in EAE are not mediated in the CNS but in the periphery. LPA2 prevents the mobilization of T cells into the circulation, which may be responsible for the delayed onset of EAE and reduction in clinical signs observed in the *Lpar2* null mice (Schmitz et al., 2017).

There is currently no information about the involvement of LPA3-LPA6 in SCI. However, one cannot exclude the possibility that these receptors could exert either detrimental or beneficial effects after neurotrauma. Recently, the LPA5 antagonist, TCLPA5, was shown to significantly reduce damage after cerebral ischemia, including infarct size, apoptosis, and neurological deficits (Sapkota et al., 2020), suggesting that this LPA receptor, which is enriched in microglia (Kozian et al., 2016), may also contribute to secondary tissue damage after SCI.

Specialized pro-resolution mediators

Acute inflammation is a natural response to injury or disease that is designed to fight infections, clear damaged cells, and restore tissue homeostasis. The initiation of inflammation is therefore desirable. However, inflammation needs to be terminated in a timely fashion, to prevent chronic inflammation. Both acute and chronic inflammation can cause bystander or secondary damage to healthy tissue, particularly in the CNS, which has a limited capacity to regenerate and replace damaged neurons. About twenty years ago, Serhan's group made the discovery that effective termination of inflammation is an active process, termed 'resolution of inflammation', which is mediated by a superfamily of lipid mediators derived mainly from omega-3 fatty acids, DHA and EPA but also lipoxins derived from AA (Fig. 2) (Levy et al., 2001). These are collectively referred to as Specialized Pro-resolution Mediators (SPMs). On the other hand, the initiation of inflammation, is mediated by PGs and leukotrienes derived from the omega-6 fatty acid, AA. The transition from acute inflammation to resolution is therefore defined as involving a lipid mediator class switch from pro-inflammatory eicosanoids to pro-resolution SPMs (Fig. 3) (Levy et al., 2001; Schwab et al., 2007).

In previous sections, we have reviewed that lipid mediators generated by PLA_2s are important triggers for the initiation of inflammation in different neurological conditions. However, it is important to note that paradoxically, PLA_2s are also important for the resolution of inflammation. This is clear from experiments on sciatic nerve injury in cPLA2 GVIA null mice or mice treated with an $iPLA_2$ inhibitor (FKGK11) (Lopez-Vales et al., 2008). In these experiments, the early influx of macrophages into the sciatic nerve is reduced at 7 days after injury in the experimental groups indicating that these PLA_2 play a role in the initiation of inflammation. However, at day 21 post-lesion, when resolution of inflammation indicated by the marked reduction in macrophage numbers is evident in the control mice with nerve injury, the lack of $cPLA_2$ and $iPLA_2$ activity impairs the clearance of macrophages, demonstrating that the resolution of inflammation is impaired (Lopez-Vales et al., 2008). Similar observations are also seen in the CNS in EAE, when mice treated with a $cPLA_2$ inhibitor (AX115) prior to onset of clinical signs of the disease reduces disease onset (i.e., reduces initiation of inflammation), while treatment after start of clinical signs of EAE, prevents the remission phase of the disease Kalyvas et al., 2009. Therefore, PLA_2 enzymes have a dual role in regulating inflammation in the PNS and CNS since they are critical for both, initiation and resolution of inflammation.

Although most of the attention on PLA_2 biology has been focused on the actions of the lipid mediators derived from omega-6 PUFA, mainly from AA, these family of enzymes also yield omega-3 (n-3) PUFAs, such as, alpha linoleic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Lopez-Vales and David, 2019). DHA and EPA are synthesized through desaturation and elongation reactions from their precursor, an 18-carbon atom fatty acid, ALA, which is available by diet (Samaddar, 2016). In humans there is restricted conversion of ALA to DHA because of the lack of the desaturase enzyme needed to transform ALA to DHA and EPA, and thus they must be obtained from food intake, especially from fish, fish oil, walnuts, flaxseed, flaxseed oil, and leafy vegetables. Indeed, DHA deficits are associated with various physiological disorders such as some forms of cancer, rheumatoid arthritis, cardiovascular disease and neurological disorders like Alzheimer's disease, depression, attention deficit hyperactivity disorder (ADHD) and unipolar disorder, among others (Michael-Titus and Priestley, 2014). n3-PUFA have powerful anti-inflammatory actions (Lopez-Vales and David, 2019). Initial evidence of the anti-inflammatory properties of n-3 PUFAs come from epidemiological studies on indigenous peoples living in the north that consume large amounts of n-3 PUFAs from fish and seal meat (Dyerberg and Bang, 1979; Kromann and Green, 1980). Dietary supplementation with fish oil reduces the circulating levels of cytokines and oxidative stress markers (Freund-Levi et al., 2006; Kiecolt-Glaser et al., 2012) and ameliorates to some extent symptoms in neurological conditions including multiple sclerosis (MS) (Stewart and Bowling, 2005; Weinstock-Guttman et al., 2005) and moderate cognitive loss (Freund-Levi et al., 2006; Lee et al., 2013). However, the evidence of the beneficial actions of n-3 PUFA in neurotrauma come from animal studies.

After SCI, there is increased levels of free AA and reduced DHA at the lesion site (Lopez-Vales et al., 2011b). As these two PUFA have antagonistic effects on inflammation, this imbalance in PUFA homeostasis is likely to contribute to an exacerbated and chronic inflammatory response that occurs after neurotrauma. Indeed, several strategies aimed at boosting n-3 PUFA levels after CNS injury have proven beneficial. For instance, systemic administration or dietary supplementation of ALA, EPA or DHA improves neurological recovery, minimizes oligodendrocyte and neuronal loss and alleviates inflammation in various models of SCI in mice and rats (Huang et al., 2007; King et al., 2006; Lim et al., 2013b; Paterniti et al., 2014). In fact, even a single bolus of DHA was effective in promoting functional recovery after SCI (Liu et al., 2015a). Transgenic expression of the *Caenorhabditis elegans* fat-1 gene, which encodes an omega-3 fatty acid desaturase that converts n-6 to n-3 PUFA, also enhances functional recovery and improves histological outcomes after SCI (Lim et al., 2013a). We have tested a pharmacological strategy to correct imbalance of these two PUFAs with fenretinide, a semi-synthetic analog of retinoic acid (Lopez-Vales et al., 2011b). Treatment of SCI mice with fenretinide reduces AA and increases DHA levels in the plasma and spinal cord after contusion injury. This treatment also attenuates neurological deficits, even when treatment is initiated 24 h after injury (Lopez-Vales et al., 2011b).

The beneficial effects of n-3 PUFA in neurotrauma are thought to be mediated via multiple mechanisms, including their ability to reduce glutamate efflux (Vreugdenhil et al., 1996), modulate various transcription factors, such as retinoid X receptors (de Urquiza et al.,

2000), and bind to G protein-coupled receptors (GPR) such as, GPR40 and GPR120 (Honore et al., 2013; Oh et al., 2010). However, the most important actions of n-3 PUFA in attenuating inflammation are likely to be mediated via SPMs (Serhan, 2014). A recent study reported that maternal dietary deficiency in n-3 PUFA increases microglial phagocytosis of synaptic elements in the developing mouse hippocampus in part via activation of the 12/15 LOX/12-HETE signaling pathway and impairs cognitive function (Madore et al., 2020). These findings reveal an important new role for n-3 PUFA in modulating and restraining microglial phagocytosis. If this also occurs in the adult CNS, it could be of importance in SCI where n-3 PUFA could control excessive phagocytosis by microglia and thus prevent damage to intact components of the CNS. It will be of interest to know if n-3 PUFAs would also have a similar effect on MDMs that enter the CNS after injury.

SPMs encompasses a super family of bioactive lipids identified from inflammatory exudates over the last two decades that actively promote resolution of inflammation (Serhan, 2014). These chemical mediators are derived from n-3 PUFAs, mainly from EPA and DHA, or from n-6 PUFA, AA (Fig. 2). There are four main SPM families: (i) lipoxins; (ii) resolvins; (iii) protectins and (iv) maresins (Serhan, 2014; Serhan and Levy, 2018). SPMs act as ligands for various G protein-coupled receptors (Fig. 2) that are present in many cell types, mostly immune cells. SPMs activate specific mechanisms that trigger the resolution of inflammation (Serhan, 2014; Serhan and Levy, 2018) including: (i) clearance of the inciting stimuli and normalization of pro-inflammatory mediator gradients, such as cytokines and prostaglandins; (ii) silencing of intracellular pro-inflammatory signaling pathways, such as NF-κβ, MAPK and JAK/STAT; (iii) cessation of neutrophil migration; (iv) recovery of vascular permeabilization and reabsorption of oedema; death of neutrophils, mainly via apoptosis; (v) infiltration of non-phlogistic macrophages and/or conversion of macrophages present in the challenged site into non-phlogistic macrophages; (vi) removal of apoptotic neutrophils, cell debris and foreign agents/microbes; (vi) clearance of phagocytes via lymphatic system or blood and (vii) initiation of healing processes and tissue repair to return to normal tissue function and homeostasis (Lopez-Vales and David, 2019; Serhan, 2014).

Failure to produce adequate amounts of SPMs or to bind to their receptors leads to resolution deficit and may lead to chronic inflammation. Indeed, several reports reveal defective synthesis of SPMs in conditions characterized by excessive or chronic inflammation, and that the exogenous administration of SPMs results in potent beneficial therapeutic effects, including in cardiovascular diseases, chronic inflammatory conditions, inflammatory pain, infections and cancer (Schwab et al., 2007; Serhan, 2014; Serhan and Levy, 2018). We have reported that there is inadequate production of SPMs in the lesioned spinal cord (Francos-Quijorna et al., 2017) and exogenous administration of SPM results in improved recovery. Defective production of SPMs also occurs in Alzheimer's disease and MS (Pruss et al., 2013; Wang et al., 2015). Thus, administration of SPMs or synthetic ligands could be developed as novel therapeutics for the treatment of neurological disorders. In the next section we will provide more details on different members of the SPM family.

Resolvins (Rv) are generated from n-3 PUFA and belong to two main Rv subfamilies – the E-series (RvE) derived from EPA and the D series (RvD) derived from DHA (Fig. 2). RvE are produced from EPA by the action of cytochrome P450 monooxygenase or aspirin-treated cyclooxygenase-2. This reaction generates the intermediate18R-hydroperoxy-EPA (18-HEPE) which is finally converted to RvE1, RvE2, RvE3 and 18*S*-Rv1 by 5-LOX. Animal studies have revealed that RvE are synthesized by polymorphonuclear leukocytes (neutrophils) and cause the inhibition of leukocyte/neutrophil migration associated with a reduction in the release of pro-inflammatory cytokines and an increase in phagocytic activity of macrophages, which in turn cause tissue cleaning (Serhan, 2014). The anti-inflammatory effects of RvE1 and RvE2 can be attributed to their ability to bind to the ChemR23, also termed as chemokine receptor-like 1 (CMKLR1). ChemR23 is expressed on macrophages, dendritic cells, innate lymphoid cells as well as on epithelial cells. RvE1 can also act on LTB4 receptor BLT1 (Arita et al., 2005; Schwab et al., 2007). BLT1 is found on neutrophils, eosinophils, monocytes, macrophages, T cells, mast cells, and dendritic cells as well as in vascular tissues (Serhan, 2014). Currently, there are no studies addressing the effects of RvE in SCI. However, RvE1 reduces the number of rod microglia after traumatic brain injury and enhances post-traumatic sleep but does not improve functional or cognitive outcomes after brain trauma (Harrison et al., 2015).

RvD are generated from DHA and docosapentaenoic acid (DPA). These n-3 PUFA are converted to 17S-hydroperoxy-DHA (17(S)-HpDHA) by either LOX15, cytochrome P450 monooxygenase or aspirin-treated cyclooxygenase-2, which is then reduced to 17S-hydroxy-DHA (17(S)-HDHA). This intermediate is then metabolized to different RvD (RvD1–RvD6) by the action of 5-LOX (Chiang and Serhan, 2017, 2020; Dalli and Serhan, 2019). These six RvD possess a 17S-hydroxy residue. However, if aspirin-treated cyclooxygenase-2 is the initiating enzyme, they contain a 17R-hydroxy residue and are termed 17R-RvDs, aspirin-triggered-RvD1-6, or AT-RvD1-6 (Serhan, 2014; Serhan and Levy, 2018).

RvD mitigates neutrophils infiltration to challenged tissues, enhances macrophage efferocytosis and exerts potent analgesic actions in different non-neurological conditions. These effects are mediated by signaling through different G protein-coupled receptors. RvD1, RvD3 and their aspirin triggered epimers bind to the LX receptor, ALX/FPR2. In addition, RvD1, RvD2 together with RvD3 and RvD5 stimulate GPR32, which is present in neutrophils, monocytes and vascular endothelial cells. Additionally, RvD2 is also a ligand for GPR18, a receptor for endogenous lipid neurotransmitters that is present in microglia and other immune cells (Dalli and Serhan, 2019). RvD1 has been better characterized than

other members of the RvD subfamily in animal studies but its actions in SCI are not known. However, RvD1 alleviates inflammation and has therapeutic effects in a model of brain trauma (hemicerebellectomy) (Bisicchia et al., 2018), cerebral ischemia/reperfusion injury (Chen et al., 2020) and traumatic brain injury (Ren et al., 2020). The beneficial actions of RvD1 in hemicerebellectomy seem to be mediated via ALX/FPR2 since the administration of neutralizing antibodies for this receptor counteracts its therapeutic effects (Bisicchia et al., 2018). These results suggest that RvD1 is likely to be beneficial in SCI and needs testing. The only RvD member that has been tested in animal models of SCI is the RvD3. A recent study shows that intrathecal administration of RvD3 promotes locomotor recovery and neuroprotection after SCI (Kim et al., 2021). This work also shows that RvD3 reduces the expression of proinflammatory cytokines in the injured spinal cord, attenuates astrogliosis and reduces the expression levels of CD68 on microglia/-macrophage (Kim et al., 2021).

Protectin (PD1) like RvD is generated from the intermediate 17(S)-HDHA. This intermediate is then converted to a 16S,17S-epoxide which is then hydrolyzed, likely by a soluble epoxide hydrolase, to protectin D1 (PD1) or AT-PD1 if this is generated by the action of aspirin. PD1 is synthesized by peripheral blood mononuclear cells, Th2 CD4+ T cells and microglia (Chiang and Serhan, 2017; Dalli and Serhan, 2019; Hong et al., 2003). When PD1 is generated in the CNS, it is called neuroprotectin D1 (NPD1) (Fig. 2). Like RvDs, PD1 exerts potent immunomodulatory effects that include the inhibition of neutrophil migration, polarization of macrophages towards an anti-inflammatory phenotype, suppression of Th1 inflammatory cytokines and T-cell migration, and induction T-cell apoptosis (Dalli and Serhan, 2019). These effects are mediated, in part, by signaling via GPR37, which is expressed on macrophages. Although GPR37 is present in the CNS, immunohistological analysis reveals that this receptor is not expressed on microglia, suggesting that neurons and/or other glial cells are the target of PD1/NPD1 (Bang et al., 2018). Studies on brain ischemia reveal that NPD1 reduces functional deficits and tissue damage and attenuates different aspects of inflammation (Belayev et al., 2018; Marcheselli et al., 2003). Its effects on SCI have not been tested.

Maresins (macrophage mediators in resolving inflammation; MaR) is another SPM family member derived from DHA (Fig. 2). MaRs are produced by macrophages and include three different members: maresin 1 (MaR1), maresin 2 (MaR2) and the maresin conjugate in tissue regeneration (MCTR) (Dalli and Serhan, 2019; Serhan, 2014). MaR appears in later stages of the inflammatory response and is released by resolution phase macrophages. They arise from DHA by the actions of 12-LOX, (12/15-LOX in mice) which generates an intermediate epoxide (13S,14S-epoxide-4Z,7Z,9 E,11E,16Z,19Z-DHA), which is subsequently hydrolyzed by an unknown hydrolase to produce MaR1 and MaR2. MaR can also be produced from DPA by similar reactions to give rise to $MaR1_{n-3}$, $MaR2_{n-3}$. MaR epoxide intermediate can also enzymatically bind to peptides and form active mediators known MCTR1-3 (Dalli and Serhan, 2019). MaR counter regulates proinflammatory chemical mediators, controls pain and enhances tissue regeneration (Dalli and Serhan, 2019; Serhan, 2014). The effects of MaR1, but not MaR2 or MCTR, on inflammation are mediated extracellularly via leucine rich repeat containing G protein-coupled receptor 6 (LGR6) (Chiang et al., 2019). MaR1 can also act intracellularly as it is an endogenous ligand of the retinoic acid–related orphan receptor alpha (RORα) (Han et al., 2019).

MaR1 exerts different pro-resolving actions on inflammation after SCI. Our work has shown that although this SPM does not reduce the infiltration of neutrophils in SCI, it fosters their clearance. This is remarkable when assessing the resolution index of neutrophils, which is the time required to reduce the number of neutrophils to 50% from their maximal counts. The value of this parameter is ~86 h in untreated SCI controls and reduced by 55% (to 37 h) after MaR1 treatment. MaR1 not only accelerates the clearance of neutrophils from the injured spinal cord but it also reduces their persistent accumulation in the neural tissue (Francos-Quijorna et al., 2017). The effects of MaR1 on neutrophil clearance are, in part, due to the ability of this SPM to modulate macrophage function. In particular, MaR1 increases the ability of macrophages to phagocytose neutrophils in the injured spinal cord (Francos-Quijorna et al., 2017). Moreover, it also attenuates their accumulation in the injured spinal cord and promotes the expression of anti-inflammatory markers (Francos-Quijorna et al., 2017). In addition to modulating immune cell functions, MaR1 also reduces the protein levels of various pro-inflammatory cytokines such as CXCL2, CXCL1, IL-6 in the lesioned spinal cord and silences the pro-inflammatory JAK/STAT and MAPK pathways (Francos-Quijorna et al., 2017). Importantly, the actions of MaR1 on inflammation in SCI result in enhancement of functional recovery and improved histological outcomes, as has also been seen after cerebral ischemia (Xian et al., 2016). However, to what degree the beneficial actions of MaR1 in the CNS injury are mediated by LGR6 or RORα needs to be elucidated.

Lipoxins (LX). These bioactive lipid mediators are unique within the SPM superfamily because they are generated from n-6 PUFA, AA (Fig. 2). LX encompasses three members: LXA4, LXB4 and aspirin-triggered LX (ATL). LX are produced via three different synthetic pathways. In the first route, LX are generated from AA-derived metabolite, LTA4, by 12-LOX. In the second route of synthesis, AA is converted to 15-hydroxy peroxyeicosatetraenoic acid (15-HPETE) by 15-LOX and then to LXA and LXB via 5-LOX or 12-LOX. Finally, the third route is dependent on aspirin. Aspirin irreversibly acetylates COX-2 to generate 15R-hydroxy eicosatetraenoic acid (15(R)-HETE) from AA, which is then converted to ATL via 5-LOX (Serhan, 2014). Double-blinded clinical trial in healthy subjects shows that low-dose aspirin (81 mg daily) significantly increased aspirin-triggered ATL levels (Chiang et al., 2006), which

is likely responsible of mediating the anti-inflammatory actions of aspirin.

LX elicits multicellular responses via binding to the G protein-coupled lipoxin A4 receptor (ALX) also known as formyl peptide receptor (FPR2). ALX/FPR2 is mainly expressed in myeloid cells, and to a lower extent, lymphocytes, dendritic cells and CNS resident cells (Bennett and Gilroy, 2016). LXA attenuates inflammation and exerts therapeutic actions after spinal cord contusion in rats (Lu et al., 2018) and ischemia/reperfusion injury in rabbits (Liu et al., 2015b). Similarly, administration of the ALX/FPR2 synthetic agonist, BML-111, leads to locomotor recovery after SCI in rats, suggesting that the beneficial actions of LXA in neurotrauma are mediated, at least in part, via FPR2 (Liu et al., 2020). Importantly, LXA also alleviates neuropathic pain after spinal cord hemisection (Martini et al., 2016).

SPMs and pain. There is a large body of literature on the effects of SPMs in pain which we cannot cover here. We refer the reader to original publications and other excellent reviews on these topics. Since pain is often associated with SCI, we would like to mention briefly that various members of the SPM family reduce pain in a number of models, e.g., acute inflammatory pain (formalin, capsaicin, and carrageenan), chronic pain (complete Freund's adjuvant (CFA), and arthritic), neuropathic pain (chronic constriction injury (CCI), and spinal cord injury), postoperative pain (soft tissue, bone fractures), and cancer pain (Tao et al., 2020). For most conditions, RvD1 and RvD2 were found to be effective in reducing pain. NPD1 and MaR1 were also found to be effective in reducing pain in formalin, capsaicin, CFA, and CCI (NPD1), and capsaicin, chemotherapy and post-operative (MaR1) pain (Tao et al., 2020). In a model of post-operative pain after bone fracture, in which a number of SPMs were tested, intrathecal administration (500 ng) of NPD1, MaR1, and RvD1 and RvD5, but not RvD3 and RvD4, were effective in reducing pain (Zhang et al., 2018). In the spinal cord hemisection injury model in rats and mice, Lipoxin A4 (300 pmol, intrathecal injection at 4 and 24 h after injury) reduced mechanical allodynia over 35 days, and also reduced microglial reactivity and TNF expression (Martini et al., 2016). Other SPMs were not tested in this SCI model.

FUTURE PERSPECTIVES

Advances in medicinal chemistry leading to the design and generation of small molecule inhibitors of PLA_2, eicosanoid synthetic enzymes, and various eicosanoids and their receptors; and the ability to generate mice with genetic deletion of genes of interest have not only opened-up the field to critical analysis of the functions of these bioactive lipids that mediate inflammation but has also ushered in an era of development and testing of small molecule agonists and antagonists to treat human diseases of the central nervous system.

Despite the work done on PGs, SPMs, other eicosanoids and PLA_2s, no treatments have reached clinical use for SCI. This is likely because many aspects of the neuropathological response to CNS injury can be both beneficial or detrimental depending on the cell type and timing after injury. For example, the early microglial response after injury appears to be beneficial as it prevents expansion of the lesion, while later chronic activation can have detrimental effects. Similarly, neutrophils are detrimental and cause secondary damage via enzymes and other factors released from cytoplasmic granules after their entry into the injured CNS. However, phagocytosis of apoptotic neutrophils by MDMs induce expression of SPMs that resolve inflammation. In addition, the early entry and infiltration of MDMs may be beneficial as they become anti-inflammatory when they phagocytose damaged myelin. They can also inactivate microglia and prevent chronic microglial activation (Greenhalgh et al., 2018). On the other hand, MDMs that phagocytose RBC at the site of hemorrhage and those that are located in areas with high levels of TNF would acquire a pro-inflammatory, cytotoxic phenotype (Kroner et al., 2014). Furthermore, microglia and macrophages interact with other CNS glia (astrocytes and oligodendrocytes) to modulate the inflammatory and cytotoxic or cytoprotective responses (Greenhalgh et al., 2020). This points to just some of the complexities of the inflammatory response that make finding single therapeutics for SCI very challenging. It may also be why acute high dose treatment with methylprednisolone only has minimal effects in the treatment for SCI (Fehlings et al., 2017). One potentially promising area is targeting multiple PLA_2s by a single pan-PLA_2 inhibitor but one that only partially blocks their activity. Many PLA_2 inhibitors have been developed and tested for other conditions in animal models and in clinical trials that have reached phase III trials but proven unsuccessful thus far. This may be due in part to their multiple roles, for example, in generating PG and leukotrienes that initiate inflammation but also release DHA and EPA that meditate resolution. In addition, they also play important physiological roles in membrane turnover and homeostasis. Inhibitors which partially block the activity of several PLA_2s may therefore be more desirable. As better inhibitors are developed (Nikolaou et al., 2019), they need to be tested in pre-clinical models. Another area of optimism is the advances made in SPMs. Although dozens of SPMs derived from DHA, EPA and AA have been identified, only a few have so far been tested rigorously in SCI. A wide screen to test other SPMs in SCI is needed to identify which SPMs are most effective in reducing secondary damage and restore functional recovery. Remarkably, pre-clinical studies have shown that even a single bolus of DHA was effective in promoting functional recovery after SCI (Liu et al., 2015a). Clinical trials are therefore warranted to test DHA intravenously or orally in SCI. Another approach is to develop drugs that are more effective than fenretinide in correcting the balance between omega-6 (AA) and omega-3 (DHA) fatty acid in the injured spinal cord (Lopez-Vales et al., 2011b). With our increasingly better understanding of the mechanisms that control pro- and anti-inflammatory aspects of inflammation after CNS injury, and the ability to target different aspects of the inflammatory response, we can expect to see the development of effective therapies for SCI within the next decade.

ACKNOWLEDGEMENTS

SD was supported by grants from the Canadian Institutes of Health Research (CIHR) (MOP-142231), the Wings for Life Spinal Cord Research Foundation, and the ERA-NET NEURON. RLV was supported by by grants from Spanish Ministry of Economy and Competitiveness (SAF2016-79774-R), Wings for Life Spinal Cord Research Foundation, Red de Terapia Celular (TERCEL) and funds from "la Caixa" Foundation under agreement LCF/TR/CI17/10020018 and LCF/PR/HA17/52170001. We also thank Jose Rosas and Dr. Antje Kroner for their edits and suggestions.

DECLARATIONS OF INTEREST

None.

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(Received 12 March 2021, Accepted 23 April 2021)
(Available online 2 May 2021)