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One immune system plays many parts: the dynamic role of the immune system in chronic pain and opioid pharmacology

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Abstract

The transition from acute to chronic pain is an ongoing major problem for individuals, society and healthcare systems around the world. It is clear chronic pain is a complex multidimensional biological challenge plagued with difficulties in pain management, specifically opioid use. In recent years the role of the immune system in chronic pain and opioid pharmacology has come to the forefront. As a highly dynamic and versatile network of cells, tissues and organs, the immune system is perfectly positioned at the microscale level to alter nociception and drive structural adaptations that underpin chronic pain and opioid use. In this review, we highlight the need to understand the dynamic and adaptable characteristics of the immune system and their role in the transition, maintenance and resolution of chronic pain. The complex multidimensional interplay of the immune system with multiple physiological systems may provide new transformative insight for novel targets for clinical management and treatment of chronic pain.

Graphical Abstract

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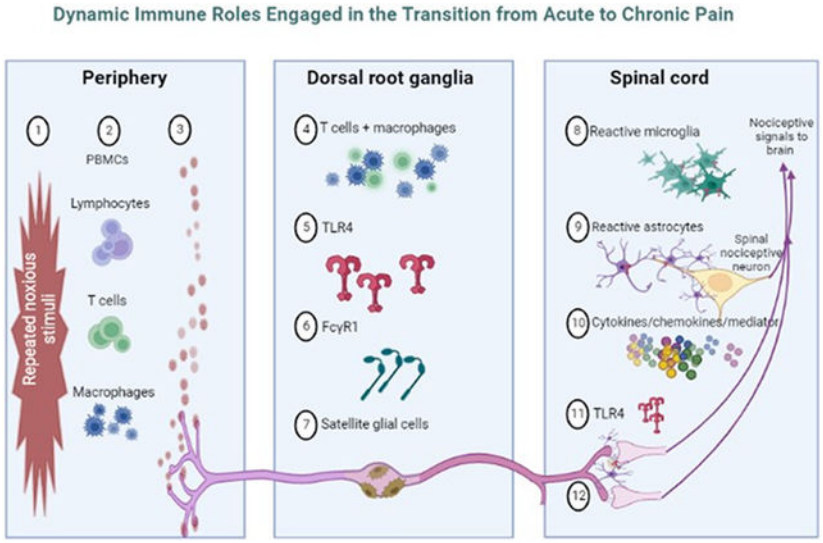

Noxious stimuli results in upregulation of pro-inflammatory cytokines, chemokines or inflammatory mediators which initiate peripheral nociceptor activation. (1) Repeated stimuli results in recruitment of immune cells (PBMCs) to the injury site. (2) Repeated stimuli and immune signals from the region result in hyperexcitation of peripheral nociceptors leading to peripheral sensitization. (3) Recruitment of peripheral macrophages and (4) upregulation of TLR4 in the dorsal root ganglia play key roles in the development/maintenance of peripheral sensitization. Classical immune receptors, such as (5) FcγR1 are expressed on immune cells, dorsal root ganglia and neurons and play critical roles in regulating immunity and pro-nociceptive signaling, including chronic pain states. Peripheral sensitization and the immune-mediated interactions at the DRG/trigeminal ganglia level lead to maladaptive responses in the spinal cord and higher order brain regions. (6) Microglia and (7) astrocytes in the spinal dorsal horn detect danger signals from the periphery and transforming into their reactive phenotypes causing subsequent (8) release of pro-inflammatory cytokines, chemokines and mediators playing a pivotal step in the initiation of central sensitization. (9) TLR4 are upregulated in dorsal spinal cord (9a) microglia and (9b) astrocytes. (10) Astrocytes mediate synaptic transmission modulation which contributes to the sensitization of second order nociceptive neurons.

Keywords

Chronic pain; Neuroimmune interactions; Toll-like receptors; Fcγ receptors (FcγRs); A20

1. The Burden of Chronic Pain

Chronic pain is a leading cause of disability globally (Vos et al., 2017; Vos et al., 2020). The impact of chronic pain extends beyond the 20% of the population directly experiencing symptoms, to family members, carers, and employers. In 2019 the Global Burden of Diseases, Injuries and Risk Factors Study reported that several of the top ten most important drivers of increasing burden included low back pain, headache disorders and other musculoskeletal disorders (Vos et al., 2020). At a deeper level, pain of several

types is associated with more than three quarters of the years lived with disability. Further, as our understanding of complications arising from the use of opioids in the treatment of chronic pain conditions has expanded, we now appreciate the intimate involvement of the innate immune system in the development of maladaptive behaviours relating to addiction, tolerance, dependence, and hyperalgesia, to name a few. As such, there is an urgent need to provide better management of chronic pain, or better still, prevent it. This vision can only be achieved by gaining a deeper understanding of the multiple mechanisms that underpin chronic pain states.

Chronic pain is an umbrella term which encapsulates all types of pain, affecting any organ or anatomical location, that persists long after an injury has healed. Typical examples of such conditions include rheumatoid arthritis, fibromyalgia, neuropathic pain, persistent post-surgical pain, low back pain, chronic visceral pain, chronic migraine and cancer, including toxicities related to anti-cancer treatment (Grace et al., 2021; Grundy et al., 2019; Gulur and Nelli, 2019; Li et al., 2021; Mathias et al., 2021; May and Schulte, 2016; Nijs et al., 2016; Secombe et al., 2019; Sluka and Clauw, 2016; Staff et al., 2017). For many years, chronic pain has been classified as either nociceptive or neuropathic. Nociceptive pain is described as pain that is the result of real or threatened ongoing tissue damage. Neuropathic pain occurs as a result of damage to the peripheral or central nervous system (CNS). Acknowledging that around 5-15% of the general population suffers from chronic pain that occurs neither via nociceptive nor neuropathic pain, the International Association for the Study of Pain (IASP) has recently introduced a new term, ‘nociplastic pain’ (Fitzcharles et al., 2021; Raja et al., 2020). Nociplastic pain has been defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” (Raja et al., 2020).

It is now widely accepted that the role of the immune system extends far beyond classical host defence. In fact, the very characteristics and mechanisms that allow the immune system to detect, respond and protect us from invading pathogens are also ideal for the detection of danger signals that lead to the creation, transition, and persistence of chronic pain conditions. Indeed, such danger signals may also arise through the use of opioids for the management of pain conditions. The immune system’s vast network of cells, inherent mobility and ability to adapt to dynamic environments has evolved to relay the presence of a multitude of ‘danger’ signals to the CNS and thereby modulate the neural circuits responsible for detecting nociceptive stimuli. The immune competent cells of the nervous system are perfectly positioned at the microscale to alter nociception and to drive structural adaptations that underpin chronic pain. Therefore, the complex and multidimensional interplay of the immune system with multiple physiological systems may provide new transformative insights into the mechanisms responsible across these types of pain and point to a future where precision main medicine might be possible. In this review, this multidimensional role of the immune system in plasticity underlying chronic pain will be examined with the presentation of transformative opportunities to beneficially manipulate the immune system.

2. The Role of Central Immune Signaling in Chronic Pain

Central immune signaling encompasses an integrated and highly regulated response involving neuronal and non-neuronal cell types that is crucial for the maintenance of brain and spinal cord health, but also the creation and persistence of disease states. Importantly, central immune signaling can drive functional changes that contribute to plasticity driving chronic pain. Of particular importance to the very early, and generalisable across multiple types of parallel central immune signalling events, is the activation of the innate immune system, which drives the increase of the expression of inflammatory mediators, such as Interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), IL-6, C-C motif ligand 2 (CCL2) and iNOS enzymes (Jensen et al., 2013). Although these inflammatory mediators may initially serve to eliminate acute insults by enhancing repair systems (Ransohoff and Brown, 2012), they are now recognised to play a pivotal role in a loss of neuronal homeostatic functions, contributing to a myriad of chronic conditions, including neurological disorders, neuropathic pain states and the negative side-effects and toxicities associated with pharmacological interventions, such as opioids and chemotherapy.

A feature that elevates the importance of the innate immune system in central immune signalling events is the unifying presence of endogenous danger signals. Endogenous danger signals can be derived from stressed-to-damaged-dying cells and are sufficient to activate central immune signaling via their recognition by pattern recognition receptors (PRRs). Importantly, such a central immune signalling event can occur in entirely sterile conditions. Among the PRRs identified to respond to endogenous danger signals, Toll-like Receptors (TLRs) have been extensively examined for their distinct involvement in chronic pain, including their expression on neurons, microglia and astrocytes.

TLRs recognise a broad range of signals of both endogenous and exogenous sources, derived during both sterile and non-sterile incursions. Endogenous danger signals fall into a class of factors termed damage- or danger-associated molecular patterns (DAMPs) from dying or damaged cells. whilst pathogen-associated molecular patterns (PAMPs) can be derived from bacteria and viruses (Patel, 2018; Vijay, 2018). TLRs activate a wide array of signaling pathways that can produce pro-inflammatory cytokine/chemokine and other inflammatory mediators associated with minor changes in central immune signalling through to a complete immune response. The multidimensional nature of these innate immune responses means that both PAMP and DAMP driven central immune signaling events are sufficient to create exaggerated pain states (Hutchinson et al., 2007; Lacagnina et al., 2018).

At the synaptic level, the central immune signaling-induced pro-inflammatory microenvironment facilitated by recruitment of microglial and astrocytic reactivity plays a crucial role in multiple forms of pain, discussed in detail later. Over the last three decades, the advancement of targeted animal models, molecular tools and cellular systems have identified that chronic pain states are not explained by solely neuronally-mediated mechanisms. Rather, bidirectional communication pathways encompassing central immune signalling, including glia, neurons, immune cells and their mediators are critical players in the phenomenon. Moreover, the spatial relationships between these cellular systems, termed

the neuroimmune interface deepens this multidimensional complexity (Grace et al., 2014; Grace et al., 2021).

3. The Sensitization of Pain by Parallel Immune Signaling Systems

The multi-parallel and multi-layered redundancy of immune signalling means that there are many ways in which central immune signalling and the neuroimmune interface can be altered, many of which can lead to heighted pain states, either directly or indirectly. Whether the initial physiological incursion occurs in the periphery or centrally, the creation of danger signals and the subsequent activation of innate immune signaling is sufficient to cause neuronal plasticity and the development and/or maintenance of chronic pain. Therefore, a combination of at least four different routes may be involved in the sensitization of nociception. These pathways (illustrated in figure 1) (Aspelund et al., 2015; Louveau et al., 2015) are instrumental in the passage of signals via humoral, neuronal, cell-to-cell and cellular routes (Capuron and Miller, 2011). The importance of these multi-parallel pathways is emphasised by the recent highlighting of the meningeal lymphatics system by two groups in 2015 (Aspelund et al, and Louveau et al 2015) and recently reviewed (Alves de Lima et al., 2020)). Such anatomical and functional discoveries provide the missing pieces to complete the dynamic nature of a moving and bidirectional flow of molecular information between the periphery and the brain with profound impact on our understanding of the origins and contributors to chronic pain.

Peripheral Sensitization – key immune cellular and molecular events

The neuroimmune interface and its relevance to exaggerated pain states needs to be explored in multiple neuroanatomical compartments. For example, peripheral immune interactions that drive altered pain states can also occur at the dorsal root ganglia (DRG) or trigeminal ganglia. Neutrophils and macrophages express a myriad of inflammatory mediators which include pro-inflammatory cytokines implicated in neuropathic pain, such as IL-1β and TNF-α (Sommer and Kress, 2004). As such, several immune cells have been implicated in the development of neuropathic pain. Neutrophil, macrophage, lymphocyte and dendritic cell infiltration can occur not only at the injury sites across a range of nerve injury models, but also at the ipsilateral DRG (Kim and Moalem-Taylor, 2011; Morin et al., 2007). Peripheral macrophage recruitment at the DRG interface can result in additional neuroimmune interactions capable of influencing the onset of nociceptive hypersensitivity. This was recently evidenced by the deletion of DRG macrophages in a spared injury model delaying the onset of mechanical hypersensitivity (Yu et al., 2020). Interestingly, the study also reported macrophages recruited to the DRG were a better indicator of long-term mechanical hypersensitivity than those recruited to the injury site (Yu et al., 2020). The authors demonstrated that macrophage expansion at the DRG level is required for the initiation and persistence of nerve-injury induced mechanical allodynia. This level of evidence of the importance of the creation of the neuroimmune interface was achieved in both male and female mice by depleting DRG macrophages which prevented the development and maintenance of mechanical hypersensitivity.

Additionally, subsets of peripheral macrophages (type2 angiotensin II receptor (AT2R) positive) are important to mechanical and cold hypersensitivity following peripheral nerve injury (PNI). Interestingly, antagonism of AT2R does not attenuate hypersensitivity resulting from inflammatory pain; suggesting AT2R+ peripheral macrophages are a peripheral immune factor important for peripherally initiated neuropathic pain (Shepherd et al., 2018).

Other immune-mediated responses include T cell infiltration to the lesioned DRGs as well as infiltration to undamaged ganglia adjacent to the spinal nerve injury (Hu and McLachlan, 2002). Satellite glial cells closely envelop neuronal cell bodies within the DRG. Following nerve injury and inflammation these specialised glial cells undergo phenotypic changes (Zhou et al., 1999) and proliferate (Donegan et al., 2013). In their reactive phenotype, satellite glial cells can regulate chronic pain by communicating with sensory neurons via gap junctions or via releasing factors with neuronal modulating effects, such as nitric oxide, or by their increased sensitivity to adenosine triphosphate (ATP) (Blum et al., 2014). Reactive satellite glial cells also increase cytokine synthesis transcription, translation and release and upregulate gap junctions, all enabling increased coupling between these cells and neurons thereby consolidating the neuroimmune interface (Hanani and Spray, 2020; Kim et al., 2016; Tang et al., 2010). Although satellite glial cells do not have voltage-dependent ion channels, they do express K+ channels which are suppressed following injury (Cherkas et al., 2004; Vit et al., 2008). It has been suggested that this may contribute to chronic pain as reduced K^+ permeability likely depolarizes satellite glial cells which results in them releasing ATP, which in turn can active neurons. Cellular, structural and functional changes at the DRG level are intrinsically involved in peripheral sensitization which, accordingly can play a role in establishment of central sensitization.

Repeated nociceptive stimuli and the subsequent release of pro-nociceptive substances, such as CSF-1, ATP, chemokines (e.g., CCL_2), trophic factors (e.g., neuroregulin 1; NRG1), integrins and endogenous danger signals results in the hypersensitivity and hyperexcitability of peripheral nociceptors, leading to peripheral sensitization. This persistent state is maintained by a mosaic of modulated ion channels, that include sodium channels (Basbaum et al., 2009) and transient potential receptor ion channels (such as TRPV1) (Iftinca et al., 2021). For example, TRPV1's activity can be triggered by IL-1β, a key pro-inflammatory cytokine in acute pain, which can act on peripheral nociceptors affecting pathological pain outcomes (Mailhot et al., 2020). This neuronal targeting by central immune signaling is exemplified by the impact of the deletion of IL-1R1, an IL-1β receptor, from a TRPV1+ nociceptor subset. Here this targeted deletion delays the onset of mechanical hypersensitivity in a mouse arthritis pain model (Mailhot et al., 2020). Further, direct peripheral application of IL-1β causes increased pain scores via TRPV1/IL-1β positive nociceptors in mice (Mailhot et al., 2020). Unsurprisingly, changes in the neuroimmune interface status by recruitment of immune cells to the injury site influences nociceptive outcomes. Importantly this example highlights the growing appreciation of non-classical roles of 'inflammatory' proteins and their actions on non-immune cell targets in chronic pain.

It is worthy to note that other novel mechanisms of peripheral sensitization are also under investigation, including the role of classical immune factors in altering the excitability of neurons via classical inflammatory independent mechanisms. Recent studies have

highlighted the role of neuronally expressed immune receptors as modulators of pain. Fcγ receptors (FcγRs) are most prominently expressed on immune cells and are critical regulators of immunity. FcγR subtype 1 (FcγR1) is also expressed on DRG neurons of rats and mice (Andoh and Kuraishi, 2004; Qu et al., 2011). This is a fascinating development, as this discovery extends the direct signalling and sensing capacity of the neuronal system to an extension of the adaptive immune antibody response. Immune complexes are able to cause activation of this 'extended' central immune signalling by neuronal antibody receptors which results in pro-nociceptive signaling. For example, utilising a mouse rheumatoid arthritis (RA) model, a recent study demonstrated that immunoglobulin G immune complex (IgG-IC), which is present in high amounts in RA patients, acts directly on neuronal FcγR1 resulting in hyper-nociception via inflammatory independent mechanisms (Wang et al., 2019). In a similar vein, a 2019 mouse study conducted by Bersellini Farinotti and colleagues demonstrated that autoantibodies against joint cartilage and collagen type II (CII) can form an immune complex with Fcγ receptors to invoke excitability of nociceptors and result in mechanical hypersensitivity in the absence of inflammatory signaling (Bersellini Farinotti et al., 2019). As such, these studies have brought Fcγ receptors to the forefront as potential novel targets for chronic joint pain management for conditions like rheumatoid arthritis.

Such novel targets of antibody immune complexes also extend to non-Fcγ receptor actions. For example, a recent elegant study has highlighted a Fcγ receptor independent role of autoantibodies in directly modulating neuronal excitability in the absence of inflammatory mediators. In this study, the transfer IgG from fibromyalgia patients to mice resulted in the development of key features of fibromyalgia in the mice (Goebel et al., 2021). Interestingly, this occurred in the absence of cytokine production and quantifiable systemic inflammation. Importantly, it was demonstrated that IgG binding was colocalised with neuronal membranes. Therefore, it is clear that autoimmune mechanisms can play a key role in the development of chronic pain (recently reviewed (Lacagnina et al., 2021)) and may provide novel targets for clinical management. As our understanding of peripheral-to-central immune signaling mechanisms and peripheral sensitization has developed, so too has our appreciation for the mechanisms involved in central sensitization. Peripheral sensitization and neuroimmune interactions at the DRG/trigeminal ganglia level can lead to maladaptive responses in the spinal cord and higher order brain regions, resulting in central sensitization.

Central Sensitization – key immune cellular and molecular events

Central sensitization can occur throughout the chain of somatosensory pathways in the dorsal horn of the spinal cord to nociceptive neurons in higher order brain regions (Basbaum et al., 2009; Ossipov et al., 2010). It is clear that a range of molecular and cellular events can drive central sensitisation. In recent years, this list has been expanded to include events within the multidimensional space of the neuroimmune interface and central immune signalling. For example, following nerve injury, primary afferent nerve fibers release colony-stimulating factor-1 (CSF-1) (Guan et al., 2016), extracellular proteases (Chen et al., 2018), caspase-6 (Berta et al., 2014), cytokines, such as IL-1β (Binshtok et al., 2008) and proteinases, like MMP-9 (Kawasaki et al., 2008). Changes in the expression levels of these pro-nociceptive substances result in microglial reactivity. Once reactive, microglial-

mediated molecular mechanisms contribute to central sensitization via the synthesis and release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-18) which act on primary afferent fibers and spinal dorsal horn nociceptive neurons. TNF-α released by microglia can act on astrocytes which results in reactive phenotypic changes increasing expression of IL-1β, IL-18 and Cx43-mediated release of ATP, glutamate and chemokines (e.g., CXCL1 and CCL2) which in turn, sensitize primary afferents and excitatory spinal dorsal horn nociceptors.

At pre-synaptic sites, activation of G-protein coupled receptors (GPCRs), ligand-gated ion channels (e.g., TRPV1) and cytokine and chemokine receptors result in phosphorylation and activation of extracellular regulated kinase (ERK) and p38 which increases glutamate release from synaptic vesicles (Ji et al., 2018). These immune signaling events are integral components in central sensitization (Reviewed in detail by (Grace et al., 2014; Grace et al., 2021). In addition to enhanced nociceptor excitation, IL-1β can suppress GABAergic and glycinergic synaptic transmission resulting in central disinhibition (Donnelly et al., 2020). In line with this, microglial purinergic receptor activation causes increased production and release of BDNF, driving neuropathic pain via central disinhibition (Trang et al., 2012). Other critical disinhibition events that drive central sensitization are N-methyl-D-aspartate (NMDA) receptor activation and ERK phosphorylation (Inquimbert et al., 2018; Ji and Woolf, 2001).

4. Chronic pain explored from the perspective of specific glial cell populations

Underpinning the multidimensional nature of chronic pain is the recognition that a range of centrally located immunocompetent non-neuronal cells are key regulators in the development and maintenance of chronic pain. These cell types include, glial cells (microglia, astrocytes and oligodendrocytes), endothelial cells, perivascular macrophages and T cells and are now regarded as far more than passive bystanders. A significant proportion of glial research in pathological pain states has focused on microglia and astrocytes.

Microglia and astrocytes are abundant in the brain and spinal cord and react to central perturbations, detecting injury or infection which may arise centrally or from the periphery. Whilst both cell types maintain different structural and functional characteristics, importantly both share the capacity to modulate neurotransmission due to their intimate relationship with neurons; this communication hub forming around the synaptic cleft is known as the neuroimmune interface. Astrocytes are uniquely physically coupled to one another via gap junctions which permits the exchange of ions and small molecules between cells (Giaume and McCarthy, 1996). They also provide structural and metabolic support to neurons, playing an active role in regulating the extracellular environment and maintaining homeostasis by balancing glutamate, potassium and water flow (Haydon, 2001). Some distinct microglial features are their ability to migrate throughout the CNS and their capacity to phagocytose tissue. Microglia constantly survey the extracellular environment for perturbations and coordinate a diverse response to the detection of injury

or infection (Nimmerjahn et al., 2005). Under pathological conditions, such as nerve injury or in response to extracellular perturbations, both cell types exhibit alterations in their morphology, gene expression, proliferation status and thus, functional capacity (Sofroniew, 2020). The reactive phenotype of microglia and astrocytes from their ramified to amoeboid state are defined (albeit poorly) by an increase in the expression of the reactivity markers, ionized calcium binding adaptor molecule 1 (IBA1) or cluster of differentiation molecule 11b (CD11b) for microglia and glial fibrillary acidic protein (GFAP) for astrocytes.

Other noteworthy adaptations observed in both reactive microglial and astrocyte phenotypes include the activation of intracellular pathways, such as the Janus kinase/Signal Transducer and activator of the transcription (JAK/STAT) pathway (Jain et al., 2021; Liu et al., 2015). This signaling cascade results in increased expression of pro-inflammatory cytokines, chemokines and mediators, which in turn, can act in a positive feedback cycle attracting more microglia to the region and signaling other astrocytes. In an acute pain response, the positive feedback loop mechanism will subside when the initial insult has resolved. However, this mechanism can fail in pathological pain models, and consequently results in the maintenance of chronic pain states. Tsuda and colleagues inhibited the JAK/STAT pathway in rats with spinal nerve injury and by doing so reversed the number of proliferating dorsal horn astrocytes resulting in the recovery from neuropathic pain as evidenced by improvements in tactile allodynia (Tsuda et al., 2011). Microglial- and astrocyte-induced reactivity can modulate synaptic plasticity and alter neural pathways which can contribute to undesirable behavioral adaptations. Under such conditions, microglia and astrocytes remain reactive and in the absence of noxious stimuli, this sensitized state is termed “primed”. Whilst both glial cells may appear morphologically reactive in their primed phenotype, they do not over produce inflammatory mediators, rather their response to subsequent challenges occurs more rapidly and in an exaggerated manner (Watkins et al., 2007). This centrally primed state can have deleterious effects when a secondary immune challenge occurs. Moreover, this primed status may stretch to multiple anatomical compartments.

An example of this multidimensional priming effect can be seen in the multiple reports of altered pro-inflammatory signaling responses, such as innate immune elicited IL-1β responses in the peripheral blood mononuclear cells (PBMCs) of chronic pain patients. Kwok and colleagues identified that the PBMCs of chronic pain patients (on and not using opioids) were more responsive to TLR2 (Pam3CSK4), TLR4 (LPS) and TLR7 (imiquimod) agonists than those isolated from pain-free controls (Kwok et al., 2012). The key findings were reflected in a rat study by the same group and importantly, both studies exemplify not only, the sensitivity of chronic pain patients to secondary immune challenges, but also highlights the potential of peripheral responses as biomarkers for chronic pain (Kwok et al., 2013). Such studies have been replicated across multiple populations by many authors (Evans et al., 2021; Schrepf et al., 2015). These observations present an opportunity and a challenge. The opportunity is to create peripheral blood-based biomarkers for pain diagnosis. The challenge is to determine if a ‘memory’ of the pain state of the individual persists in a recoverable form in the peripheral blood of the individual long term, minimising the therapeutic benefit of soley centrally targeted therapies.

Microglia are Dynamically Involved in the Plasticity of Chronic Pain

Microglial reactivity in the spinal dorsal horn, ventral tegmental area, the brainstem and hippocampus has been observed following peripheral nerve system injury (Liu et al., 2017; Taylor et al., 2015; Ueta and Miyata, 2021). These seminal studies extend the impact of central immune signalling and the neuroimmune interface beyond the bounds of just a sensory consequence to demonstrate that microglia play an active role in the emotional dimensions of pain. This broader microglial role is achieved by their disruption of the mesolimbic reward circuit (Taylor et al., 2015), remodeling synapses, and controlling thalamic map reorganization (Ueta and Miyata, 2021), and impacting memory in chronic pain states (Liu et al., 2017). Hiraga and co-workers observed the involvement of intracerebral microglia in the ectopic axonal reorganization of thalamic nociceptive circuitry following CNS injury (Hiraga et al., 2020). These results suggest that microglia in the somatosensory cortex may remotely contribute to chronic pain as ectopic sprouting and pain behaviors were reversed by depleting microglial cells via the administration of a colony stimulating factor 1 receptor inhibitor, PLX3397.

Interestingly, microglia influence somatosensory cortical plasticity and pain hypersensitivity whilst maintaining a morphologically ramified phenotype. Following peripheral nerve injury, structural and functional changes in microglial-neuron signaling in S1 showed no morphological and density changes in microglia, yet elevated expression of bone-derived neurotrophic factor (BDNF) (Huang et al., 2021). In this model, targeted removal of microglial BDNF reversed nerve injury-induced synaptic remodeling, pyramidal neuronal hyperactivity and pain hypersensitivity. In another study, microglial cells derived from bone marrow were identified in the amygdala of mice with nerve injury 28 days after they received bone transplantation from green fluorescent protein (GFP)-Tg mice. The aggregation of GFP positive microglia in the amygdala correlated with anxiety-like behaviors. While the bone derived microglia expressed high levels of IL-1β and chemokine receptor type 2, the neurons in same region expressed MCP-1, a ligand for CCR2 indicating that the MCP-1/CCR2 axis is involved in the recruitment of bone-derived microglial cells in this neuropathic pain model (Sawada et al., 2014).

The attenuation of pain behaviors following peripheral nervous system injury via blockade of microglial BDNF implies that some microglia are capable of modulating pain-related neuroplasticity through the release of a growth factor (Huang et al., 2021). Specifically, the involvement of microglial derived BDNF in pain development occurs via structural and functional synaptic adaptations that ultimately result in increased activation of pre-synaptic terminals and post-synaptic hyperexcitability (Inoue and Tsuda, 2018; Tsuda et al., 2003; Zhou et al., 2019). Outside of higher brain structures, microglia within the spinal cord facilitate degradation of peri-neuronal nets (PNNs) around projection neurons in superficial laminae following PNI. This disrupts integration of sensory processing and promotes pain-related behaviors (Tansley et al., 2022). Microglia unequivocally play a pivotal role in neuroplasticity related to chronic pain, yet the complexities around their mechanistic involvement are a much-needed topic of continued research.

Furthermore, research into the different roles microglia play in chronic pain between males and females is ever expanding. Whilst a full review on microglial sex differences falls

outside the scope of the current review, it is also important to note that the biological responses of the innate and adaptive immune systems in relation to chronic pain initiation and maintenance differs between females and males. These differences are not limited to microglia but include a myriad of responses related to immune cellular populations, suppression by hormones and disparate cellular responses (see excellent review (Sorge and Totsch, 2017)). Some recent examples include evidence that increased microglial proliferation occurs in male, not female mice following PNI (Tansley et al., 2022). Additionally, unique microglial transcriptomes are observed between male and female mice following PNI (Tansley et al., 2022). This transcriptome analysis revealed Apolipoprotein E (*Apoe*) was increased in the chronic phases of a mouse PNI model; a gene of which polymorphisms are associated with chronic pain in Humans (Tansley et al., 2022). Recognition of such findings are helping us understand not only, why there is an over-representation of women in the chronic pain population but is also offering transformative insights in guiding the development of tailored patient treatments.

A role for astrocytes in nociplastic pain

As with microglia, there is a profound depth of literature on astrocytic involvement in the creation and maintenance of chronic pain. Depending on their phenotype, astrocyte-mediated modulation of synaptic transmission can contribute to second order neuronal sensitization and influence neuronal plasticity via forming new synapses that remodel neuronal circuits (Gao and Ji, 2010; Li et al., 2019). Electrical stimulation of Aβ-fibers results in spinal astrocyte responses and anti-nociception by inducing long-term depression in neurokinin positive spinal projection neurons. In mice, increased withdrawal thresholds were observed to radiant heat following peripheral electrical stimulation, an effect blocked by astrocyte inhibition (Xu et al., 2021).

Descending inhibitory input to the spinal cord can act on astrocyte subsets to attenuate pain. Descending noradrenergic signaling contributes to the activation of a subset (*Hes5*$^{+}$) of dorsal horn astrocytes following peripheral capsaicin application (Kohro et al., 2020). *Hes5*$^{+}$ astrocytes mediate mechanical hypersensitivity following phenylephrine treatment and enhance the analgesic effect of the antidepressant duloxetine in a PNI model (Kohro et al., 2020). These findings show not all glial input drives the maintenance of chronic pain and opens up pathways to use glia as a target for pain attenuation. Regardless of the injury, the subsequent release of immune mediators results in glial and neuronal adaptations contributing to spinal cord plasticity and remodeling (Tsuda et al., 2011), thus demonstrating another key immune role contributing to neuroplasticity in chronic pain. As described above, a distinct dialogue has been established between microglia, astrocytes and neurons in not only maintaining neuroimmune reactivity across a wide array of chronic pain models but playing an instrumental role in nociplastic pain.

Whilst the classical characterisation of neuroimmune reactivity involves microglial reactivity (as first responders) and subsequent astrocyte reactivity or priming and increased expression of pro-inflammatory cytokines and mediators, not all components are necessary to induce chronic pain states. For example, when compared with a partial sciatic nerve ligation (PSNL) model, two cancer pain mouse models (bone and sciatic nerve proximal cancer)

demonstrated that astrocyte reactivity can take place independent of microglial reactivity (Hald et al., 2009). In this study, all animals expressed pain behaviours, yet microglial reactivity was only present in the neuropathic PSNL model. Additionally, in the bone cancer group the spread of astrocyte reactivity was present in adjacent spinal cord sections to the section where the primary afferent neurons innervating the femoral bone, enters the spinal cord. These findings suggest that initiation of microglial and astrocytic reactivity may occur differentially across pathological pain models and provides insight into astrocytic involvement in the spread of hyperalgesia across spinal cord sections unrelated to the pain source. Again, these data point to the highly paralleled and multidimensional nature of chronic pain.

5. Nuclear factor-kappa B signaling and its regulation as an important evolutionarily conserved pain mechanism

Nuclear factor-kappa B (NF-κB) regulated immune signaling and the downstream consequences, particularly those impacting glial cell functions, is now recognised as a fundamental feature of chronic pain. NF-κB regulates multiple receptor pathways, including TLRs, interleukins, and TNF receptors. NF-κB has been extensively characterised in the peripheral innate immune system, allowing for established experimental methods to be applied in the novel context of inflammatory driven pain. Importantly, regulatory mechanisms of NF-κB have been characterised, such as TNFAIP3/A20 which is a crucial negative regulator of NF-κB signaling (Song et al., 1996). A20 itself is regulated by NF-κB, as its expression is induced by NF-κB activation, establishing a negative feedback loop. A20 exerts its regulatory control by functioning as both a deubiquitinating and a ubiquitinating enzyme. Ubiquitin is a small protein which facilitates intracellular signaling. The deubiquitinating activity of A20 results in the cleavage of ubiquitin chains on signaling proteins, arresting downstream signaling (Das et al., 2018). For example, TRAF6 promotes polyubiquitination that mediates the signaling of many innate immune receptors, including TLR4 (Deng et al., 2000). In the context of the TLR4 signaling pathway, A20 binds to TRAF6 and cleaves the K63 linked ubiquitin chain resulting in the arrest of the signaling cascade (Das et al., 2018). Conversely, the ubiquitinating enzymatic action of A20 links a K48 ubiquitin chain to the target protein, signaling for the protein to be degraded, such as the degradation of RIP1 within the TLR4 signaling pathway, also arresting cell signaling (Das et al., 2018).

Despite its extensive characterisation in the peripheral immune system and the establishment of evolutionarily conserved features (Zammit et al., 2019), only recently has A20 been explored in the context of the CNS, with a specific focus on neurodegenerative disorders (Guedes et al., 2014; Mohebiany et al., 2020; Voet et al., 2018). Given the current understanding of inflammatory signaling in pain, a logical connection for A20 exists to the central immune signalling and neuroimmune interface discussions. Since A20 is fundamental in preventing excessive inflammatory signaling, it may be argued that it is pivotal in regulating multiple forms of chronic pain through these foundational molecular and cellular neuroimmune pathways. Further highlighting the importance of A20 in pain are recent developments in our understanding of opioid receptor biology.

As extensively reviewed by Hutchinson et al. (2011), opioids trigger a NF-κB dependent response in microglia and astrocytes which results in the subsequent release of pro-inflammatory cytokines/chemokines/mediators with repeated dosing schedules strengthening this activation (Hutchinson et al., 2011) . Moreover, opioid-induced microglial and astrocyte responses enhance nociceptive transmission, counteracting the intended therapeutic effects of opioids (Deleo et al., 2004; Thomas et al., 2015). Therefore, understanding the role of NF-κB regulation will advance both foundational pain neurobiology and opioid pharmacology fields.

NF-κB and opioids: emerging roles for A20, β-arrestin-2 and TRPVI in inflammatory signaling

While early research indicated that opioids exert immune-suppressive properties, as discussed earlier, more recently it has come to light that opioids potentiate inflammatory signaling, particularly within the CNS (Grace et al., 2015; Thomas et al., 2022). Co-treatment of LPS and morphine significantly increases microglial NF-κB mediated release of IL-1β, TNFα, IL-6 compared to LPS alone (Gessi et al., 2016). These results are supported by earlier studies focusing on peripheral immune cells, where it was shown that a low concentration of morphine (50nM) augmented LPS-induced TNF-α and IL-6 synthesis in macrophages and naloxone was able to reverse this. Interestingly, naloxone did not modulate the inhibitory effect of high concentration (50μM) morphine on LPS-induced cytokine synthesis (Roy et al., 1998). This work emphasises the dynamic and non-linear effect of opioids on NF-κB signaling.

NF-κB regulation of opioid signaling highlights the potential importance for regulatory factors, such as A20. Using HEK293t cells, it was demonstrated that A20 inhibits the recruitment of β-arrestin 2, an important regulatory adaptor protein in the mu opioid (MOP) signaling pathway (Shao et al., 2020). Additionally, this study demonstrated that global over expression of A20 in mice enhanced the analgesic effect of morphine following thermal nociceptive testing at 30- and 60-minute timepoints, however morphine tolerance remained unchanged. Furthermore, A20 was downregulated in morphine tolerant mice and morphine tolerance was attenuated by experimentally inducing the overexpression of A20. Interestingly, following chronic morphine exposure, miR-873a-5p was upregulated and targeted A20, resulting in the downregulation of A20. Furthermore, forced downregulation of miR-873a-5p and increased spinal A20 (via lentiviral delivery) respectively attenuated morphine tolerance (Huang et al., 2019).

This is particularly interesting as β-arrestin 2 recruitment is associated with many negative side effects of opioids. Early research identified that morphine analgesia is enhanced in mice lacking β-arrestin 2, and that β-arrestin 2 mediates the sensitisation of the receptor to regulate tolerance (Bohn et al., 2000; Bohn et al., 1999). Additionally, constipation and respiratory depression, two common side effects of opioid treatment, are reduced in β-arrestin 2 deficient mice (Raehal et al., 2005). If A20 is capable of regulating β-arrestin 2, and therefore morphine efficacy, it is plausible that A20 dysregulation may be implicated in chronic pain.

These findings suggest that perhaps both the early schools of thought regarding opioids as immuno-suppressive agents and the current opposing literature are correct, and this contradiction may arise from the complex and non-linear involvement of A20. It can be hypothesised that morphine exposure may result in the dysregulation of A20, leading to enhanced negative regulation. This may cause immune suppression, or reduced activity resulting in excessive inflammatory signaling, which may vary depending on the subjected system, the duration and exposure dose. While there is a clear interaction between opioid receptor signaling and A20, more research is encouraged to determine the clinical significance, particularly the role of A20 in modulating nociception in humans.

Similarly, β-arrestin 2 is implicated in an apparent functional relationship between MOP and TRPV1. This subset of nociceptive ion channels detects noxious stimuli in both the periphery and CNS and is upregulated in neuropathic pain (Caterina et al., 1997; Wu et al., 2013). Multiple studies report TRPV1 induced inhibition of MOP internalisation via altered MOP phosphorylation and disrupted β-arrestin 2 interactions (Basso et al., 2019; Scherer et al., 2017). TRPV1−/− mice show decreased peripheral morphine potency when compared to WT controls in a complete Freund's adjuvant inflammatory pain model, evidence that TRPV1 interaction is relevant to functional opioid tolerance in inflammatory pain (Basso et al., 2019).

Various studies suggest a bi-directional relationship between MOP and TRPV1. MOP activation dissociates β-arrestin 2 from TRPV1, resulting in protein kinase A (PKA) dependent sensitisation and increased calcium flux and inward current (Rowan et al., 2014). While co-administration of DAMGO, a MOP agonist and the TRPV1 agonist, capsaicin, in rat rostral ventromedial medulla (RVM) at sub-affective doses results in thermal hyperalgesia via glutamate output and ON cell inhibition (Maione et al., 2009). This bidirectional regulation of MOP and TRPV1 suggests a combination therapy is a viable possibility for opioid induced hyperalgesia (Scherer et al., 2017).

6. Journey towards Pharmaceutical Interventions for Chronic Pain

Since the realisation that glia (microglia and astrocytes) and TLR4 play critical roles in the initiation and maintenance of exaggerated pain states (see recent review, (Mustafa et al., 2022), mechanistically targeted approaches have been adopted to discover clinically relevant therapeutic interventions with the aim of more effectively controlling pathological pain. A pioneering study by Meller and colleagues showed that thermal and mechanical hyperalgesia was reversed using fluorocitrate in a rat model of PNI via inhibiting glial activation (Meller et al., 1994). Since this study, a vast amount of research has confirmed that exaggerated pain states can be blocked by pharmacologically attenuating pro-inflammatory glial cell reactivity or their pro-inflammatory products and/or actions in the spinal cord (Watkins et al., 2009; Watkins and Maier, 2003). Further, as new light has been shed on the involvement of TLR4 across a broad spectrum of diseases, including its interaction with opioids, new strategies targeting the interface of TLR4 have also been a promising angle in rendering pharmacological interventions to effectively treat chronic pain.

Several studies have shown that the opioid antagonists, naloxone and naltrexone directly interact with TLR4 (Hutchinson et al., 2008; Wang et al., 2016). Though they were primarily used to treat opioid addiction and alcoholism, both drugs came into clinical use as a low dose treatment for pain due to their high affinity to bind to TLR4 at low doses (Younger et al., 2014). (+)-Naloxone effectively reverses neuropathic pain in rats following nerve injury (Lewis et al., 2012). Repurposing already approved drugs has proved to be a fruitful approach in finding solutions that save time in gaining traction from the bench-to-the-bedside. Another recent example of this is lovastatin, a clinically approved drug for cholesterol with good blood-brain barrier permeability (Peng et al., 2019). Lovastatin successfully attenuated neuropathic pain created by sciatic nerve injury in rats by selectively inhibiting microglial activation via its antagonistic effect on TLR4. Drug repurposing should not replace the search for novel analgesics yet offers complementary strategies to alleviate and relieve persistent pain in patients.

Glycosylation, a Dynamic Mechanism for Plasticity: A Potential Therapeutic Target?

Glycosylation is a process which modifies proteins through the addition of sugar chains, termed glycans, to specific amino acids. The presence or absence of glycans can have implications in many processes that include cell interaction, immune responses, and signal transduction, and importantly in modulating pain pathways (Ohtsubo and Marth, 2006). Two main types of glycosylation exist: N- and O-linked glycosylation. These differ based on the amino acid the glycan is attached to. Numerous combinations of glycans can be created as the biosynthesis of sugars is not encoded directly by the genome or proteome, which are confined to a limited number of nucleotides and amino acids, respectively. Glycosylation occurs by collaboration between glycotransferase and glycosidase enzymes (Rini and Esko, 2015). Glycotransferases transfer glycan residues to an acceptor and glycosidases hydrolyze glycan linkages. Together, these enzymes can create a complex and varied glycan structure allowing for more diversity in protein function and stability. Therefore, adaptations to the glycans present on a protein can have wide implications across a range of biological processes, including molecular changes contributing to chronic pain.

Various components of pain processing and modulation are impacted by changes to glycosylation (Figure 2). For example, the glycosylation status of opioid receptors impacts receptor signaling and expression. Loss of specific N-glycosylation sites results in increased turnover of the MOP receptor on the plasma membrane, and reduced expression of kappa opioid receptor (KOP) (Huang et al., 2012; Li et al., 2007). In the delta opioid receptor (DOP), the absence of an N-glycan impacts the trafficking of the receptor, with more receptors being trafficked for degradation rather than expression (Lackman et al., 2014; Markkanen and Petäjä-Repo, 2008). Functional implications have been noted in DOP as well. The loss of O-glycosylation on DOP resulted in less cAMP inhibition when induced by an agonist (Lackman et al., 2018). In addition, there was a shorter half-life of the receptor on the plasma membrane and increased receptor degradation (Lackman et al., 2018). The impact of glycosylation on opioid receptors suggests that the glycan profile can have wide implications in the trafficking, stability, and signaling of these receptors that are critical in the development and maintenance of pain processing.

The importance of glycosylation on receptor activity has also been observed for TLR4. Removal of N-linked glycosylation from TLR4 and MD-2 results in inhibition of LPS induced activation (da Silva Correia and Ulevitch, 2002). Additionally, removing sialic acids, a family of sugar units, from TLR4 facilitates transduction at the receptor (Amith et al., 2010; Feng et al., 2012). Changes to a receptor's glycosylation pattern may have great consequences on wider signaling between immune cells and neurons. This is especially important in pathological pain conditions where neuroimmune signaling is prominent. It is possible that glycosylation changes create varied responses to physiological processes such as those seen in chronic pain conditions.

The location and environment of proteins is another factor to consider. The presence of glycotransferases and glycosidases, availability of glycan substrates, and access to a glycosylation site are all necessary for a protein to be glycosylated. Diversity amongst glycosylation profiles exists when comparing different brain regions in mice, with glycosylation patterns being unique not only to certain regions, but also across different developmental periods (Lee et al., 2020). This variation suggests glycosylation may play a role in functional diversity between brain regions. Another study noted evidence of the dynamic nature of glycosylation in heroin addicts. Weber and colleagues found the hippocampus of heroin addicts had increased polysialic acid neural adhesion molecule, a cell surface glycan involved in neuroplasticity (Weber et al., 2006). Beyond the general brain region, glycosylation diversity can be seen at a receptor level. A study by Huang and colleagues found that MOP had increased glycosylation in the caudate putamen in comparison to the thalamus of rat brains (Huang et al., 2008). This demonstrates that receptor glycosylation can vary depending on its location, and this has potential to allow for different functions with regional specificity.

Due to its dynamic nature, the process of glycosylation may be utilized to manipulate the function and expression of a range of proteins. In chronic pain conditions, it is possible that adaptations to the microenvironment may impact glycosylation profiles leading to changes in receptor function. Changes observed in TLR4 receptors demonstrate that immune signaling has the potential to be altered by glycosylation mechanisms. The literature on opioid receptors provides another interesting perspective. Not only can endogenous opioids act differently at the receptor level, but the use of opioids for treatment may also result in varied responses depending on the glycosylation status of the opioid receptor. Thus, glycosylation and associated targets may be a plausible mechanism and method of regulation to explore when developing pharmaceuticals for pain treatment.

7. Inflammatory Signaling and Pain Resolution

Inflammatory signaling is often associated with negative connotations of damage leading to pathophysiological states, especially with respect to "neuroinflammation" or "glial reactivity" associated with chronic pain. However, it is important to highlight that inflammation plays a crucial role in the restoration and maintenance of normal physiological functions. Acute inflammation is a host-protective response, mounted to alert various physiological systems to tissue injury and therefore plays a vital step in the initiation of injury resolution.

As our understanding of inflammatory signaling in pain has evolved, research is now beginning to highlight that inflammatory signaling also plays a key role in pain resolution. In addition, a paradigm shift has occurred, whereby the CNS is no longer viewed as a site of immune privilege. In fact, it is now apparent that peripheral immune cells (e.g., lymphocytes, macrophages, neutrophils etc.) are highly important in maintaining CNS homeostasis and are therefore involved in the regulation of pain states. For example, although natural killer (NK) cells are traditionally viewed as pro-inflammatory, they also play a functionally important role in pain resolution.

Following nerve injury, NK cells are recruited to damaged sensory axons where they mediate the degradation of these injured neurons. Davies and colleagues suggested that this degradation of the sensitized neurons prevents them from signaling, thus reducing hyper-nociception (Davies et al., 2019). Similarly, acute inflammatory neutrophil responses are important in the resolution of temporomandibular disorders, a musculoskeletal pain condition. This was explored further in mice, where prolonged depletion of neutrophils exacerbated mechanical allodynia (Parisien et al., 2022). Parisien and colleagues further demonstrated the importance of inflammatory signaling in pain resolution by reporting higher neutrophil mediated inflammatory responses in individuals who resolved acute lower back pain than those who developed chronic pain. In addition, patients transitioning to chronic lower back pain also did not exhibit dynamic transcriptional changes observed in those who resolved pain (Parisien et al., 2022). This study suggests initial inflammatory signaling is important for pain resolution, therefore the use of anti-inflammatories in the early stages of pain may be detrimental to long term positive outcomes. However, the role of neutrophils in the perturbation of allodynia is complex, with studies demonstrating somewhat contradictory results. For example, following “immune priming” in an experimental autoimmune encephalomyelitis (EAE), neutrophil signaling contributes to the development of pain (Harada et al., 2019; Zhang et al., 2019). Injury resolution in the CNS following inflammatory signaling is highly regulated. This is evidenced in recent literature, where it is increasingly apparent that regulatory T-lymphocytes (T cells) play a fundamental role in pain resolution. Typically, T- cells are defined by surface expression markers of either CD8 (cytotoxic t-cell) or CD4 (T helper cells). There are many subsets of CD4+ T cells each with specialized functions. It is increasingly apparent that many of these T cell subsets are important in various aspects of pain processing. Regulatory T cells (Tregs), marked by their expression of FOXP3 and CD4 are important in pain resolution. Specifically, depletion of Treg’s inhibits the recovery of mechanical allodynia in mice (Fischer et al., 2019). Interestingly, mice harboring TNFα receptor 2 (TNFR2) deficient Tregs do not recover from chronic constriction injury-induced allodynia (Fischer et al., 2019). Collectively these results suggest that Treg TNFR2 signaling is important in the resolution of pain. Subsequently it has also been demonstrated that Tregs suppresses microglial responses and that depletion of Tregs leads to an increase in allodynia following immune induction of pain, in female mice (Kuhn et al., 2021). Despite the importance of Treg mediated suppression, it seems likely that a fine balance between inflammation and suppression is required for pain resolution. This is evidenced by work demonstrating an elevation of Treg compared to Th17 (a pro-inflammatory subset of CD4+ cells) in the human serum of patients with neuropathic pain. As identified by the recent works

of Parisien and colleagues, a certain degree of inflammatory signaling is essential for pain resolution (Parisien et al., 2022). Along these lines, although cytotoxic CD8+ T cells are responsible for the termination of infected or otherwise damaged cells, recent work suggests they also play an important role in regulating pain. Following cisplatin (a chemotherapy agent) induced neuropathic pain, CD8+ T cells were found to release IL-13, signaling for macrophages to release IL-10, resulting in the resolution of mechanical allodynia. Prevention of the CD8+ T cell mediated IL-13 signaling inhibits pain resolution. Importantly this occurs within the DRG, highlighting that this is not an immune privileged area following cisplatin treatment (Singh et al., 2022).

Microglial reactivity is often a hallmark feature of ‘neuroinflammation’; however, it has become clear that this may not be the most reliable marker for maladaptive inflammation. With the advances in next generation cell sequencing, subtle microglial phenotypes are being elucidated, revealing the dynamic function and high level of microglial heterogeneity. Pertinent to this is the identification of an immunosuppressive glial phenotype (Abellanas et al., 2019). Strikingly, this study identified a midbrain population of microglia that undergo morphological changes akin to “microglial activation” following LPS exposure yet, they exhibit an immune suppressive response to LPS (Abellanas et al., 2019). In addition, the study identified markers indicative of a crosstalk capacity with Treg following LPS exposure (Abellanas et al., 2019).

Further emphasizing the importance of microglial heterogeneity, is the emergence of a spinal microglial subset critical for the resolution of pain hypersensitivity following PNI. Kohno and colleagues have characterized this subset of microglia is unique in its surface expression of CD11c (Kohno et al., 2022). To investigate the role of these microglia in pain, it has been shown that mice deficient in CD11c+ microglia are unable to recover from pain hypersensitivity following PNI. Furthermore, the same study showed that deletion of CD11c+ microglia following recovery from PNI induced hypersensitivity relapses the pain hypersensitivity.

The findings presented here are important in solidifying the notion that “glial reactivity/responses” is/are not always clear cut and assigning “glial reactivity/responses” or inflammation as causal in any pathology should be done with extreme caution. The literature to date demonstrates that the role of inflammatory signaling in pain resolution is complex and results must be interpreted with consideration for the pain models utilized and other potential variables. It is clear, inflammatory signaling is not detrimental in all circumstances and models and this distinction further highlights the fundamental role inflammatory signaling plays in injury resolution.

Evidence presented throughout this review suggests that both hyperactive inflammatory signaling and total suppression of inflammatory signaling lead to the development of chronic pain. Specifically, where immune signaling is suppressed by hyper-regulation, pro-resolving signaling cannot occur. However, unregulated immune signaling results in detrimental inflammation. Ultimately immune regulatory factors, such as A20 may play a fundamental role in regulating the balance between suppression and inflammation to aid pain resolution. However, further research is required to elucidate the underlying mechanisms (Figure 3).

8. Conclusion

It is now clear the immune system plays instrumental roles in physiology and pathophysiology beyond host protection. The immune system's large network of cells, intrinsic mobility and dynamic plasticity allows it to interact with multiple and classically unrelated physiological systems to drive structural adaptations in neural circuits responsible for detecting nociceptive triggers.

In this review we have highlighted many complex mechanisms by which the immune system interacts and modulates neural circuits via modulations of the central immune signalling and neuroimmune interfaces leading to the transition and maintenance of chronic pain. It is fair to conclude that although currently there is a limited understanding of the complex mechanisms at play, there is a greater appreciation of the importance of re-assessing roles that were historically attributed to the immune system and the components within it. There is a need to assess the role/function of the immune system in the context of geography and microenvironment and not whether it fits into a binary classification of pro- or anti-inflammatory. It is becoming apparent that immune signaling should be viewed as a is multidimensional state and therefore pro-resolution treatments are unlikely to be successful if only a linear single dimensional anti-inflammatory (immune suppressive) approach is taken. Instead, we are presented with an opportunity to develop novel pharmaceuticals which allow 'tuning' of signaling within this multidimensional state, enabling precision medicines that act selectively in specific tissues and different phases of the inflammatory signaling. Only when the complexity of our treatments matches the complexity of the challenge that chronic pain sets forth will we be able to achieve the level of interventional success that chronic pain deserves.

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Abbreviations

CNS	central nervous system
DRG	dorsal root ganglia
TRP	transient potential receptor ion channels
IL-1	Interleukin-1
IL-8	interleukin-8
AT2R	type2 angiotensin II receptor
PNI	peripheral nerve injury
FcγRs	Fcγ receptors
CIPN	chemotherapy induced peripheral neuropathy

TLR4	Toll-Like Receptor 4
RA	rheumatoid arthritis
IgG-IC	immunoglobulin G immune complex
CII	collagen type II
IgG	Immunoglobulin G
ATP	adenosine triphosphate
C-C	chemokines
CCL_2	chemokine motif ligand 2
NRG1	neuroregulin 1
GPCRs	G-protein coupled receptors
NMDA	N-methyl-D-aspartate
ERK	extracellular regulated kinase
PRRs	pattern recognition receptors
PAMPs	pathogen-associated molecular patterns
DAMPS	damage-associated molecular patterns
IBA1	ionized calcium binding adaptor molecule 1
CD11b	cluster of differentiation molecule 11b
GFAP	glial fibrillary acidic protein
JAK/STAT	Janus kinase/Signal Transducer and activator of the transcription Pathway
PBMCs	peripheral blood mononuclear cells
PNS	peripheral nervous system
PSNL	partial sciatic nerve ligation
LPS	lipopolysaccharide
NF-kB	nuclear factor-kappa B
BDNF	bone-derived neurotrophic factor
MOP	mu opioid receptor
DOP	delta opioid receptor
KOP	kappa opioid receptor

MD-2	myeloid differentiation factor 2
MyD88	myeloid differentiation primary response 88
cAMP	cyclic adenosine monophosphate
TRPV1	transient receptor potential cation channel subfamily V member 1
KOP	kappa opioid receptor
DOP	delta opioid receptor
NK	natural killer cells
EAE	experimental autoimmune encephalomyelitis
T-cells	T-lymphocytes

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Highlights

1. Neuroimmune interactions drive structural adaptations in neural circuits
2. Classical immune factors alter excitability of neurons via inflammatory independent mechanisms
3. Inflammatory signaling plays a role in injury resolution

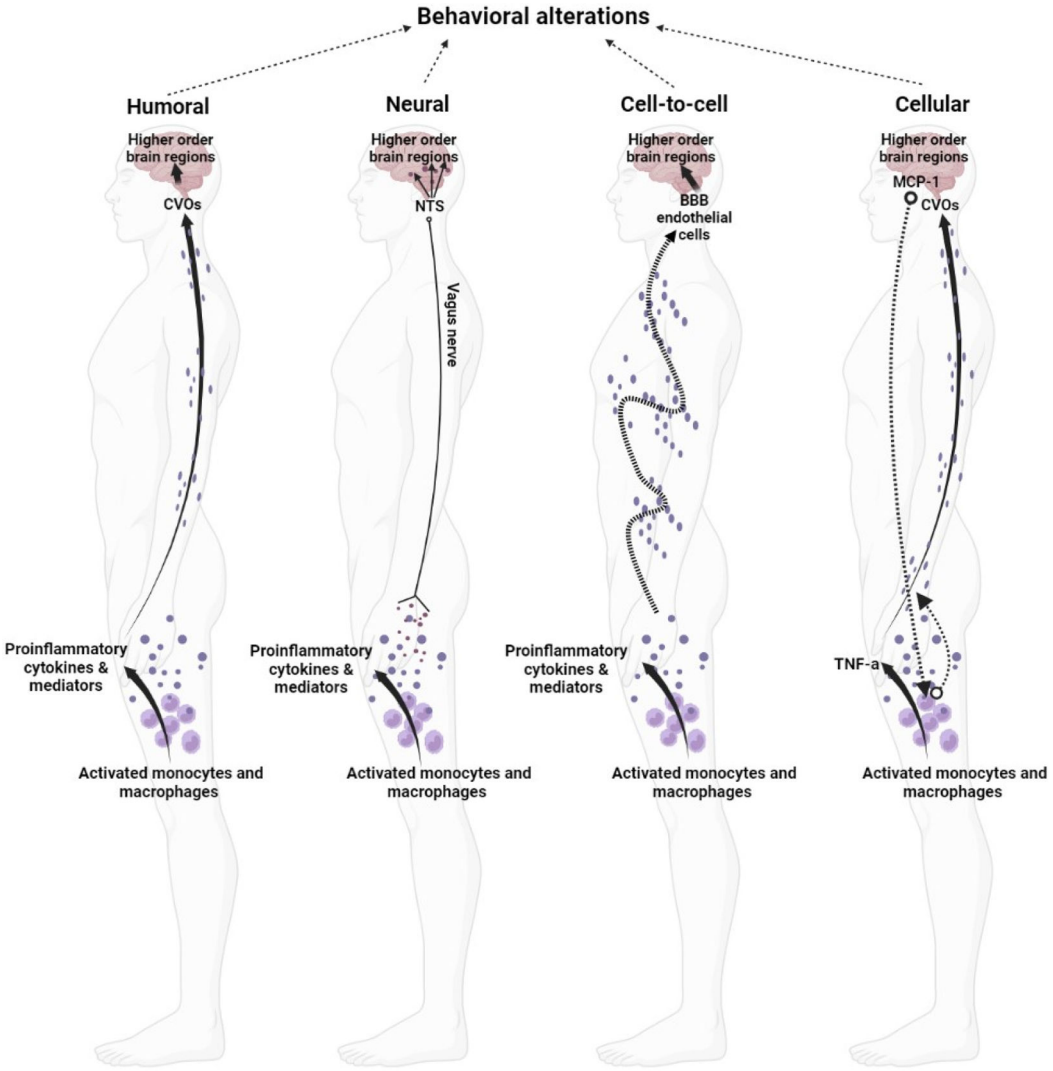

Figure 1.

Adapted from (Capuron and Miller, 2011). Peripheral-to-central immune signaling pathways. The humoral pathway involves peripherally released factors crossing the BBB (e.g., circumventricular organs; CVO) and directly influencing neuronal function and eliciting glial effects. The neuronal pathway involves the transduction of immune messages to a neural message in primary afferent neurons, which is then relayed to higher order brain regions via the nucleus tractus solitarius (NTS); vagal innervation and pro-inflammatory cytokine activity at peripheral nociceptors are examples of this. The cell-to-cell route relies on immune signals to roll along the blood vessel walls that engage with endothelial cells at the BBB, forming the interface between the blood and the brain. Endothelial cells become reactive and act as an immune signal translator to elicit central responses. Finally, the cellular route occurs when peripherally reactive pro-inflammatory cytokines, such as TNF-α, stimulate microglia which results in the release of factors such as monocyte chemoattractant type-1 (MCP-1) which recruits monocytes into the brain (D'Mello et al., 2009), and in specific brain nuclei to provide support for changes in neuronal function. Figure created in BioRender.com.

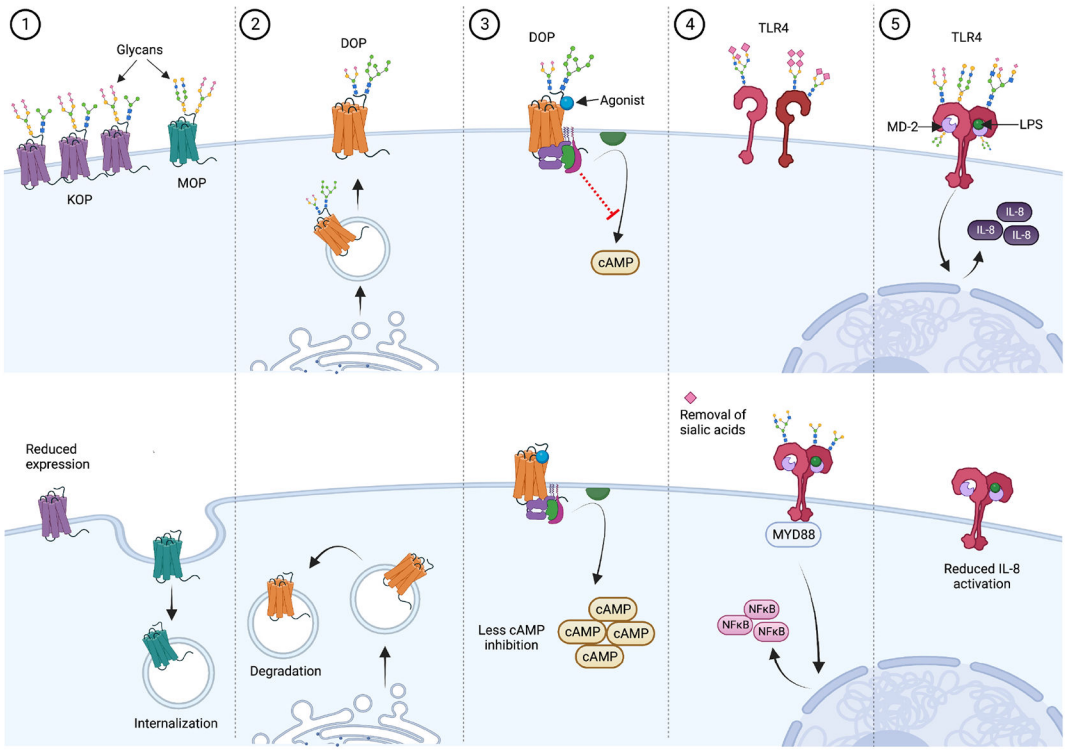

Figure 2:

Reduced expression of KOP and increased internalization of MOP when N-glycosylation is absent (Huang et al., 2012; Li et al., 2007). **2**: Glycosylation on DOP plays a role in trafficking of the receptor to the plasma membrane or for targeting the receptor for degradation (Lackman et al., 2014; Markkanen and Petäjä-Repo, 2008). **3**: Reduced inhibition of cAMP production in de-glycosylated DOP compared to the wild-type glycosylated receptor (Lackman et al., 2018). **4**: Removal of terminal sialic acids from glycans on TLR4 facilitates receptor dimerization and coupling with MyD88 allowing for signaling which activates NFkβ (Amith et al., 2010; Feng et al., 2012). **5**: Removal of N-glycosylation from TLR4 and MD-2 results in impairment to the IL-8 signal transduction pathway compared the glycosylated receptors (da Silva Correia and Ulevitch, 2002). Figure created in BioRender.com.

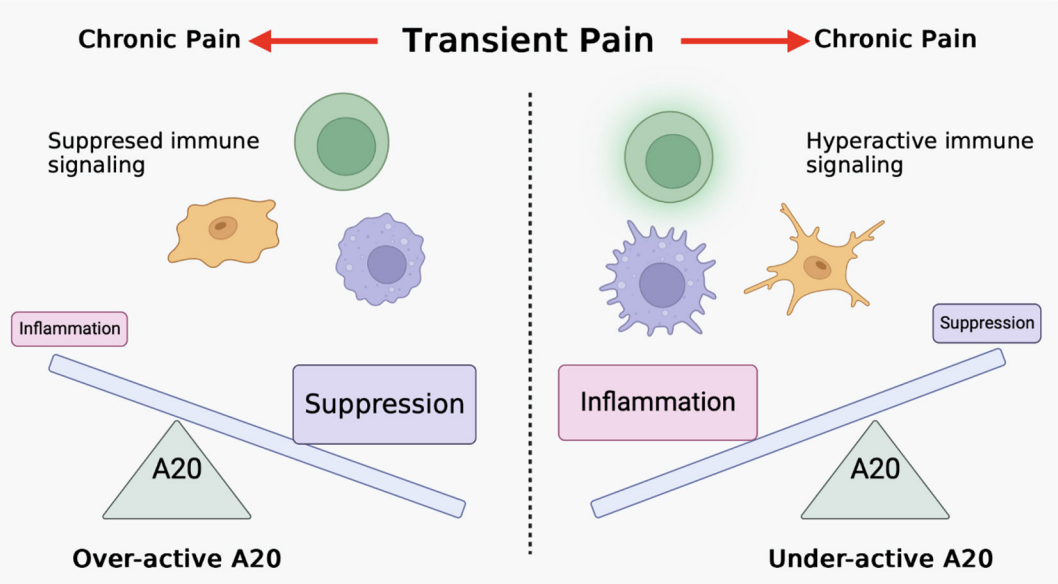

Figure 3:

Proposed mechanism by which both complete immune suppression and hyperactive immune signaling facilitate the development of chronic pain mediated by regulatory protein, A20. The “see-saw” like balance between suppression and inflammation illustrates that a fine balance between the two is required for pain resolution. Where too much immune regulation suppresses necessary pro-resolving signaling, while too little causes damaging inflammation, each of which leads to the development of chronic pain. Figure created in BioRender.com.