The interplay between M1/M2 macrophages and sensory neurons in pain modulation

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January 30, 2024

Abstract

Pain is a signal of inflammation that can be both protective and pathogenic. Macrophages, a significant component of the immune system, play an essential role in the occurrence and development of pain, particularly in neuroimmune communication. Macrophages exhibit two distinct phenotypes: pro-inflammatory M1-like and anti-inflammatory M2-like phenotypes. Sensory neurons can promote macrophages into the M1 phenotype to produce pro-inflammatory mediators to defend against infection while causing tissue damage and inducing pain. However, this can be inhibited by M2 macrophages, facilitated by sensory nerves, resulting in pain resolution. This article provides an overview of the interplay between sensory nerves and M1/M2 macrophages during the induction and resolution of pain.

The interplay between M1/M2 macrophages andsensory neurons in pain modulation

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Abstract

Pain is a signal of inflammation that can be both protective and pathogenic. Macrophages, a significant component of the immune system, play an essential role in the occurrence and development of pain, particularly in neuroimmune communication. Macrophages exhibit two distinct phenotypes: pro-inflammatory M1-like and anti-inflammatory M2-like phenotypes. Sensory neurons can promote macrophages into the M1 phenotype to produce pro-inflammatory mediators to defend against infection while causing tissue damage and inducing pain. However, this can be inhibited by M2 macrophages, facilitated by sensory nerves, resulting in pain resolution. This article provides an overview of the interplay between sensory nerves and M1/M2 macrophages during the induction and resolution of pain.

Key words :M1/M2 macrophages, pain, sensory neuron, inflammation

Introduction

Inflammation is a protective response of the body to injury and infection, characterized by five cardinal signals: tumor (edema), calor (heat), dolor (pain), rubor (redness), and fuctio laesa (loss of function). Acute pain is one of these signals (1). However, pain can persist beyond the duration of the injury and become chronic (neuropathic pain), which can have detrimental effects and diminish the quality of life.

After tissue injury and infection, immune cells, including macrophages, initiate communication with sensory neurons, leading to hyperalgesia (an increased pain response to noxious thermal and mechanical stimuli) and allodynia (an increased pain response to normally innocuous stimuli) in both the peripheral and central nervous systems (PNS and CNS) (2).

Macrophages have three primary functions during inflammation: phagocytosis, antigen presentation, and cytokine production (3). These cells exhibit tremendous plasticity and marked functional heterogeneity, with various phenotypes, including pro-inflammatory M1-like and anti-inflammatory M2-like phenotypes (4, 5). M1-like macrophages generate cytokines and chemokines to remove pathogens during infection and promote pain, while M2-like macrophages secrete growth factors that facilitate tissue repair and pain resolution. This phenomenon of the two different M1/M2 phenotypes is referred to as 'macrophage polarization' (6). The interaction between neurons and macrophages is critical in both the induction and resolution of pain. Macrophages have the ability to activate and resolve inflammation, playing distinct roles in both the induction and resolution of pain.

In this review, we will discuss recent advances in our understanding of the mechanisms that underlie the role of M1/M2 macrophages in the induction and resolution of pain, with a specific focus on the relationship between macrophages, inflammation, and sensory nerves.

2. The main mechanism of macrophages to induce pain

Acquirement of M1 phenotype

Under conditions of nerve injury or infection, activated sensory neurons in the DRG or spinal cord release neuropeptides and cytokines such as TNF, promoting macrophage programming to an M1 phenotype (7, 8). The neuropeptides Substance P (SP) and calcitonin gene-related peptide (CGRP) have been shown to cause a significant increase in IL-1β and TNF production by macrophages alone or in coordination with each other, enhancing the macrophage-mediated inflammatory response (9) (Figure 1a). TNF not only prevents the myelin phagocytosis-mediated switch from M1 to M2 but also mediates the increased IL-4-polarized M2 cells to M1, maintaining M1 polarization in the injured spinal cord (10). Additionally, the central terminals of sensory neurons communicate with microglia via the release of the cytokine colony-stimulating factor 1 (CSF1). In the spinal cord, CSF1 activates the CSF1 receptor in microglia via the transmembrane protein (DAP-12) (P2X4 independent pathway) and up-regulates genes critical to the development of allodynia(11).

Additionally, miRNAs have been found to regulate macrophage polarization (12). For example, miR-21-5p in DRG neurons has been shown to promote macrophages to acquire a pro-inflammatory phenotype (13). Similarly, miR-9-5p transferred from neurons to microglia has been shown to promote M1 polarization in microglia, leading to an over-release of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, exacerbating neurological damage (14).

Inflammatory cytokine

Macrophages use various mechanisms to induce pain. Typically, M1 macrophages release a multitude of inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α)(15, 16), interleukin-6 (IL-6) (17, 18), nerve growth factor (NGF) (19), insulin-like growth factor 1 (IGF-1) (20), COX2 and PGE2 (21), which stimulate their specific receptors expressed in the nociceptive neurons. This activation leads to the generation of various neuronal cell signals, such as Ca2+ and cAMP, PKA, PKC, PI3K, MAPKs (ERK, p38, and JNK), NF-ϰB, JAK, STAT, and Src. These kinases cause hypersensitivity and hyperexcitability of nociceptor neurons by enhancing the activity of pro-nociceptive cation channels, such as TRPA1 and TRPV1, and sodium channels NaV1.7, NaV1.8, and NaV1.9 (22, 23, 24, 25) (Figure 1b). Moreover, macrophages release reactive oxygen species (ROS) that maintain their infiltration into the injured nerve and send paracrine signals to activate TRPA1 of Schwann cells surrounding nociceptors (26). Schwann cell TRPA1 can release M-CSF to sustain peripheral nerve resident macrophage expansion and generate oxidative stress that targets neuronal TRPA1, thereby sustaining mechanical allodynia (27). Moreover, heterodimerization between TLR4 and TLR2 or TLR4 and TLR6 in microglial cells and macrophages

trigger inflammatory responses via a MyD88-dependent mechanism (28, 29).

The peripheral inflammation causes CNS hyperactivity, which leads to the development of central sensitization, a state characterized by hyperactivity and hyperexcitability of neurons in the spinal cord and brain (30). Recent studies suggest that TRPV4 channels expressed in spinal microglia play a crucial role in converting peripheral nerve injury to spinal central sensitization and neuropathic pain. The microglial TRPV4 channels mediate microglial activation and proliferation and enhance the synaptic transmission and plasticity of excitatory neurons by releasing LCN2 (31).

It is important to note that SNX25 expression in dermal macrophages, but not DRG macrophages, has been shown to inhibit the ubiquitination and proteasomal degradation of Nrf2, which is involved in maintaining the production of NGF and contributes to the maintenance of pain sensitivity. This SNX25-Nrf2 pathway in dermal macrophages may help to optimize the concentration of NGF, which modulates neuronal responses to mechanical stimuli under both normal and pain-inducing conditions(32).

Chemokine

Chemokines play a crucial role in the communication between neurons and macrophages, leading to the induction of peripheral and central sensitization. Among these, CCL2 (monocyte chemoattractant protein 1, MCP1) is produced by both macrophages and neurons, and its primary receptor is CCR2. Upon binding to CCR2, CCL2 recruits peripheral macrophages or spinal microglia to the site of nerve damage, including the cell body and peripheral and central axons of neurons, through proliferation, infiltration, or migration(3, 23, 33, 34, 35). CCL2/CCR2 signaling is involved in the development of peripheral sensitization by enhancing the activity of tetrodotoxin-resistant (TTX-R) sodium channel Nav1.8 and upregulating the expression and function of the capsaicin-sensitive TRPV1 ion channel (36). Additionally, CCL2 can regulate neuronal and synaptic plasticity underlying central sensitization through CCR2 in the spinal cord (37). CX3CR1, the only receptor for CX3CL1, is specifically expressed in microglia and is commonly used as a marker for resident macrophages in tissues and microglia in the spinal cord and brain. CX3CL1 is secreted by DRG neurons and spinal neurons following nerve injury, and it binds to CX3CR1, leading to the activation of p38 MAPK in spinal microglia, which promotes chronic pain (23, 33) (Figure 1c).

Macrophages in PNS and microglia in CNS

Peripheral nerve injury triggers a considerable increase in the number of DRG macrophages, alongside a pronounced proliferation and activation of microglia. Both DRG macrophages and microglia (the tissue-resident macrophages of CNS) are strongly implicated in the development of neuropathic pain(38, 39).

In most tissues, two classes of macrophages can be distinguished: infiltrating and tissue-resident macrophages (22, 34). In conditions such as osteoarthritis (OA) pain and radiculopathy, the increase of DRG macrophages is dominated by CC2R+ macrophages, suggesting that the accumulation of macrophages is at least partially due to infiltration of circulating monocytes into the DRG(8, 40). However, studies have shown that after peripheral spinal nerve injury, 99% of myeloid cells in the spinal cord are resident microglia, indicating that persistent pain is primarily driven by the proliferation of resident microglia (31, 41).

The main mechanism of macrophages to resolve pain

M1 macrophages are pro-inflammatory, while M2 macrophages are anti-inflammatory and have potent phagocytosis capacity, scavenging debris and apoptotic cells, promoting tissue repair and wound healing, which can contribute to pain resolution (6). As we mentioned above, neuropeptides SP and CGRP not only can promote the M1 phenotype to activate inflammation but also produce anti-inflammatory actions by facilitating the M2 switch of macrophages (42) (Figure 1a). SP can directly induce macrophages to become M2-like macrophages through the activation of the PI3K/Akt/mTOR/S6kinase pathway and the induction of Arginase-1, CD163, and CD206 (43). Similarly, CGRP can inhibit inflammation and promote the transformation through the PI3K/AKT signaling pathway (44). Under various pathological conditions, macrophages can rapidly switch from one phenotype to the other. For example, activation of NF-$\varkappa$B or IRF family members in macrophages by TLR4 or other TLRs can drive macrophage polarization towards either M1 or M2

phenotype in response to surrounding microenvironment (45).

M2 macrophages secrete anti-inflammatory cytokines, such as IL-10, TGF-β, and GPR37, which play a key role in inhibiting neuropathic pain. IL-10 is a potent anti-inflammatory cytokine that can downregulate TTX-S and Nav1.8 sodium channels and counteract the effects of TNF-α on sodium channel regulation in DRG neurons (46). TGF-β inhibits inflammatory cytokine production through cross-talk between MAPKs, specifically ERK-dependent inhibition of p38 MAPK caused by up-regulation of MAPK phosphatase-1 (47). TGF-β appears to promote the expression of endogenous opioids and inhibit the neuroimmune responses of glial cells and neurons in the spinal cord following peripheral injuries (48). Furthermore, TGF-β down-regulates CCL4 expression through ERK1/2 signaling activation to inhibit inflammatory responses in the DRG and prevent pain development (49). Neuroprotectin D1 (NPD1), one of the specialized pro-resolving mediators (SPMs), has potent anti-nociceptive effects on different pain pathologies. GPR37, expressed by macrophages but not microglia, can increase the NPD1-evoked iCa2+ via Gi-coupled signaling, thereby triggering macrophage phagocytosis via signaling through G protein subunit Gi/o, ERK, and PI3K/AKT (50, 51) (Figure 1d). Both IL-10 and GPR37 can regulate macrophage phenotypes(52, 53), and the combination of IL-10 with its receptor (IL-10R) results in activating transcription factor STAT3 and promotes M2 phenotype (45).

In addition, M2 macrophages induced by IL-4 may release opioid peptides such as Met-enkephalin, dynorphin, and β-endorphin that bind to opioid receptors on nociceptors and attenuate neuropathic pain (3, 25) (Figure 1d). A recent study has revealed a novel mechanism for the active resolution of inflammatory pain, demonstrating that CD206+ M2-like macrophages accumulate in the DRG and transfer mitochondria to sensory neurons, which recovers the oxidative phosphorylation in sensory neurons to resolve inflammatory pain (54). Furthermore, tissue-resident ganglionic macrophages exhibit an M2 phenotype after nerve injury and proliferate rapidly. They enter between satellite glial cells and neurons and directly contact neurons, leading to tissue repair (55).

Conclusion and perspective

It is commonly accepted that M1 macrophages promote pain by releasing pro-inflammatory mediators, whereas M2 macrophages alleviate pain by producing anti-inflammatory mediators. However, resolving inflammation alone is not sufficient to completely address pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as COX-2 inhibitors are known to suppress inflammation to manage acute pain, but they may also prolong inflammation, potentially leading to chronic pain (56). Therefore, maintaining a dynamic balance of inflammation related to macrophage polarization is critical in preventing acute pain from developing into chronic pain, which may represent a novel therapeutic target for neuropathic pain in the future.

Author Contributions: Xiaoye Zhu and Xiaoyan Zhu designed the structure of this article and wrote the manuscript. Zhigang Cheng and Qulian Guo reviewed the manuscript. Yuqi Zhang and Yunchuan Xiong made substantial and intellectual contributions to the work. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Xiaoyan Zhu, Natural Science Foundation of Hunan Province (2021JJ41060), Changsha Municipal Natural Science Foundation (kq2014280), Research Program Project of Hunan Health Commission(B202304119634), Yunchuan Xiong, Natural Science Foundation of Hunan Province (2021JJ31113).

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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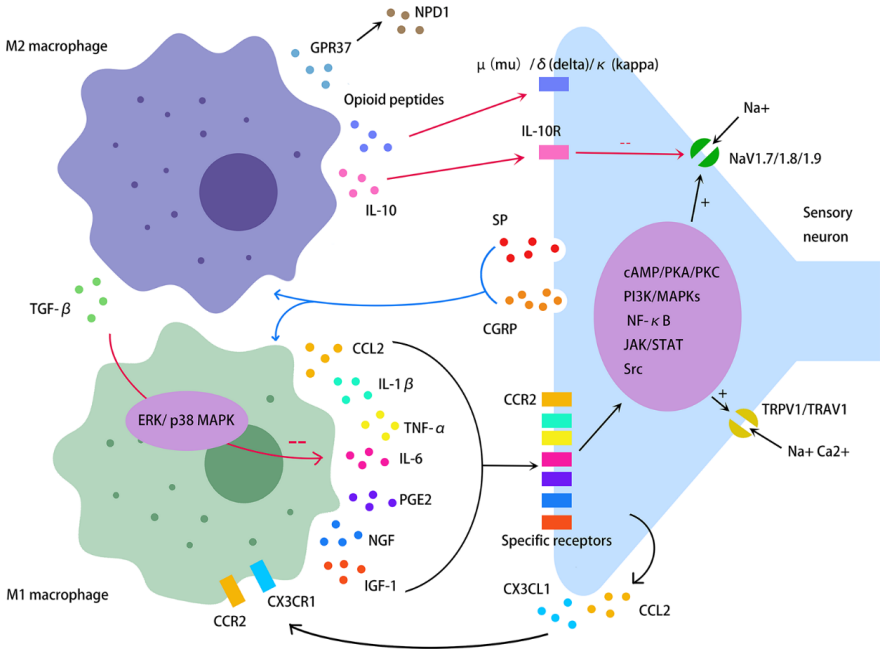

Figure legends:

Figure 1. The interaction between macrophages and sensory nerves.

1. Sensory nerves release SP and CGRP promote either M1 phenotype or M2 phenotype.
2. M1 macrophages produce pro-inflammatory cytokines including CCL2, IL-1β, TNF-α, IL-6, PGE2, NGF, IGF-1 which combine to the specific receptors on sensory nerves and enhance the activity of cation channels like TRPV1/TRAV1 and NaV1.7/1.8/1.9 via cell signals (cAMP, PKA, PKC, PI3K, MAPKs, NF-ϰB, JAK, STAT, and Src).
3. Sensory nerves secret CCL2 and CX3CL1 which stimulate CCR2 and CX3CR1 on macrophages and microglia.
4. M2 macrophages express IL-10, TGF-β, GPR37, opioid peptides. IL-10 can downregulate TTX-S and Nav1.8 sodium channels. TGF-β inhibit pro-inflammatory cytokine production through p38 MAPK. Opioid peptides bind to opioid receptors μ (mu), δ (delta) and ϰ (kappa). Activation of GPR37 induces phagocytosis.