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Topical review

Marzia Malcangio*

Role of the immune system in neuropathic pain

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Abstract

Background: Acute pain is a warning mechanism that exists to prevent tissue damage, however pain can outlast its protective purpose and persist beyond injury, becoming chronic. Chronic Pain is maladaptive and needs addressing as available medicines are only partially effective and cause severe side effects. There are profound differences between acute and chronic pain. Dramatic changes occur in both peripheral and central pathways resulting in the pain system being sensitised, thereby leading to exaggerated responses to noxious stimuli (hyperalgesia) and responses to non-noxious stimuli (allodynia).

Critical role for immune system cells in chronic pain: Preclinical models of neuropathic pain provide evidence for a critical mechanistic role for immune cells in the chronicity of pain. Importantly, human imaging studies are consistent with preclinical findings, with glial activation evident in the brain of patients experiencing chronic pain. Indeed, immune cells are no longer considered to be passive bystanders in the nervous system; a consensus is emerging that, through their communication with neurons, they can both propagate and maintain disease states, including neuropathic pain. The focus of this review is on the plastic changes that occur under neuropathic pain conditions at the site of nerve injury, the dorsal root ganglia (DRG) and the dorsal horn of the spinal cord. At these sites both endothelial damage and increased neuronal activity result in recruitment of monocytes/macrophages (peripherally) and activation of microglia (centrally), which release mediators that lead to sensitisation of neurons thereby enabling positive feedback that sustains chronic pain.

Immune system reactions to peripheral nerve injuries: At the site of peripheral nerve injury following chemotherapy treatment for cancer for example, the occurrence of endothelial activation results in recruitment of CX3C chemokine receptor 1 (CX_3CR_1)-expressing monocytes/macrophages, which sensitise nociceptive neurons through the release of reactive oxygen species (ROS) that activate transient receptor potential ankyrin 1 (TRPA1) channels to evoke a pain response. In the DRG, neuro-immune cross talk following peripheral nerve injury is accomplished through the release of extracellular vesicles by neurons, which are engulfed by nearby macrophages. These vesicles deliver several determinants including microRNAs (miRs), with the potential to afford long-term alterations in macrophages that impact pain mechanisms. On one hand the delivery of neuron-derived miR-21 to macrophages for example, polarises these cells towards a pro-inflammatory/pro-nociceptive phenotype; on the other hand, silencing miR-21 expression in sensory neurons prevents both development of neuropathic allodynia and recruitment of macrophages in the DRG.

Immune system mechanisms in the central nervous system: In the dorsal horn of the spinal cord, growing evidence over the last two decades has delineated signalling pathways that mediate neuron-microglia communication such as P_2X_4/BDNF/$GABA_A$, P_2X_7/Cathepsin S/Fractalkine/CX_3CR_1, and CSF-1/CSF-1R/DAP12 pathway-dependent mechanisms.

Conclusions and implications: Definition of the modalities by which neuron and immune cells communicate at different locations of the pain pathway under neuropathic pain states constitutes innovative biology that takes the pain field in a different direction and provides opportunities for novel approaches for the treatment of chronic pain.

Keywords: microglia; monocytes; macrophages; cytokines; chemokines; purinoreceptors; microRNAs.

List of abbreviation: P_2X_4 P_2X_7, purinoreceptor 4/purinoreceptor 7.

1 Introduction

An increased occurrence of pain has drastic and costly effects on the European population in terms of their

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***Corresponding author: Marzia Malcangio,** Wolfson Centre for Age-Related Diseases, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, E-mail: marzia.malcangio@kcl.ac.uk

performance at work and daily quality of life. Specifically, moderate to severe chronic pain occurs in 19% of adult Europeans and in 50% of these cases, patients receive inadequate treatment for their chronic pain [1]. Novel, more effective treatments are therefore required, and the identification of new mechanisms and pathways provide essential guidance to drug-discovery programmes.

Lesions or disease of the nervous system may result in pain persisting beyond the resolution of damage. Such pathological pain is a maladaptive mechanism that remains difficult to treat with current medicines. An emerging concept in the pain research area is that the *immune response* associated with damage in the central nervous system (CNS) and peripheral nervous system (PNS) may contribute to a variety of pain states, encompassing those that have either a peripheral or CNS origin [2]. Indeed, although the pain research field initially focused on the role of neurons in pain mechanisms, it has now shifted focus onto the role of non-neuronal cells, including their communication with neurons, that occurs as a consequence of their response to altered neuronal activity [3, 4].

We know that peripheral nerve damage results in neuronal sensitization and inflammatory reactions locally through macrophage accumulation and cyto(chemo) kine production, which activate the vascular endothelium and alter the sensory transduction properties of nociceptive axons, causing recurrent activity (*peripheral sensitization*) [5].

Moreover, this peripheral damage also results in increased neuronal firing in the spinal cord (central sensitization), remotely from the injury. Both central and peripheral sensitizations are fundamental for the generation of allodynia, hyperalgesia and spontaneous pain [2]. In the spinal cord, an excessive neuronal firing causes significant activation of immune cells, namely microglia, which leads to neuroinflammation [6, 7]. Spinal microglial activity plays an important role in central sensitisation, as attenuation of microglial activation correlates with reduced pain-like behaviours in models of chronic pain [8].

2 Microglia and neuropathic pain

The causal role of microglia in neuropathic pain was initially established following the observation that ipsilateral dorsal horn microglia *de novo* express purinoreceptor P_2X_4 following nerve injury [9]. Adenosine triphosphate (ATP)-induced activation of P_2X_4 in microglia causes release of brain-derived neurotrophic factor (BDNF), which by acting on the tropomyosin receptor kinase B (TrkB) receptors in dorsal horn neurons downregulates the chloride transporter chloride potassium transporter (KCC2) so that intracellular chloride concentration increases. As consequence of this shift, ionotropic receptor for GABA ($GABA_A$) receptors activation results in anions flooding out of neurons and GABAergic inhibition becomes less effective in superficial laminae. The overall effect is an enhanced nociceptive transmission [10]. Modulation of this P_2X_4/BDNF microglial pathway through enhancing KCC2 activity and blocking P_2X_4 with a centrally-penetrant monoclonal antibody or intrathecally delivered-small molecule antagonists has shown significant antinociceptive effects in the neuropathic pain models [11–13]. However, topical evidence indicates this pathway is more relevant in male than in female mice [14].

Whilst the release of ATP that engages this pathway is likely to occur from dorsal horn neurons [15], sensory neuron central terminals communicate with microglia via release of the cytokine colony-stimulating factor 1 (CSF1), which is *de novo* expressed in injured neurons after nerve injury. In the spinal cord CSF1 activates CSF1 receptor in microglia via the transmembrane protein (DAP-12) (P_2X_4 independent pathway) and up-regulates genes that are critical to development of allodynia [16], suggesting that DAP12 is a microglial target that could be considered for neuropathic pain.

A neuron-microglia signalling pathway that plays a role in the maintenance of neuropathic pain mechanisms also requires a purinoreceptor, which is however the low affinity P_2X_7 receptor whose activation causes release of the enzyme Cathepsin S (CatS) by microglia. Extracellular CatS cleaves the chemokine domain of neuronal membrane-bound fractalkine, which in turn interacts with microglia CX3C chemokine receptor 1 (CX_3CR_1) receptor and promotes release of cytokines that sensitise neurons in the dorsal horns [17–21]. As CatS inhibitors, P_2X_7 receptor antagonists and CX_3CR_1 receptor antibodies exert antinociceptive effects, they can all be microglia-expressed targets for neuropathic pain [22, 23].

This suggestion is strengthen by intriguing evidence which suggests that FKN activation of CX_3CR_1 receptor as well as CSF-1 signalling via CSF-1R in spinal microglia regulate nociceptive synaptic strength independently of neuronal activity [24], and microglia is a critical determinant for the occurrence synaptic plasticity associated with persistent neuropathic allodynia [25].

The mounting preclinical evidence on the role of microglial activity in the establishment and maintenance of neuropathic allodynia has been substantiated and validated by clinical studies, including imaging studies, which demonstrate glial cells activation in the brain of chronic low back pain patients [26] and in chronic pain conditions such as fibromyalgia (FM) [27]. Relevantly, in FM patients there is generalised cortical activation of microglia [27], and elevation of fractalkine levels in the cerebrospinal fluid [28] suggesting that microglial activation of CX_3CR_1 receptors may contribute to the symptoms of FM, and specifically widespread pain.

3 Monocytes/macrophages and neuropathic pain

Moving scenario from spinal cord to peripheral nerves, the FKN-CX_3CR_1 signalling pathway still plays a role in the establishment of nociception that is the major dose-limiting side-effect of chemotherapy treatment for cancer. Notably, in the periphery the location of FKN and CX_3CR_1 is different from the CNS as FKN is expressed by endothelial cells and CX_3CR_1 receptors by circulating monocytes that infiltrate peripheral nerves following injury.

Neuropathy, occurring in excess of 85% of patients, constitutes the major dose-limiting side-effect of chemotherapy. The key symptom of this condition reported by patients is pain, which is poorly controlled by available analgesics, thus there is an unmet clinical need for the development of new strategies that ideally prevent the onset of chemotherapy-induced neuropathy by interfering with the mechanism by which the neuropathy occurs, without altering the cancer fighting abilities of anti-neoplastic agents [29].

Chemotherapeutics, such as the vinca alkaloid vincristine, can cross the blood-nerve-barrier and as a result they promote peripheral nerve toxicity which manifests clinically as pain and sensory dysfunction. In rodents, treatments with vincristine are associated with allodynia and concomitant infiltration of macrophages in the sciatic nerve [30, 31]. Specifically, vincristine induces alteration in endothelial cell adhesion properties, which promote the infiltration of CX_3CR_1-expressing monocyte/macrophages into the sciatic nerve. In macrophages, endothelial-derived FKN promotes formation of reactive oxygen species (ROS) in a CX_3CR_1-dependent fashion and ROS then activate transient receptor potential ankyrin 1 (TRPA1) channels on sensory neurons, which evokes a pain response [30]. Therefore, the inhibition of monocyte trafficking into the sciatic nerve with CX_3CR_1 antagonists provides a strategy for the prophylactic treatment of chemotherapy-induced pain that is based on a target expressed by immune cells.

4 Role of microRNAs in neuron-macrophage communication in neuropathic pain

A consequence of nerve injury which has received significant attention in recent years is the substantial dysregulation of non-coding RNAs, including microRNAs, expression in the cell bodies of sensory neurons in the dorsal root ganglia (DRG). MicroRNAs are non-coding RNAs of 19–25 nucleotides that regulate gene expression by RNA interference, and their own expression is altered in pain related areas under chronic pain states. MicroRNAs target many genes and co-target genes both within and between pathways [32]. A number of miRNAs have been shown to regulate neuronal processes in chronic pain states [33–35], and in DRG neurons miR-lethal-7b binds toll- like-receptor-7 (TLR7) coupled to TRPA1 receptor to exerts a pro-nociceptive effect [36] whilst miR-21 activates TLR8 and increases nociceptive neuron activity and induces pain hypersensitivity [37].

Besides being recognised by nucleic acid sensor TLR8 and exert a pro-nociceptive role in DRG neurons where it is up-regulated after axonal injury, miR-21 also promotes neuronal axon growth [38], and upon noxious stimulation miR-21 is released by DRG neuron cell bodies packaged in extracellular vesicles, namely exosomes, a unique feature not shared by sensory axons [39]. Exosomes are readily engulfed by macrophages and the transfer of miR-21 polarises these immune cells towards a pro-inflammatory and pro-nociceptive phenotype. Critically, intrathecal delivery of a miR-21 antagomir or conditional deletion of miR-21 expression in sensory neurons (miR-21 cKO) both prevent the development of neuropathic allodynia and macrophage infiltration in DRG. Based on these observations, the suggestion is that sensory neuron-derived miR-21 regulates the nature of macrophage infiltrate in the DRG and facilitates pain signalling following peripheral nerve injury [39]. Thus miR-21 can be regarded as a target for neuropathic pain with the caution that neuronal miR-21 should not be affected whilst macrophage-expressed miR-21 would constitute a safer option. The delivery of nanoparticles containing miR-21 antagomir in a tissue-specific manner to target neuron-macrophage communication may prove to be an innovative strategy to prevent neuropathic pain development. There is a substantial effort in establishing the clinical application of miRs with diagnostic and therapeutic potentials in endocrine-related cancer as a single miR can address a multitude of genetic and epigenetic changes that occur in cancer patients [40]. So far, phase I trials with miR-34 and miR-16 mimics, encapsulated in nanoparticle-based formulation to enhance drug availability, have shown that drugs were well tolerated (NCT01829971). Thus, companies developing miR-based strategies for cancer may find a rationale for exploring miRs with an application for chronic pain.

5 Conclusions

In the last two decades pre-clinical research has provided compelling evidence in support of the role of immune cell infiltration in peripheral nerve and microglial activation in spinal cord dorsal horn in mechanisms for chronic neuropathic pain. Neuroimaging studies in humans have led to the suggestion that investigation of neuroimmune dysfunction offers scope for therapeutic option for chronic pain [27].

Therefore, further examinations of neuro-immune interactions could reveal new pathogenic mechanisms operative in chronic pain and offer novel and effective therapeutic approaches.

Author's statements

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