

## EDITORIAL

## Purinergic Pathways in the Spinal Microglia as a Putative Target for Treatment of Chronic Abdominal Pain



*"These pains you feel are messengers. Listen to them."  
Rumi, The Essential Rumi*

This year's Nobel Prize in Medicine was awarded to Dr. David Julius and Dr. Ardem Patapoutian for their groundbreaking discoveries of the transient receptor potential cation channel subfamily V member 1 (TRPV1), the transient receptor potential cation channel subfamily M member 8 (TRPM8), and Piezo channels.<sup>1</sup> Their pioneering work established the framework to understand how heat, cold, and mechanical force initiate nerve impulses, allowing us to sense and interpret the environment and adapt to the world around us. Their findings had also important clinical implications by increasing the understanding of the mechanisms underlying mechanical, neuropathic, and inflammatory pain.<sup>2</sup> Although knowledge in this area has grown dramatically in the last 2 decades, pain management remains a major clinical challenge,<sup>3</sup> in part because of persistent knowledge gaps in genesis of chronic pain.

Abdominal pain is the most common symptom reported by patients with chronic gastrointestinal disorders, including those with inflammatory bowel disease (IBD). Although in many patients with IBD, pain is triggered by active inflammation, in others, pain can persist despite histologic and inflammatory biomarker normalization.<sup>3</sup> A British survey reported that up to 50% of patients with Crohn's disease and 37% of patients with ulcerative colitis suffered from abdominal pain, regardless of whether the disease was in relapse or remission.<sup>4</sup> A large European study of almost 5000 patients with IBD found that 62% of them reported pain during colitis remission,<sup>5</sup> suggesting that mechanisms underlying chronic pain are independent of active inflammation.

Pain management in IBD is challenging because available therapies, such as nonsteroidal anti-inflammatory drugs, antispasmodics, or opiates, often provide inadequate relief, may contribute to morbidity, and pose risk of addiction.<sup>3</sup> Indeed, opiate usage among patients with IBD is common, with a recent study reporting opioid prescription in more than a third of patients when being discharged from the emergency department.<sup>6</sup> Thus, there is an urgent need to develop safer and novel treatment modalities to effectively manage chronic abdominal pain, which requires better understanding of its pathophysiology.

Chronic abdominal pain is a complex process, involving peripheral and central mechanisms.<sup>7</sup> During acute pain, visceral nociceptive stimuli stimulate pain receptors on the distal processes of sensory dorsal root ganglia neurons, which then transmit nociceptive information via the dorsal horn of the spinal cord to the brain. One of the key

mechanisms responsible for the genesis of chronic pain is peripheral sensitization, characterized by increased excitability (with lower threshold for activation and increased magnitude of a response) of visceral nociceptive nerves, following tissue injury or inflammation. Central sensitization, which results from changes in the properties of neurons in the spine and the brain, is also believed to play a role in chronic abdominal pain, although its underlying mechanisms are still poorly understood.

Spinal cord microglia may link gut inflammation and chronic abdominal pain. Increased microglia reactivity has been shown to contribute to persistent pain in several preclinical models, including models of colitis, by secreting proinflammatory cytokines and neurotrophins, which persist after acute colitis resolves. Furthermore, granulocyte colony-stimulating factor signaling in spinal microglia is a central factor in the sensitization of visceral afferents that express TRPV1, ultimately leading to visceral hyperalgesia.<sup>8</sup>

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Defaye et al<sup>9</sup> provide novel insight into the mechanisms governing chronic abdominal pain and suggest that targeting purinergic signaling in spinal microglia could be harnessed to treat pain in patients with IBD whose colitis is in remission. The authors used designer receptors exclusively activated by designer drugs expressed in TRPV1-containing visceral neurons that innervate colon and studied the role of neuronal activity in microglia activation. They found that chemogenetic inhibition of TRPV1-expressing visceral afferents prevents microglial activation in the spinal cord and visceral hypersensitivity in mice with experimental colitis induced by dextran sodium sulphate. In contrast, in healthy mice, chemogenetic activation of TRPV1 induced microglial activation and subsequent visceral hypersensitivity. Furthermore, Defaye et al<sup>9</sup> identified a specific signaling mechanism mediated by neuronal ATP and microglial Purinergic Receptor P2Y12 that underlies development of visceral hyperalgesia. Interestingly, inhibition of microglial P2RY12 during the acute and recovery phase of colitis normalized visceral sensitivity.

Although these results need to be validated in chronic models of colitis, they strongly suggest that modulation of microglial purinergic pathways could provide a novel therapeutic target to treat chronic postinflammatory pain. However, it remains to be determined whether this approach would be also effective in patients who develop chronic pain in the absence of a known inflammatory episode. Given the growing importance of microbiome-host interactions regulating many aspects of neuroimmune functions, it is expected that future research will build on these findings and provide insights on additional pain

triggers that may include microbial metabolites with nociceptive properties, with the ultimate goal of developing effective and safe therapies for all patients with chronic abdominal pain.

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### Conflicts of interest

The author discloses no relevant conflicts.

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2352-345X  
<https://doi.org/10.1016/j.jcmgh.2021.12.016>