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Immunotherapies in chronic pain through modulation of neuroimmune interactions

Junli Zhao[a], **Yul Huh**[a,b], **Andrey Bortsov**[a], **Luda Diatchenko**[c,d], **Ru-Rong Ji**[a,b,e]

[a]Center for Translational Pain Medicine, Department of Anesthesiology, Duke University Medical Center, Durham, NC 27710, USA

[b]Department of Cell Biology, Duke University Medical Center, Durham, NC 27710, USA

[c]Alan Edwards Centre for Research on Pain, McGill University, Montréal, QC H3A 0G4, Canada.

[d]Faculty of Dental Medicine and Oral Health Sciences, Department of Anesthesia, Faculty of Medicine and Health Sciences, McGill University, Montréal, QC H3A 0G4, Canada.

[e]Department of Neurobiology, Duke University Medical Center, Durham, NC 27710, USA

Abstract

It is generally believed that immune activation can elicit pain through production of inflammatory mediators that can activate nociceptive sensory neurons. Emerging evidence suggests that immune activation may also contribute to the resolution of pain by producing distinct pro-resolution/anti-inflammatory mediators. Recent research into the connection between the immune and nervous systems has opened new avenues for immunotherapy in pain management. This review provides an overview of the most utilized forms of immunotherapies (e.g., biologics) and highlight their potential for immune and neuronal modulation in chronic pain. Specifically, we discuss pain-related immunotherapy mechanisms that target inflammatory cytokine pathways, the PD-L1/PD-1 pathway, and the cGAS/STING pathway. This review also highlights cell-based immunotherapies targeting macrophages, T cells, and mesenchymal stromal cells for chronic pain management.

Keywords

Immunotherapy; PD-1/PD-L1 pathway; cGAS/STING pathway; Pro-inflammatory cytokines; Cell therapy

Correspondence should be addressed to: Ru-Rong Ji: ru-rong.ji@duke.edu; Tel: 919-684-9387, Center for Translational Pain Medicine, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, NC 27710, USA.

Declaration of Competing Interest

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1. Introduction

According to the revised definition of the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (Raja, et al., 2020). Chronic pain is defined as pain that persists or recurs for more than 3 months and usually accompanied by central sensitization. Chronic pain includes but is not limited to chronic neuropathic pain following nerve injury, spinal cord injury, and stroke (Costigan, Scholz, & Woolf, 2009), chronic cancer-related pain, chronic musculoskeletal pain, and chronic headache or orofacial pain. While physiological pain or acute pain serves a protective purpose, chronic pain is detrimental to the quality of life of an individual. Chronic pain also places a substantial economic burden on health care resources with an annual cost of over $600 billion in the United States (Gereau, et al., 2014). Chronic pain can be characterized as spontaneous pain, as well as evoked pain such as hyperalgesia (increased painful response evoked by a noxious stimulus) and allodynia (painful reaction to a normally innocuous stimulus), with mechanical or tactile allodynia presenting as a cardinal symptom of chronic pain.

Pain is initiated by the activation of pain sensing neurons (nociceptors). Nociceptor neuron cell bodies are located in sensory ganglia in the peripheral nervous system (PNS), including the dorsal root ganglia (DRG) and trigeminal ganglia (TG). Primary sensory neurons project to the spinal cord and brain stem, and secondary order neurons project from these regions to the thalamus and other brain regions, which mediate the sensory and emotional aspects of pain (Kuner & Flor, 2017). Nociceptors express different types of transducer molecules, including transient receptor potential (TRP) ion channels (e.g., TRPV1, TRPM8) and piezo ion channels to detect heat pain, cold pain, mechanical pain, and chemical pain (Ji & Lee, 2021; Julius & Basbaum, 2001; Kim, Coste, Chadha, Cook, & Patapoutian, 2012), as well as pathogen-induced pain (Chiu, et al., 2013; Donnelly, Chen, & Ji, 2020). Furthermore, nociceptors can be sensitized by inflammatory mediators, in the process of peripheral sensitization, through the activation of protein kinases such as protein kinase A and C (PKA and PKC) and MAP kinases (MAPK) (Gold, Levine, & Correa, 1998; Ji, Gereau, Malcangio, & Strichartz, 2009; Reichling & Levine, 2009). Recent progress has revealed that the DRG and TG consist of different classes of primary sensory neurons and nociceptors in mice and humans (Tavares-Ferreira, et al., 2022; Usoskin, et al., 2015; Yang, et al., 2022). Preclinical studies have also identified specific neurocircuits for the regulation of mechanical and thermal pain (Duan, et al., 2014; Peirs & Seal, 2016; H. Wang, et al., 2022).

Central sensitization is characterized by synaptic plasticity (i.e. increased excitatory synaptic transmission and decreased inhibitory synaptic transmission) in CNS pain circuits and carries significant clinical implications. It has a critical role in the induction and maintenance of chronic pain and the spread of pain beyond the initial site of injury (Treede, Hoheisel, Wang, & Magerl, 2022; Woolf, 1983, 2011). Thus, blockade of nerve conduction and neurotransmission in the PNS and CNS by local anesthetics, ion channel blockers, opioids, and anticonvulsants are major pharmacological treatments for pain (Finnerup, Sindrup, & Jensen, 2010). However, these treatments usually provide only transient pain relief and have been unable to promote complete resolution from injury.

The immune system has gained increasing attention in its critical role in the induction and resolution of pain via interactions with the nervous system (Marchand, Perretti, & McMahon, 2005; Ren & Dubner, 2010; Talbot, Foster, & Woolf, 2016). In particular, non-neuronal cells, including but not limited to, immune cells, glial cells, keratinocytes, cancer cells, stem cells, as well as bacterial cells, can interact with nociceptors to modulate pain (Ji, Chamessian, & Zhang, 2016). These non-neuronal cells also regulate inflammation and neuroinflammation, a localized inflammation of the PNS and CNS, for the induction and resolution of pain (Ellis & Bennett, 2013; Ji, Xu, & Gao, 2014; Ji, Xu, Strichartz, & Serhan, 2011). Immunotherapy represents a wide variety of therapies using cytokines, vaccines, antibodies, and adoptive transfer of cells. In this review, we discuss different forms of immunotherapies that target pro-inflammatory cytokines, the PD-L1/PD-1 axis, the STING/IFN pathway, and immune cells/mesenchymal stem cells, with a specific focus on emerging therapies.

2. Immunotherapy targeting pro-inflammatory cytokines in chronic pain

Cytokines are small, secreted proteins that have specific effects on cellular interactions and communication. They can act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or on distant cells (endocrine action) (J. M. Zhang & An, 2007). Cytokines are categorized into two main groups, namely pro-inflammatory and anti-inflammatory. Pro-inflammatory cytokines include tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17), and granulocyte-macrophage colony-stimulating factor (GM-CSF). The expression of these cytokines is elevated in animal pain models (DeLeo, Colburn, & Rickman, 1997; Kalpachidou, Riehl, Schopf, Ucar, & Kress, 2022; Sommer & Kress, 2004). On the other hand, anti-inflammatory cytokines include interleukin 4 (IL-4), interleukin 10 (IL-10), and transforming growth factor beta (TGF-β), which have been shown to reduce pain when used as treatments in animal pain models (Dai, et al., 2019; Echeverry, et al., 2009; Ledeboer, et al., 2007). Current clinical immunotherapies are primarily focused on targeting pro-inflammatory cytokines (Table 1).

2.1 TNF-α and its receptors

TNF-α is a transmembrane protein that can be transformed into a soluble form (sTNF-α) through cleavage by a metalloprotease called TNF-α-converting enzyme (TACE or ADAM17). Soluble TNF-α can then bind to its specific membrane-bound receptors TNFR1 (p55/p60) and TNFR2 (p75/p80) (Idriss & Naismith, 2000). Numerous studies have demonstrated a link between TNF-α and different types of pain (Schafers, et al., 2008; J. M. Zhang & An, 2007). TNF-α drives nociceptor sensitization by regulation of TRPV1 expression and sensitization of DRG neurons (Constantin, et al., 2008; X. H. He, et al., 2010; X. Jin & Gereau, 2006; B. Liu, Li, Brull, & Zhang, 2002; Park, et al., 2011; S. Wei, Qiu, Jin, Liu, & Hu, 2021). TNF-α further promotes neuropathic pain by inducing glial activation and central sensitization (Berta, et al., 2014; Bezzi, et al., 2001; Kawasaki, Zhang, Cheng, & Ji, 2008; Zhong, et al., 2010).

Anti-TNF-α-based immunotherapies, including IgG antibodies (Infliximab, Adalimumab and Golimumab), a PEGylated Fab fragment (Certolizumab-pegol), a fusion protein (Etanercept), and a nanobody (Ozoralizumab), have been approved by the FDA for the treatment of painful inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (Table 1). Several clinical studies have investigated the use of TNF-α inhibitors in the treatment of chronic pain conditions. A pilot study using subcutaneous etanercept (TNF inhibitor as a soluble receptor) to treat patients with acute severe sciatica showed improved pain scores compared to the control group (Genevay, Stingelin, & Gabay, 2004). An open-label study using infliximab also revealed promising results, with a significant reduction in pain intensity reported by patients with chronic low back pain (Grainger & Harrison, 2007). Overall, the prominent role of TNF-α in pain modulation and promising results from preclinical and clinical studies using TNF-α inhibitors suggest that this signaling pathway is a viable target for pain management. However, further research is needed to fully understand the mechanisms and timing underlying the effects of TNF-α inhibitors on pain and to determine their efficacy and safety in different pain conditions. It is noteworthy that the complications of anti-TNF-α-based immunotherapies is the small but significant risk of life threatening opportunistic infection (Ali, et al., 2013).

2.2 IL-1β and its receptors

IL-1β is a protein that belongs to the interleukin-1 family of cytokines. IL-1β exerts its effects through binding to its receptor, IL-1 receptor 1 (IL-1R1) (O'Neill & Dinarello, 2000). IL-1β has been implicated in the pathogenesis of chronic pain conditions such as rheumatoid arthritis, osteoarthritis, and neuropathic pain (Kirkham, 1991; Mailhot, et al., 2020). Studies on animals have demonstrated that exogenous IL-1β can induce both mechanical and thermal hyperalgesia, while treatment with anti-IL-1β inhibitors or antibodies can reduce pain symptoms (Milligan, et al., 2001; Sweitzer, Martin, & DeLeo, 2001; Thom, et al., 2019; T. Wei, Guo, Li, Kingery, & Clark, 2016; X. H. Wei, et al., 2012; Zelenka, Schafers, & Sommer, 2005). Similar to TNF-α, IL-1β was found to induce peripheral sensitization in DRG neurons and central sensitization in spinal cord and brain stem neurons (Binshtok, et al., 2008; W. Guo, et al., 2007; Kawasaki, Zhang, et al., 2008; Mailhot, et al., 2020; Sung, et al., 2017; M. H. Yi, et al., 2021).

IL-1β or IL-1 receptor (IL-1R)-based immunotherapies has been investigated as a potential treatment for chronic pain conditions associated with inflammation (Kalpachidou, et al., 2022) (Table 1). Current available immunotherapies targeting IL-1β or IL-1R include IL-1β antagonists (Canakinumab and Gevokizumab) and IL-1R antagonists (Anakinra and Rilonacept) (Goldbach-Mansky, et al., 2008). These antagonists are approved for the treatment of chronic pain-associated conditions, including rheumatoid arthritis and other autoinflammatory disorders (Aitken, et al., 2018; Goldbach-Mansky, et al., 2006; Ridker, et al., 2017). In clinical studies, canakinumab has been shown to reduce pain in patients with osteoarthritis, and anakinra was found to reduce pain and improve function in patients with complex regional pain syndrome (CRPS) (Helyes, et al., 2019; Ridker, et al., 2017). However, side effect of anti-IL-1β treatment (e.g., canakinumab) was also reported (Table 1) and more research is needed to fully understand the effectiveness and safety of IL-1β or

IL-1R immunotherapy, as well as the timing and duration, for the treatment of chronic pain conditions.

2.3 IL-6 and its receptors

IL-6 is a member of the IL-6 family, which consists of polypeptide cytokines comprised of four–α-helix structures. The biological activity of IL-6 is mediated through its interaction with the IL-6 receptor (IL-6R). IL-6 can activate signaling pathways through two different modes of receptor activation: classical signaling and trans-signaling (Heinrich, et al., 2003). In classical signaling, IL-6 binds to the membrane-bound IL-6Rα subunit, leading to the recruitment and activation of gp130. This process results in the activation of downstream signaling pathways, including the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway and the MAPK pathway. In trans-signaling, IL-6 can also bind to a soluble form of the IL-6 receptor (sIL-6R), which is generated by alternative splicing or proteolytic cleavage of the membrane-bound IL-6Rα subunit. The sIL-6R can form a complex with IL-6, which can then bind to gp130 on cell membranes that do not express the membrane-bound IL-6Rα subunit. This allows IL-6 to activate downstream signaling pathways in a broader range of cells.

IL-6 and its receptor play a crucial role in the modulation of pain, especially in chronic pain conditions. IL-6 is produced by immune cells and other cell types in response to tissue damage, inflammation, or nerve injury and can activate signaling pathways that contribute to the development and maintenance of chronic pain. IL-6 drives peripheral sensitization via activation of JAK/STAT3, extracellular-signal regulated kinases (ERK, a MAPK family member), and protein translation signaling pathways, leading to subsequent upregulation of TRPV1 and voltage-gated sodium channels Nav1.7 and Nav1.8 or downregulation of potassium channel KCNA4 (Alvarez, Bogen, & Levine, 2019; Atmaramani, Black, de la Pena, Campbell, & Pancrazio, 2020; Dominguez, Rivat, Pommier, Mauborgne, & Pohl, 2008; Fang, et al., 2015; Kalpachidou, et al., 2022). IL-6 further regulates central sensitization in spinal cord pain circuits (Kawasaki, Zhang, et al., 2008).

Multiple immunotherapies have been developed to target IL-6 or IL-6R, including anti-IL-6 monoclonal antibodies (Siltuximab and Clazakizumab) and anti-IL-6R monoclonal antibodies (Tocilizumab and Sarilumab) (Table 1). These immunotherapies have been shown to be effective in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, multicentric Castleman disease, as well as COVID-19 (Kishimoto, 2005; Mease, et al., 2016; Potere, et al., 2021; Smolen, et al., 2008). Several preclinical studies have shown that blocking IL-6 or its receptor can alleviate pain in animal models of chronic pain. However, the results of clinical trials have been mixed. Some clinical trials have shown that blocking IL-6 or its receptor can reduce pain in patients with rheumatoid arthritis or chronic low back pain, while others failed to show significant benefits (Choy, et al., 2020; Genovese, et al., 2015; Yip & Yim, 2021). One challenge in developing IL-6 or IL-6R immunotherapy for pain is that IL-6 also plays an important role in normal immune function and its blockade can increase the risk of infections and other adverse effects (Gale, et al., 2019; Monemi, et al., 2016). Therefore, it is essential to carefully consider the potential risks and benefits of this approach before using it to treat chronic pain.

2.4 IL-17 and its receptors

IL-17 is a cytokine that is produced by various immune cells, including T-helper 17 (Th17) cells, gamma-delta T cells, and natural killer T cells. It plays an important role in the immune response to infections and in the development of autoimmune diseases. IL-17 signals through a receptor complex known as IL-17 receptor (IL-17R), which is expressed on a wide variety of cells, including epithelial cells, fibroblasts, and immune cells such as macrophages and neutrophils (Gu, Wu, & Li, 2013). IL-17RA is the primary signaling subunit and is required for most of the biological effects of IL-17. Upon IL-17 binding to its receptor, a signaling cascade is initiated, which ultimately leads to the activation of several downstream pathways, including the NF-κB and MAPK pathways. These pathways regulate the expression of various proinflammatory genes, such as cytokines, chemokines, and matrix metalloproteinases, which contribute to the immune response and tissue damage (Gaffen, 2009). Animal studies have shown that IL-17 is involved in the development and maintenance of neuropathic pain, inflammatory pain, and cancer pain (X. Jiang, et al., 2022). Exogenous IL-17 injection is sufficient to induce pain hypersensitivity in naïve animals, while blocking IL-17/IL-17R signaling decreased arthritic and neuropathic pain in animals with arthritis, nerve injury, and chemotherapy-induced neuropathy (H. Luo, et al., 2019; Luo, et al., 2021; Meng, et al., 2013; Richter, et al., 2012; Segond von Banchet, et al., 2013). Notably, the IL-23/IL-17A axis regulates mechanical pain via macrophage-nociceptor interaction in a sex-dependent manner (Luo, et al., 2021; Z. Tan, Lin, Wu, & Zhou, 2022). Nociceptive sensory neurons express IL-17R in rodents and humans and neuronal IL-17R was shown to regulate peripheral sensitization (Luo, et al., 2021; McNamee, et al., 2011; Richter, et al., 2012; Yang, et al., 2022).

Currently, two IL-17A antibodies, secukinumab and ixekizumab, are approved for the treatment of plaque psoriasis, ankylosing spondylitis and psoriatic arthritis (Table 1). Several preclinical studies have investigated the use of IL-17 and IL-17RA antagonists as potential treatments for chronic pain. Blocking IL-17RA with a monoclonal antibody reduced mechanical allodynia and thermal hyperalgesia in a rat model of neuropathic pain (Ultenius, Linderoth, Meyerson, & Wallin, 2006). It was also found that IL-17 neutralizing antibody reduced pain-like behaviors in a mouse model of osteoarthritis (Faust, et al., 2020). Clinical trials are currently in progress to investigate the efficacy of IL-17 and IL-17RA antagonists for the treatment of various chronic pain conditions, such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (Mease, et al., 2017; van den Berg & Miossec, 2009). Results from these trials have shown promising effects on reducing pain and improving physical function (Jaller Char, Jaller, Waibel, Bhanusali, & Bhanusali, 2018).

2.5 GM-CSF and its receptor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that regulates the proliferation, differentiation, and activation of hematopoietic cells. The biological effects of GM-CSF are mediated through binding to its specific receptor, GM-CSFR. The binding of GM-CSF to GM-CSFR leads to the activation of downstream signaling pathways, including JAK2/STAT5, PI3K/Akt, Ras/MAPK, and NF-κB pathways, which can promote cell growth, differentiation, and inflammatory responses (Lehtonen, Matikainen, Miettinen, & Julkunen, 2002). The expression of GM-CSFR in DRG neurons was found to regulate

nociceptor sensitization in mice, likely by phosphorylating the heat transducer ion channel TRPV1 through p38 MAPK and TrkA signaling (Donatien, et al., 2018; L. Zhao, et al., 2022). Treatment with GM-CSF led to the upregulation of TRPV1, sodium channels, and potassium channels, leading to peripheral sensitization (Tewari, et al., 2020; F. Zhang, et al., 2019).

Several monoclonal antibodies that target GM-CSF (Namilumab, Otilimab (MOR103)) or GM-CSFR (Mavrilimumab) are approved for treating chronic pain related conditions, including rheumatoid arthritis and multiple sclerosis (Behrens, et al., 2015; Nair, Edwards, & Moots, 2012; Taylor, et al., 2019) (Table 1). In mouse models of bone cancer, administration of a GM-CSF neutralizing antibody significantly reduced cancer pain behaviors and inhibited the upregulation of TRPV1 and Nav1.7 channels in DRG neurons (F. Zhang, et al., 2019). In a neuropathic pain model, treatment with a GM-CSFR antibody reduced mechanical allodynia and thermal hyperalgesia in mice (Nicol, et al., 2018). Treatment with a GM-CSF neutralizing antibody in a preclinical model of arthritis led to reductions in synovial inflammation and joint destruction and pain-related behaviors (Saleh, et al., 2018). Clinical trials are ongoing to evaluate the safety and efficacy of GM-CSF and GM-CSFR antagonists in the treatment of chronic pain. Preliminary results from a phase 2 clinical trial in patients with osteoarthritis have shown that treatment with a GM-CSF neutralizing antibody significantly reduced pain compared to placebo (Taylor, et al., 2019). However, Mavrilimumab was also shown to cause non-specific headache in some patients (Table 1).

In addtion to pro-inflammatory cytokines, matrix metalloproteases (MMPs) are extracellular matrix proteins with major roles in neuroinflammation and neurological diseases (Vandooren, Van Damme, & Opdenakker, 2014). MMP-9 is one of the best known members of the MMP family and is tighely regulated by pro-inflammatory cytokines such as TNF-α in peripheral neuropathy (Shubayev & Myers, 2000). MMP-9 was shown to drive neuropathic pain via activation of IL-1β and glial cells in the PNS and CNS (Kawasaki, Xu, et al., 2008). Through functional screening, a selective monoclonal antibody was developed against mouse/human MMP-9 and displays efficacy in attenuating neuropathic pain (Lopez, et al., 2019). Thus, MMP-9 monoclonal antiboids may offer new therpetutics for treating chronic pain, but the specfic pain conditions and timing of the treatment remain to be defined.

3. Immunotherapies targeting PD-L1/PD-1 pathway in chronic pain

The Programmed cell death 1 (PD-1) receptor, also named CD279, is a 288-amino acid protein first identified as an apoptosis molecule by Tasuku Honjo and colleagues at Kyoto University in 1992 (Ishida, Agata, Shibahara, & Honjo, 1992). In 1999, the team further discovered that PD-1 functions as a critical negative regulator of the immune response, contributing to self-tolerance of the immune cells, especially T cells. The Programmed cell death ligand 1 (PD-L1 or *Pdcd1lg1*, CD274, B7-H1) is a 290-amino acid protein first identified as a molecule with homology to B7-1 and B7-2 by Lieping Chen and colleagues at Mayo Clinic in 1999 (Dong, Zhu, Tamada, & Chen, 1999). In the year 2000 another research group led by Gordon Freeman at the Dana-Farber Cancer Institute collaborated with the

Genetics Institute at Cambridge and found that this B7-1 like molecule was a ligand for PD-1, and named it PD-L1 (Freeman, et al., 2000).

3.1. PD-L1/PD-1 signaling in different cell types

PD-1 is a type I transmembrane protein consisting of an extracellular region, a transmembrane region, and a cytoplasmic region. The extracellular region contains an IgV-like domain and an IgC-like domain, which are connected by a hinge region. The IgV-like domain is composed of seven β-strands that fold into two antiparallel β-sheets and responsible for binding to its ligands, PD-L1 and PD-L2 (Zak, et al., 2015). Compared to PD-L1, PD-L2 has very limited expression (Latchman, et al., 2001; Lazar-Molnar, et al., 2008). The transmembrane domain is composed of a single α-helix that anchors the protein in the cell membrane. The cytoplasmic tail contains two tyrosine residues in its immune receptor tyrosine-based inhibitory motif (ITIM) and an immune receptor tyrosine-based switch motif (ITSM) that play a crucial role in PD-1 downstream signaling (X. Zhang, et al., 2004). PD-L1 is a type I transmembrane glycoprotein that is composed of an extracellular domain, a transmembrane domain, and a cytoplasmic domain (Perry, et al., 2019). The extracellular domain consists of two Ig-like domains, a V-like domain and a C-like domain, which are connected by a flexible hinge region (Lin, et al., 2008). The V-like domain, which is structurally similar to other B7 family members and mediates the interaction between PD-L1 and its receptor PD-1. The transmembrane domain anchors PD-L1 to the cell membrane while the cytoplasmic domain interacts with intracellular signaling pathways.

The PD-1 protein is primarily found on the surface of certain immune cells, such as activated T cells, B cells, natural killer cells, monocytes, and dendritic cells (Bally, Austin, & Boss, 2016). However, recent studies have identified the expression of PD-1 on neurons in several regions of the brain, including the hippocampus, cortex, thalamus, and hypothalamus (C. Jiang, et al., 2020; Zeisel, et al., 2015). The PD-L1 protein is expressed on a range of cells, including activated immune cells like T cells, B cells, dendritic cells, macrophages, and tumor cells, as well as neurons (G. Chen, et al., 2017; Dorand, et al., 2016).

In T cells, PD-1 activation initiates several downstream signaling cascades that reduce the secretion of inflammatory cytokines (IFN-γ, IL-2, TNF-α) and promote the secretion of immune inhibitory cytokines (IL-10 and IL-4) in order to inhibit T cell activation, proliferation, and survival (Riley, 2009). PD-1 activation inhibits T cell receptor (TCR)-mediated signaling by recruiting the tyrosine phosphatases SHP-1/2 (Src homology region 2 domain-containing phosphatase-1/2) to the immune synapse where TCRs are engaged with antigen-presenting cells (APCs) (Hui, et al., 2017; Patsoukis, et al., 2020; Plas, et al., 1996; Yokosuka, et al., 2012). PD-1 activation also inhibits the PI3K/Akt/mTOR and Ras/MAPK/Erk pathways, leading to decreased cytokine production and T cell proliferation (Patsoukis, et al., 2012; R. Zhao, et al., 2019). PD-1 signaling upregulates other immune inhibitory molecules, such as cytotoxic t-lymphocyte antigen-4 (CTLA-4) and lymphocyte-activation gene 3 (LAG-3) (Chocarro, et al., 2021; Ribas & Wolchok, 2018), which regulate the balance between immune activation and suppression. Finally, PD-1 signaling inhibits the activity of transcription factors, such as NFAT and AP-1, resulting in reduced cytokine production and T cell activation (Oestreich, Yoon, Ahmed, & Boss, 2008; G. Xiao, Deng,

Liu, Ge, & Liu, 2012). Therefore, PD-1 plays a critical role in adaptive immune resistance that allows tumor cells to counteract endogenous anti-tumor activity. In this pathway, PD-L1 is often upregulated in tumor cells or non-transformed cells within the tumor microenvironment. When PD-L1 binds to PD-1 on activated T cells, it suppresses the function of cytotoxic T cells within the tumor microenvironment, thereby facilitating tumor growth and progression.

In macrophages and microglia, PD-1 activation inhibits macrophage/microglia function by recruiting phosphatases SHP-1/SHP-2 to ITIM and/or ITSM domains in the PD-1 tail. This recruitment leads to the inhibition of the PI3K/NF-κB signaling pathway (H. He, et al., 2018). Specifically, PD-1 signaling suppresses the activity of IFN-γ-activated M1 macrophages by reducing the phosphorylation of STAT1 and the secretion of interleukin-12 (IL-12). Furthermore, PD-1 signaling promotes the activity of IL-4-activated M2 macrophages by increasing STAT6 phosphorylation (Liang, et al., 2021; Yao, et al., 2014; J. Zhao, Roberts, Wang, Savage, & Ji, 2021).

Accumulating evidence indicates an active role of PD-1 in neurons in the PNS and CNS. Activation of PD-1 directly regulates neuronal excitability, synaptic transmission, and plasticity via the SHP-1/ERK signaling pathway and modification of ion channels, including sodium, calcium, and potassium channels (e.g., Kv4.2 channels), as well as NMDA/AMPA receptors and GABA receptors. Thus, the PD-L1/PD-1 axis may also serve as a neuronal checkpoint to regulate various functions of the nervous system, such as learning, memory, anesthesia, analgesia, and pain (C. Jiang, et al., 2020; J. Zhao, et al., 2021).

3.2. PD-L1/PD-1 axis in pain and opioid analgesia

Preclinical and clinical studies suggest an important role of PD-L1 and PD-1 in regulating physiological and pathological pain (Table 2). Mice with a deficiency of PD-L1 (B7-H1) showed enhanced inflammation and neuropathic pain after nerve injury via immune modulation (Uceyler, et al., 2010a). The PD-L1/PD-1 axis also controls pain via neuromodulation. *Pdcd1* global knockout (KO) mice exhibited increases in baseline pain sensitivity to thermal and mechanical stimuli compared to wild-type mice; and furthermore, mouse DRG neurons from KO mice showed increased excitability and increased action potential frequency (G. Chen, et al., 2017). Administration of PD-L1 via intraplantar or intrathecal (spinal) injection is sufficient to increase the pain threshold in non-injured naïve mice (G. Chen, et al., 2017). Additionally, *in situ* hybridization and immunohistochemistry revealed *Pdcd1* transcript and PD-1 protein expression in the neuroaxis of pain, including primary sensory neurons and spinal cord dorsal horn neurons (C. Jiang, et al., 2020; B. L. Liu, Cao, Zhao, Liu, & Zhang, 2020; Livni, et al., 2022; Meerschaert, et al., 2022; Wanderley, et al., 2022; L. Zhao, et al., 2022). Moreover, primary sensory neurons, especially peptidergic neurons, express PD-L1 (G. Chen, et al., 2017; Deng, et al., 2023; Meerschaert, et al., 2022). Mechanistically, PD-L1 produces antinociception in mice through phosphorylation of SHP-1 in DRG sensory neurons (G. Chen, et al., 2017; B. L. Liu, et al., 2020; L. Zhao, et al., 2022). Activation of SHP-1 in DRG neurons results in increased ERK activation, decreased function of sodium channels (e.g. Nav1.7) and TRPV1, and increased potassium channel activity (TREK2) in DRG neurons (Figure 1), as well as

decreased excitatory synaptic transmission in spinal cord neurons and increased GABAergic neurotransmission in CNS neurons (G. Chen, et al., 2017; C. Jiang, et al., 2020; B. L. Liu, et al., 2020; X. Xiao, et al., 2015). PD-L1 may also modulate nociception through direct interaction with TRPV1 (Meerschaert, et al., 2022). Interestingly, a PD-1 binding peptide, H20, identified by *in silico* modeling, elicited more potent pain inhibition than PD-L1 in several mouse models through induction of SHP-1 phosphorylation and inhibition of nociceptive neuron activity (L. Zhao, et al., 2022).

PD-1 also regulates opioid analgesia and opioid-induced adverse effects such as antinociceptive tolerance and hyperalgesia (Z. Wang, et al., 2020). Opioids are a mainstay treatment for postoperative pain and cancer pain, but also have harmful side effects including addiction and respiratory inhibition. Opioids inhibit pain in part by suppressing Ca^{2+} channels in primary sensory neurons and inhibiting neurotransmitter release (Ballantyne & Mao, 2003; Corder, Castro, Bruchas, & Scherrer, 2018; P. W. Mantyh, Clohisy, Koltzenburg, & Hunt, 2002). It was found that PD-1 may interact with mu opioid receptors (MORs) in sensory neurons, suggesting a crosstalk between these pain inhibitory systems. Morphine's inhibitory effects, including analgesia, suppression of Ca^{2+} currents in DRG neurons, and suppression of spinal cord synaptic transmission required PD-1 expression and reduced in *Pdcd1* KO mice. Strikingly, PD-1 interaction with opioid receptors can be validated in nonhuman primates, as intrathecal morphine-induced antinociception is largely blocked by anti-PD-1 treatment (Z. Wang, et al., 2020).

PD-L1 and PD-1 levels are also regulated by the process causing the pain or hyperalgesia (Table 2). In female mice, PD-L1 levels were increased in late-pregnancy but decreased following delivery, and furthermore, PD-L1 is required for pregnancy-induced analgesia (H. Tan, et al., 2021). Electroacupuncture alleviated inflammatory pain via upregulation of the PD-L1/PD-1/SHP-1 pathway in DRG neurons of rats (Deng, et al., 2023). In patients with osteoarthritis, different exercise modalities (e.g., Tai Chi, Baduanjin, stationary cycling) relieved arthritic pain and increased serum PD-1 levels (J. Liu, et al., 2019). Further investigation is needed to test whether this upregulation serves as a biomarker or has causative role in pain. Taken together, these findings indicate that the PD-L1/PD-1 axis may act as a checkpoint to pain (Hirth, Gandla, & Kuner, 2017).

3.3. PD-1 and PD-L1 based immunotherapies and cancer pain

PD-1 immunotherapy involves the use of monoclonal antibodies that target the PD-1 receptor or its ligand, PD-L1, to restore the anti-tumor activity of T cells (Tumeh, et al., 2014). These antibodies bind to PD-1 (Nivolumab, Pembrolizumab, Cemiplimab, Sintilimab and Camrelizumab) or PD-L1 (Atezolizumab, Durvalumab, Avelumab and Cemiplimab) and block their interaction, which allows T cells to be re-activated and attack cancer cells (Bagchi, Yuan, & Engleman, 2021; Carlino, Larkin, & Long, 2021). PD-1/PD-L1 immunotherapies have shown remarkable clinical success in the treatment of various cancer types, including melanoma, non-small cell lung cancer, and bladder cancer, among others. However, only a portion of patients responds to PD-1 immunotherapy, and resistance mechanisms have been identified, including the upregulation of alternative immune checkpoint molecules and alterations in the tumor microenvironment. Ongoing research is

focused on identifying biomarkers that can predict response to PD-1/PD-L1 immunotherapy as well as developing combination therapies that can enhance the effectiveness of PD-1 blockade (Chow, et al., 2019; Doroshow, et al., 2021; Dudley, Lin, Le, & Eshleman, 2016; M. Yi, et al., 2018).

PD-L1 was found to mask cancer pain in a mouse model of melanoma. Notably, hindpaw inoculation of melanoma resulted in robust tumor growth but did not elicit signs of cancer pain in 4 weeks (G. Chen, et al., 2017). Cancer pain in this model was masked by melanoma-induced PD-L1. Thus, blockade of PD-1/PD-L1 signaling evoked robust spontaneous pain with mice licking and flinching the melanoma-bearing hindpaw. *In vivo* recordings of mouse sciatic nerve showed that nivolumab treatment significantly increased the spontaneous firing of nerve fibers, suggesting that anti-PD-1 treatment can enhance pain sensitivity by increasing the excitability of primary afferent fibers. Interestingly, the increased pain sensitivity was observed only in the acute phase (first 3 hours) after PD-1/PD-L1 blockade, and not in the late phase (24 hours), suggesting that the pain inducing effect by nivolumab may be short-lived. This acute treatment did not change the levels of T cell markers (CD2, CD3), a macrophage marker (CD68), and inflammatory cytokine markers (TNF, IL-1β, IL-6, IFN-γ, CCL2), suggesting that PD-1 signaling masks pain via unconventional neuronal modulation (G. Chen, et al., 2017). It will be of great interest to investigate whether PD-L1 released from sensory neurons contributes to the development of melanoma. A recent study demonstrated that nociceptive neurons promote melanoma development via suppressing T cell immunity in mice (Balood, et al., 2022).

PD-L1/PD-1 signaling was also found to be involved in a mouse model of bone cancer pain, induced by femoral inoculation of Lewis Lung carcinoma cells. Bone cancer pain typically results from metastatic cancer cells reaching the bone, leading to the formation of osteolytic bone lesions and fractures (Andriessen, Donnelly, & Ji, 2021; P. Mantyh, 2013). PD-L1 can promote osteoclastogenesis in cancer-bearing bone marrow through activation of JNK (c-Jun N-terminal kinase, a MAPK family member) and subsequent secretion of the chemokine (C-C motif) ligand 2 (CCL2). Anti-PD-1 treatment was found to transiently increase bone cancer pain in the early phase of treatment due to neuronal modulation. However, in the late phase of treatment, Anti-PD1 treatment persistently reduced bone cancer pain through the suppression of osteoclastogenesis and protection from bone destruction (K. Wang, et al., 2020). Thus, the effects of anti-PD-1 treatment on bone cancer pain may depend on both neuromodulation and immunomodulation (Figure 1). Overall, immunotherapy targeting the PD-L1/PD-1 pathway has the potential to produce long-term benefits by preserving bone structure and alleviating bone cancer pain. However, further research is needed to fully understand the mechanisms underlying these effects and to optimize the ideal time window of the treatment (e.g. right before and during bone metastasis).

4. Immunotherapies targeting the cGAS-STING pathway in chronic pain

4.1. STING signaling in different cell types

Stimulator of interferon genes (STING) is also known as transmembrane protein 173 (TMEM173). It was first identified in 2008 as a critical mediator of innate immune responses to viral and bacterial infections (Ishikawa & Barber, 2008). STING is a

transmembrane protein expressed in various cell types, including immune cells such as dendritic cells, macrophages, and T cells, as well as microglia, fibroblasts, epithelial cells, and neurons (Q. Chen, Sun, & Chen, 2016; Donnelly, et al., 2021a; M. Jin, et al., 2021; Mosallanejad & Kagan, 2022). The STING protein has four domains: an N-terminal transmembrane domain, a cytoplasmic domain, a linker domain, and a C-terminal domain. The N-terminal domain contains four tandem repeats of a conserved sequence motif called the STING domain. The cytoplasmic domain of STING contains a binding site for cyclic GMP-AMP (cGAMP), produced by activation of cGAMP synthase (cGAS), and the cytoplasmic C-terminal tail of STING interacts with downstream signaling molecules (H. Liu, et al., 2019; X. Zhang, Bai, & Chen, 2020). In addition to infections, STING is induced by DNA damage and cellular stress. In its inactive state, STING is primarily localized to the endoplasmic reticulum. Upon activation, STING translocates to the Golgi complex and further translocation to perinuclear vesicles is key for its function in the cGAS-STING pathway (W. Sun, et al., 2009). Upon binding to double-stranded DNA, the enzyme cGAS catalyzes the production of cGAMP, which functions as a second messenger and activates the STING pathway (Figure 2). Upon binding to cGAMP, STING undergoes a conformational change that activates the TANK-binding kinase 1 (TBK1) and the inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKKε) (Gui, et al., 2019; C. Zhang, et al., 2019). TBK1 and IKKε then phosphorylate the transcription factor interferon regulatory factor 3 (IRF3), which triggers the expression of Type I interferons (IFN-I: IFN-α and IFN-β) that initiate an immune response to combat viral infections. Activation of the STING pathway also leads to the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) via the activation of nuclear factor-kappa B (NF-κB) (Q. Guo, et al., 2021; Messaoud-Nacer, et al., 2022; Yum, Li, Fang, & Chen, 2021). These cytokines play an essential role in the recruitment and activation of immune cells to the site of infection, aiding in the clearance of the invading pathogen. In addition to viral infections, STING has been implicated in autoimmune and neurodegenerative diseases (Fritsch, Kelly, & Pickrell, 2023).

4.2 STING signaling in acute and chronic pain

Increasing evidence points to a role of STING in regulating physiological and pathological pain. STING has been identified as a critical regulator of nociception through IFN-I signaling in DRG sensory neurons. Studies have shown that administration of synthetic (DMXAA and ADU-S100) or biological (cGAMP) STING agonists can increase mechanical pain thresholds in uninjured and neuropathic pain mice and produce analgesia in nonhuman primates. Conversely, mice lacking STING displayed enhanced pain hypersensitivity and heightened nociceptor excitability. Activation of STING drives the production of IFN-I family members IFN-α and IFN-β. Mice lacking IFN-I receptor (IFNAR1), including global ($Ifnar1^{gt/gt}$) and sensory neuron-selective ($Ifnar1^{fl/fl}$;$Na_v1.8$-Cre) knockout mice, exhibited robust nociceptor hyperactivity. Mechanistically, IFN-I was found to suppress sodium channel activity in DRG neurons and EPSCs in spinal cord neurons (Donnelly, et al., 2021b; P. H. Tan, Ji, Yeh, & Ji, 2021). Therefore, STING signaling through IFN-I serves as a critical regulator of nociception and a promising target for immunotherapy to treat chronic pain.

As a pro-inflammatory signaling molecule, STING activation may also activate NF-κB signaling and produce pro-inflammatory cytokines and chemokines to trigger pro-nociceptive signaling. It was found that spared nerve injury (SNI) leads to a significant increase in double-stranded DNAs, which can activate the STING/TBK1/NF-κB pathway (J. Sun, et al., 2022). Intrathecal administration of STING antagonist C-176 in the early phase (1st week of nerve injury), but not at later time points can attenuate SNI-induced pain hypersensitivity, microglial activation, release of proinflammatory factors, and JAK2/STAT3 phosphorylation in the spinal cord dorsal horn (J. Sun, et al., 2022). However, the analgesic effect of C-176 is greatly reduced in the presence of recombinant IL-6 following SNI surgery, suggesting the involvement of this cytokine in the mechanism of action of C-176 (Wu, et al., 2022). Thus, the STING pathway may differentially regulate neuropathic pain via distinct signaling mechanisms (IFN-I vs. IL-6). Notably, at high doses, IFN-I may also trigger pronociceptive signaling (Barragan-Iglesias, et al., 2020; P. H. Tan, et al., 2021).

4.3 STING based immunotherapies

Tumor cells often have genomic instability that causes the release of endogenous DNA into the cytoplasm. The resulting cGAMP or DNA can activate the cGAS-STING pathway, leading to the production of IFN-Is, pro-inflammatory cytokines, and chemokines that attract immune cells such as T cells, natural killer cells, and dendritic cells to the tumor microenvironment (Corrales, et al., 2015; Li & Chen, 2018; Xia, Konno, Ahn, & Barber, 2016). This immune response can also stimulate the activation, maturation, and differentiation of T cells, leading to adaptive immune responses. Activation of the cGAS-STING pathway in cancer cells also triggers programmed cell death, or apoptosis, contributing to the elimination of cancer cells (Woo, Corrales, & Gajewski, 2015). Thus, the targeting of the cGAS-STING pathway has shown great potential for anti-tumor immunotherapy. Several clinical trials are currently underway to evaluate the effectiveness of cGAS-STING pathway-targeted immunotherapies for cancer treatment, such as STING agonists ADU-S100 (MIW815) (NCT02675439), MK-1454 (NCT03010176), GSK3745417 (NCT03843359), and E7766 (NCT04144140) (Chang, et al., 2022; K. C. Huang, et al., 2022; Le Naour, Zitvogel, Galluzzi, Vacchelli, & Kroemer, 2020; Messaoud-Nacer, et al., 2022). These trials aim to test the efficacy of these agents in patients with advanced solid tumors or lymphomas. These clinical trials will provide crucial insights into their effectiveness against cancer.

Activation of the STING pathway by synthetic agonists such as DMXAA and ADU-S100 has been shown to enhance anti-tumor immunity and promote bone formation in murine bone autoimmune disease models (Baum, et al., 2017; Corrales, et al., 2015). Additionally, STING activation can be used as a treatment for bone cancer pain with metastasis. STING-mediated IFN-I signaling directly controls bone cancer pain via neuromodulation, resulting in rapid pain inhibition by decreasing the neuronal excitability of mouse DRG neurons (K. Wang, et al., 2021). Moreover, STING-mediated IFN-I signaling also suppressed cancer-induced osteoclastogenesis, inhibiting osteoclast-mediated bone destruction that elicits severe pain (K. Wang, et al., 2020). Finally, in mouse bone cancer, systemic administration of STING activator DMXAA increased the proportion of $CD8^+$ T cells in the bone marrow tumor microenvironment, inhibiting tumor growth. Thus, STING agonists can

have immunomodulatory and neuromodulatory effects, which additively or synergistically suppress cancer pain (Figure 2). Studies have also shown that STING activation plays a critical role in driving bone cancer pain in mice through TBK1/NF-κB-mediated induction of IL-1β, IL-6, and TNF-α in the DRG, and STING inhibitor C-176 significantly alleviated hyperalgesia in the bone cancer pain model (Y. Zhang, et al., 2023). Overall, these findings suggest that STING may play different roles in regulating bone cancer pain through distinct regulations of gene expression (IFN-I vs. IL-1β, IL-6, and TNF-α) by STING activators and inhibitors under different conditions.

5. Cell-based immunotherapies in pain management

The immune system consists of innate and adaptive immune system. Increasing number of studies are pointing towards a potential role of immune cells in pain management. Notably, immune cells, such as T cells, macrophages, and neutrophils have been shown to be both pronociceptive and anti-nociceptive, contributing to the induction and resolution of pain in a context-dependent manner (Ji, et al., 2016).

5.1 Macrophages in the development and resolution of pain

It is well established that crosstalk between macrophages, including tissue-resident macrophages in DRGs, and sensory neurons contributes to the induction and maintenance of inflammatory and neuropathic pain (O. Chen, Donnelly, & Ji, 2019). Nerve injury and chemotherapy cause significant increases in macrophage numbers in DRGs. The causative role of macrophages in promoting pain was examined by pharmacological and genetic ablations of macrophages in neuropathic pain models. Ablation of DRG macrophages with clodronate reduced mechanical allodynia in a nerve injury model of neuropathic pain in mice (Yu, et al., 2020). In a mouse model of rheumatoid arthritis, CX3CR1 expressing monocytes/macrophages in the DRG contribute to arthritis pain (Oggero, et al., 2022). DRG macrophages were also shown to maintain osteoarthritis pain in mice (Raoof, et al., 2021). Macrophages drive chronic pain by producing various pro-inflammatory cytokines/chemokines, such as TNF-α, IL-6, IL-17, and CXCL1, which can interact with nociceptor neurons to modulate their activity (Luo, et al., 2021; X. Luo, et al., 2019; Oggero, et al., 2022). In addition to pathological pain, macrophages also play a role in physiological pain. Dermal macrophages were shown to regulate baseline pain sensitivity by modulating the production of nerve growth factor, which is required for setting normal pain sensitivity (Tanaka, et al., 2023).

Recent studies indicate that macrophages also regulate the resolution of inflammatory and neuropathic pain following inflammation and nerve injury. One study demonstrated that macrophages from the spinal cord of sham surgery animals had increased expression of the anti-inflammatory mediator CD163 and alleviated nociceptive hypersensitivity via the cytokine IL-10, compared to macrophages from animals with nerve injury. Furthermore, neuropathic pain symptoms (mechanical hypersensitivity) could be reversed by increasing macrophage CD163 expression (Niehaus, Taylor-Blake, Loo, Simon, & Zylka, 2021).

GPR37 was recently implicated as a potential receptor for neuroprotectin D1 (NPD1), a SPM derived from fish oil. GPR37 in macrophages contributes to the resolution of

inflammatory pain and infection-induced pain (Q. Zhang, Bang, Chandra, & Ji, 2022). In GPR37 knockout mice, macrophages have deficits in phagocytic activity, a major function of macrophages for the resolution of inflammation. GPR37-deficient macrophages also displayed dysregulations of pro- or anti-inflammatory cytokines, switching to the pro-inflammatory M1 phenotype and delaying the resolution of zymosan-induced inflammatory pain (Bang, et al., 2018). A partial depletion of dermal macrophages delayed the resolution of zymosan-induced inflammatory pain, and conversely, adoptive transfer of wild-type macrophages facilitated inflammatory pain resolution (Bang, et al., 2018). Intriguingly, the anti-malarial drug artesunate can act as a ligand of GPR37. Activation of GPR37 by artesunate enhanced the resolution of bacterial infection-induced pain. Adoptive transfer of macrophages primed with GPR37 activators could protect against infections induced by listeria and parasites, providing a new mechanism of action of artesunate as an immunotherapy (Bang, et al., 2021; Q. Zhang, et al., 2022). Thus, specific targeting of macrophage-bound GPR37 with its agonists may serve as an immunotherapy to control pain and other inflammatory disorders (Figure 3).

Recent research efforts also point to mitochondrial transfer from macrophages and neurons as a novel mechanism for pain resolution. Inflammation impairs mitochondrial function in neurons. Notably, M2-like macrophages infiltrate the DRG during the resolution phase of inflammatory pain resolution. This infiltration in the resolution phase is correlated with sensory neuron's recovery of mitochondrial function (e.g., oxidative phosphorylation). Mechanistically, the resolution of inflammatory pain by mitochondrial transfer requires the expression of CD200 receptor by macrophages and CD200R-ligand iSec1 by sensory neurons (van der Vlist, et al., 2022).

5.2 T cells in the development and resolution of pain

Early studies evaluated the pronociceptive roles of T cells by comparing pain behaviors between wild-type mice and mice with different types of T cell deficiencies, including *Rag1*$^{-/-}$, *Rag2*$^{-/-}$, nude and SCID mice. Notably, there is no significant difference in baseline pain sensitivity between wild type and T cell-deficient mice (Cao & DeLeo, 2008; Luo, et al., 2021). In neuropathic pain models, T cells infiltrated the nervous system after nerve injury, mainly in damaged nerves and DRGs, and some in spinal cord, contributing to neuropathic pain (Costigan, Moss, et al., 2009; Singh, et al., 2022; Sorge, et al., 2015). It was also found that T cell ablation in nerve injury models resulted in reduced neuropathic pain symptoms (e.g., mechanical allodynia) (Costigan, Moss, et al., 2009; Kleinschnitz, et al., 2006). Mice lacking T cells (*Rag1*$^{-/-}$ or *Rag2*$^{-/-}$ KO mice) exhibited deficits in the development of neuropathic pain (Cao & DeLeo, 2008). In contrast, depletion of Foxp3^{+} Treg cells promotes neuropathic pain hypersensitivity, partially by increasing the concentration of RANTES, IL-2 and IL-5, and significant decreasing IL-12 and IFN-γ (Lees, Duffy, Perera, & Moalem-Taylor, 2015).

T cells have also been shown to regulate the resolution of chronic pain (Kavelaars & Heijnen, 2021). In paclitaxel or cisplatin-induced CIPN models, *Rag1*$^{-/-}$ or *Rag2*$^{-/-}$ mice developed neuropathic pain like wild-type mice, however, the resolution of neuropathic pain was prolonged in these T cell deficient mice. Importantly, reconstitution of CD8^{+} T

cells was sufficient to resolve pain in these T cell-deficient CIPN mice by secretion of IL-10 (Krukowski, et al., 2016; Singh, et al., 2022) (Figure 3). A similar mechanism also applies to inflammatory pain, and the severity of complete Freund's adjuvant (CFA)-induced mechanical allodynia was identical in wild-type and T cell-deficient mice, but the recovery of inflammatory pain was impaired in mutant mice (Laumet, Edralin, Dantzer, Heijnen, & Kavelaars, 2019; Petrovic, et al., 2019). Adoptive transfer of $CD8^+$ T cells was shown to resolve neuropathic pain after chemotherapy (Kavelaars & Heijnen, 2021). Adoptive transfer of regulatory T cells (Tregs) via intrathecal administration alleviated neuropathic pain in mice (X. J. Liu, et al., 2014). One clinical study revealed that transfusion of immune cells in patients with advanced cancer is associated with reduced opioid consumption and pain intensity due to the activation of $CD4^+$ T lymphocytes and increased production of endogenous opioids (X. Zhou, et al., 2020). Finally, in the recent human genome-wide association study, partitioned heritability identified enrichment for B and T cells specific genes that are associated with chronic postoperative pain (Parisien, et al., 2023). In both the plantar incision and the laparotomy mouse models, the prolonged duration of mechanical allodynia in *Rag1*$^{-/-}$ mice compared to wild-type mice was observed. Adoptive transfer of T cells did not significantly affect the time course of mechanical allodynia in *Rag1*$^{-/-}$ mice, however, B cell supplementation, or combined B and T supplementation, significantly shortened the duration of post-surgery allodynia (Parisien, et al., 2023).

5.3 Neutrophils in the development and resolution of pain.

Neutrophils make up the majority (~60%) of white blood cells in human and act as the body's first line of defense to eliminate infections by bacteria and fungi. During tissue injury and inflammation, neutrophils are the first responders, and neutrophil infiltration serves as a cardinal sign of acute inflammation. Following zymosan-induced inflammation, neutrophils were found to be accumulated in inflamed hind paw within hours (Bang, et al., 2018). Neutrophils contribute to the development of inflammatory, postoperative, and neuropathic pain (Ghasemlou, Chiu, Julien, & Woolf, 2015). Plantar incision causes CXCL1 upregulation leading to neutrophil accumulation and postoperative pain via activation of CXCR1/2 receptor. Additionally, depletion of neutrophils reduced immediate postsurgical pain in mice (Carreira, et al., 2013). Neutrophils release multiple pro-nociceptive enzymes, such as elastase, and inhibition of leuckocyte elastase was found to reduce neuropathic pain in rodents (Bali & Kuner, 2017). Interestingly, it was found that mice that are protected from neuropathic pain express SerpinA3N, a serine protease inhibitor secreted in response to nerve damage by DRG neurons that counteracts the induction of neuropathic pain (Vicuna, et al., 2015).

Recent research also demonstrated a critical role of neutrophils in the resolution of acute pain and prevention of pain chronification. Depletion of neutrophils delayed the resolution of CFA-induced inflammatory pain, and this inflammatory pain can further be extended for several months in animals treated with steroids (dexamethasone for 6 days) or nonsteroidal anti-inflammatory drugs (NSAIDs) at the acute pain stage. Conversely, adoptive transfer of neutrophils is sufficient to confer protection against the development of steroid-induced chronic pain in the CFA model (Parisien, et al., 2022). Mechanistically, neutrophils resolve pain by secretion of S100A8/A9 proteins. These are Ca^{2+} binding proteins of the S100

family and participate in inflammatory process (Figure 3). Finally, in patients with low back pain, transient upregulations of neutrophil-driven inflammatory responses is protective against the transition to chronic pain (Parisien, et al., 2022). Conversely, the adoptive transfer of neutrophils but not other blood cells from fibromyalgia patients created a state of prolonged hyperalgesia in naïve mice (Caxaria, et al., 2023), suggesting that neutrophils can be both beneficial and detrimental.

5.4. Mesenchymal stem cells (MSCs) in the resolution of pain

Regenerative pain medicine uses the body's own recovery mechanisms to heal pain (Buchheit, Huh, Maixner, Cheng, & Ji, 2020). Mesenchymal stem cells, also known as mesenchymal stromal cells (MSCs) or bone marrow stem cells (BMSCs) are present in nearly all organs in the perivascular space and are most prominent in the bone marrow with their ability to differentiate into other mesodermal cells, including cartilage, fat, muscle, and bone cells. Studies from many laboratory studies have shown analgesic efficacy of MSCs in different animal models of pain (Huh, Ji, & Chen, 2017). However, there is not clear evidence of tissue regeneration after MSC treatment. Instead, several lines of evidence indicate that MSCs resolve pain via neuroimmune modulation (Buchheit, et al., 2020).

Systemic or local injection of rat MSCs were shown to reverse long-lasting inflammatory pain in rats following a tendon injury (W. Guo, et al., 2011). This effect appears to depend on endogenous opioid production, as the opioid receptor antagonist naloxone can block the analgesia by MSCs in injured rats. Moreover, the same group found that the activation of monocytes is required for the analgesic actions of MSCs (W. Guo, et al., 2017). It was also found that a single intrathecal injection via lumbar puncture of 250,000 BMSCs resulted in long-term relief of neuropathic pain (mechanical allodynia and heat hyperalgesia) for more than six weeks in mouse models of neuropathic pain after nerve injury (G. Chen, Park, Xie, & Ji, 2015). Further analysis revealed migration of the intrathecally injected BMSCs to DRG and the spinal cord meninges, which are the membranes that cover the spinal cord and part of DRG and containing cerebrospinal fluid (CSF), via chemotaxic signaling mediated by the CXCL12/CXCR4 axis (G. Chen, et al., 2015). Importantly, BMSCs secrete the anti-inflammatory cytokine TGF-β1 to exert the antinociceptive actions in animal models of neuropathic pain. Intrathecal BMSCs potently reduced nerve injury-induced neuroinflammation in the spinal cord, by inhibiting the activation of microglia and astrocytes and the production of inflammatory cytokines and chemokines (G. Chen, et al., 2015) (Figure 3). MSC treatment also reversed anti-nociceptive tolerance and hyperalgesia induced by chronic opioid exposure (Hua, et al., 2016). Intra-articular injections of autologous MSCs alleviated pain in patients with osteoarthritis (Harrell, Markovic, Fellabaum, Arsenijevic, & Volarevic, 2019). Therefore, MSC transplantation has great potential to resolve chronic pain in patients as an immunotherapy.

6. Time-dependent contribution of immune pathways to pain states

The contribution of inflammatory response to chronic pain progression or resolution appears to be a complex process involving multiple cell types and pathways. In normal pain resolution process, these components act concordantly in a time-dependent manner

(Figure 4, “Resolved pain” trajectory). Strong acute inflammatory response appears to be necessary to launch subsequent reparative steps leading to pain resolution in these patients (Parisien, et al., 2022). This inflammatory response coincides with neutrophil and monocyte activation. In such patients, acute inflammatory response is followed by significant decrease of inflammation and pain resolution over time. In other patients (Figure 4, “Persistent pain” trajectory), the absence of strong acute inflammatory response leads to persistent low-grade inflammation which continues to maintain chronic pain. This persistent pain group is always present with a low-grade inflammatory state characteristic of chronic painful conditions.

This conceptual model implies the important role of acute inflammation phase and subsequent anti-inflammatory processes in chronic pain resolution. Immune therapy strategies should be tailored to facilitate the recovery process depending on the phase of inflammation. Reducing inflammation too early may delay pain resolution.

7. Conclusions and future directions

Immunotherapy is recognized as a recent medical breakthrough in cancer therapy and has been awarded a Nobel Prize in Physiology or Medicine (James Allison and Tasuku Honjo, 2018). Mounting evidence also highlights emerging immunotherapies in treating autoimmune and neurodegenerative diseases, including chronic pain. The mechanisms underlying the induction and resolution of acute and chronic pain are complex and context-dependent. Thus, the potential of immunotherapy for pain management should address the multi-faceted mechanisms of chronic pain (Junli Zhao, Roberts, Huh, & Ji, 2023). Both agonists and antagonists (e.g. PD-L1/PD-1 and STING) could be beneficial if we can identify specific pain conditions and time window of the treatment. Control of abnormal inflammation in patients with autoimmune conditions could be achieved by monoclonal antibodies targeting pro-inflammatory cytokines (Table 1). However, immune suppression by steroid and anti-inflammatory treatments can delay the resolution process for inflammation and pain (Parisien, et al., 2022). Some chronic pain may be associated with immune suppression, and immune activation may promote the resolution of pain. Immune activation could also be achieved by cell therapies, such as mesenchymal stromal cells, macrophages, and T cells, as well as cell-free blood products (Buchheit, et al., 2020; 2023; W. B. S Zhou, et al., 2023). Given the current crises of chronic pain and opioid use disorders (Volkow & Collins, 2017), ongoing and future research in connecting immunotherapy and pain and targeting neuroimmune interactions will hold great promise in the management and final resolution of chronic pain.

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Abbreviations

BMSC	bone marrow stromal/stem cells
CCL2	(C-C motif) ligand 2

CFA	complete Freund's adjuvant
cGAMP	cyclic GMP-AMP
cGAS	cyclic GMP-AMP synthase
CIPN	chemotherapy-induced peripheral neuropathy
CRPS	complex regional pain syndrome
CNS	central nervous system
CTLA-4	cytotoxic t-lymphocyte antigen-4
CSF	cerebrospinal fluid
DRG	dorsal root ganglia
ER	endoplasmic reticulum
ERK	extracellular-signal regulated kinases
GM-CSF	granulocyte-macrophage colony-stimulating factor
IFN-I	type-I interferon
IFN-α	interleukin-1 alpha
IFN-β	interleukin-1 beta
IFNAR1	interferon alpha and beta receptor subunit 1
IL-1β	interleukin-1 beta
IL-4	interleukin 4
IL-6	interleukin-6
IL-10	interleukin 10
IL-12	interleukin 12
IL-17	interleukin-17
ITIM	immune receptor tyrosine-based inhibitory motif
ITSM	immunoreceptor tyrosine-based switch motif
LAG-3	lymphocyte-activation gene 3
JAK	Janus kinase (JAK)
JNK	c-Jun N-terminal kinase
KO	knockout
MAPK	mitogen-activated protein kinase

MOR	mu opioid receptor
MSC	mesenchymal stem cells
NPD1	neuroprotectin D1
PD-1	programed death protein 1
PD-L1	programed death protein ligand 1
PKA	protein kinase A
PKC	protein kinase C
PNS	peripheral nervous system
sEPSC	spontaneous excitatory postsynaptic currents
SHP-1/2	Src homology region 2 domain-containing phosphatase-1/2
sIL-6R	soluble form of the IL-6 receptor
SNI	spared nerve injury
SPM	specialized pro-resolving mediator
STAT	signal transducer and activator of transcription
STING	stimulator of interferon gene
TBK1	TANK-binding kinase 1
TCR	T cell receptors
TG	trigeminal ganglia
TGF-β	transforming growth factor beta
TMEM173	transmembrane protein 173
TNF-α	tumor necrosis factor alpha
TRPA1	transient receptor potential ion channel subtype A1
TRPV1	transient receptor potential ion channel subtype V1

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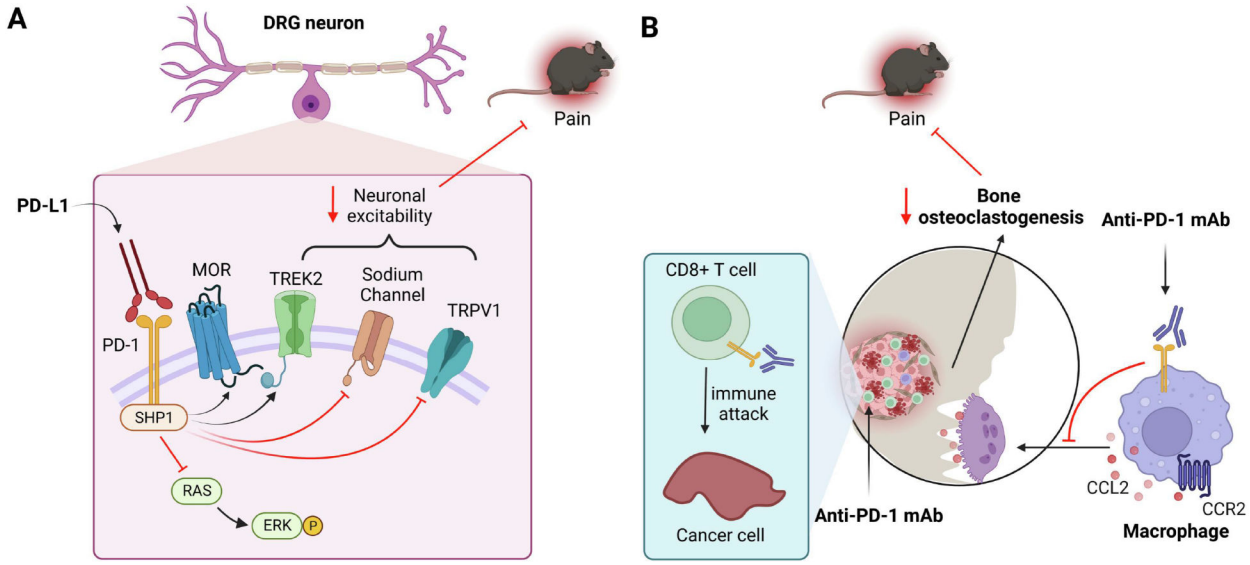

Figure 1. Immunotherapy targeting the PD-L1/PD-1 pathway in chronic pain through neuronal and immune modulation.

(A) Neuronal modulation: Activation of PD-1 in DRG sensory neurons by PD-L1 causes phosphorylation of SHP-1, leading to the activation of mu opioid receptor (MOR) and potassium channel TREK2 and inactivation of sodium channels (e.g. Nav1.7) and TRPV1. SHP-1 activation also inhibits ERK phosphorylation. Through the PD-1/SHP1-mediated signaling, PD-L1 potently inhibits physiological and pathological pain. (B) Immune modulation: In bone cancer pain, activation of PD-1 by PD-L1 on osteoclasts can promote osteoclastogenesis in cancer-bearing bone marrow, leading to CCL2 secretion and CCR2 activation on osteoclasts and nociceptors. Anti-PD-1 treatment with nivolumab inhibits bone cancer pain through suppression of osteoclastogenesis and bone destruction and reduced CCR2 signaling in nociceptors.

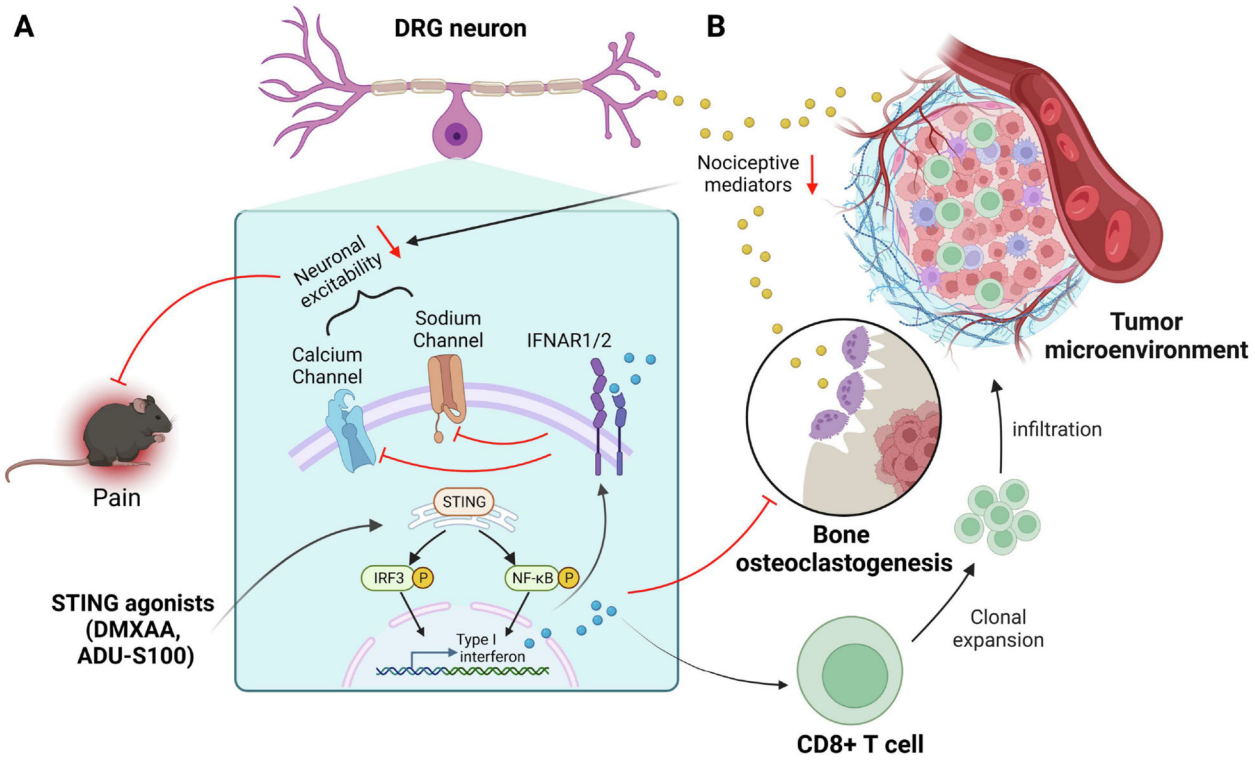

Figure 2. Immunotherapy targeting the STING pathway in chronic pain through neuronal and immune modulation.

(A) Neuronal modulation: Activation of the STING pathway by STING agonists DMXAA and ADU-S100 in DRG neurons and non-neuronal cells result in the production of Type I interferons (IFN-I, IFN-α/β). IFN-I activates its receptor IFNAR1/2 on sensory neurons to suppress the activity of calcium channels and sodium channels, leading to decreased neuronal excitability and pain. (B) Immune modulation: In bone cancer pain, IFN-α/β can also act on osteoclasts to suppress osteoclastogenesis. Treatment with STING agonists inhibits bone cancer pain through suppression of osteoclastogenesis and bone destruction, as well as activation of $CD8^+$ T cells to reduce cancer burden.

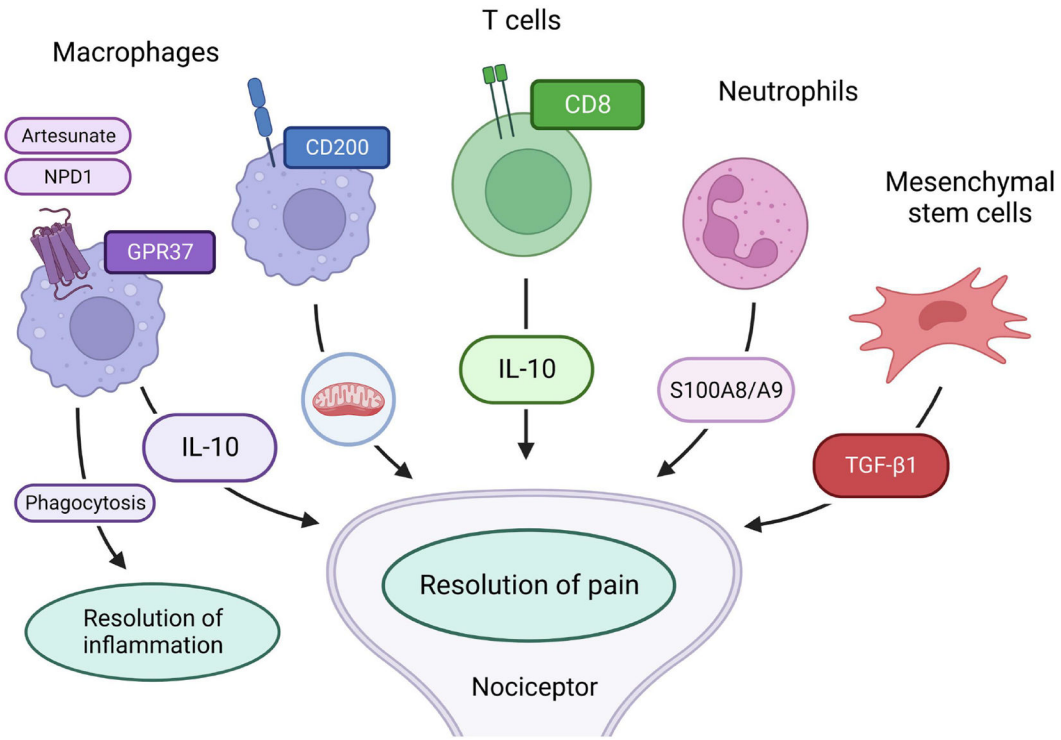

Figure 3. Cell-based immunotherapies for the resolution of chronic pain.

Adoptive transfer of GPR37^{+} macrophages, CD8^{+} T cells, neutrophils, and mesenchymal stem/stromal cells can promote pain resolution via interactions with nociceptor through secretion of anti-inflammatory and anti-nociceptive mediators such as IL-10, TGF-β1, and S100A8/A9 or mitochondria transfer. Activation of macrophage GPR37 by neuroprotectin D1 (NPD1) or artisunate, an anti-malaria, can enhance macrophage phagocytosis of cell debris and pathogens to promote the resolution of inflammation and pain.

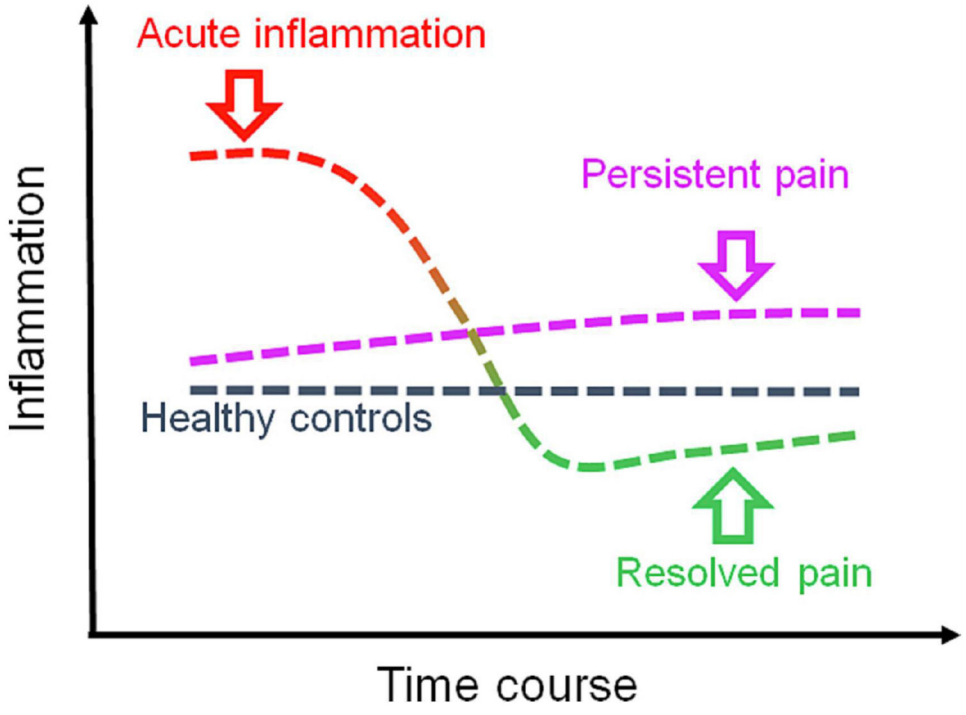

Figure 4. Conceptual model of chronic pain resolution following acute inflammation.

The overall dynamics of the inflammatory response is critical for pain resolution, but this inflammatory response is not a simple increase or decrease over the disease progression. After transitory pain period, pain in some patients resolves, the “Resolved pain” group (red-to-green line), whereas for others the pain persists, the “persistent pain” group (purple line). During the first phase, the inflammatory response in the resolved pain group is stronger than that in the persistent pain group. Over time, the inflammatory response substantially lessened in patients with resolved pain.

Table 1.

Overview of immunotherapies targeting pro-inflammatory cytokines in chronic pain related conditions.

Cytokine	Principle	Immunotherapy	Chronic pain conditions	Pain related positive and negative outcomes	References
TNF-α	Anti-TNF-α	Infliximab Adalimumab Golimumab Certolizumab-pegol Etanercept Ozoralizumab	Rheumatoid arthritis; Psoriatic arthritis; Ankylosing spondylitis;	Certolizumab-pegol treatment (12 weeks) reduced pain VAS score in psoriatic arthritis patients. Ozoralizumab treatment (24 weeks) reduced pain in VAS score in rheumatoid arthritis patients.	(Esposito, et al., 2020; Gholami, Azizpoor, Aflaki, Rezaee, & Keshavarz, 2021; Oldfield & Plosker, 2009; Takeuchi, Kawanishi, Nakanishi, Yamasaki, & Tanaka, 2022)
IL-1β	Anti-IL-1β	Canakinumab	Rheumatoid arthritis; Systemic juvenile idiopathic arthritis; Recurrent Pericarditis; Traumatic brain injury/stroke; Covid-19;	In the withdrawal phase of canakinumab treatment (32 weeks), serious adverse arm pain occurred in 1 patient with systemic juvenile idiopathic arthritis out of 50 patients. Anakinra treatment (24 weeks) improved rheumatoid arthritis pain symptom. Rilonacept treatment (6 weeks) in recurrent pericarditis patients reduced average pericarditis pain.	(Fava, et al., 2022; Helmy, et al., 2014; Kyriazopoulou, et al., 2021; Maniscalco, et al., 2020; Orrock & Ilowite, 2016)
	Anti-IL-1R	Anakinra Rilonacept			
IL-6	Anti-IL-6	Siltuximab Clazakizumab Olokizumab Sirukumab	Psoriatic arthritis; Rheumatoid arthritis; Juvenile idiopathic arthritis; Giant cell arteritis; Covid-19;	Tocilizumab treatment (24-52 weeks) improved pain VAS score in rheumatoid arthritis patients. Sarilumab treatment (2-52 weeks) showed improvements in pain VAS score in rheumatoid arthritis patients.	(Mease, et al., 2016; Tanaka, Narazaki, & Kishimoto, 2018; Vaidya, et al., 2020)
	Anti-IL-6R	Tocilizumab Sarilumab			
IL-17	Anti-IL-17A	Secukinumab Ixekizumab	Psoriatic arthritis; Ankylosing Spondylitis;	Secukinumab treatment (12-52 weeks) in patients with psoriatic arthritis showed greater improvements in the axial specific assessment of spinal pain.	(Baeten, et al., 2015; J. X. Huang, Lee, & Wei, 2020; Langley, et al., 2014; Lespessailles & Toumi, 2021)
GM-CSF	Anti-GM-CSF	Namilumab Otilimab	Rheumatoid arthritis; Psoriasis; Giant cell arteritis; Covid-19;	Namilumab treatment (12-16 weeks) in rheumatoid arthritis patients had improvements inpatient's assessment of pain. Mavrilimumab treatment caused non-specific headache and neck pain in patients with giant cell arteritis.	(Crotti, Agape, Becciolini, Biggioggero, & Favalli, 2019) (Pourhoseingholi, Shojaee, & Ashtari, 2020)
	Anti-GM-CSFR	Mavrilimumab			

Table 2.

Overview of immunotherapy targeting the PD-L1/PD-1 pathway in pain.

Pain conditions and treatments	Species	Effects	Mechanisms	References
Neuropathic pain *PD-L1*	Mouse	Reduces pain	Reduce DRG neurons excitability and EPSC in spinal cord neurons	(G. Chen, et al., 2017)
Neuropathic pain *Anti-PD-L1*	Mouse	Increases pain	Incudes higher expression of TNF-α, IL-6, and CX3CR1 in peripheral nervous tissue	(Wanderley, et al., 2022)
Neuropathic pain *PD-1 peptide agonist*	Mouse	Reduces pain	Suppresses neuronal excitability in DRGs	(L. Zhao, et al., 2022)
Neuropathic pain *Loss of PD-L1 in KO*	Mouse	Increases pain	Increases TNFα and MCP-1 levels in sciatic nerve	(Uceyler, et al., 2010b)
Inflammatory pain *PD-L1*	Mouse	Reduces pain	Reduces DRG neurons excitability and EPSC in spinal cord neurons	(G. Chen, et al., 2017)
Inflammatory pain *PD-L1*	Rat	Reduces pain	EA upregulates PD-L1 expression in peptidergic DRG neurons	(Deng, et al., 2023)
Inflammatory pain *Anti-PD-1/PD-L1*	Rat	Increases pain	Increases IL-6 and iNOS levels in DRG	(Deng, et al., 2023)
Inflammatory pain *PD-1 peptide agonist*	Mouse	Reduces pain	Suppresses neuronal excitability in DRG	(L. Zhao, et al., 2022)
Migraine *PD-1 inhibitor*	Mouse	Increases pain	Upregulates CGRP, IL-1β, TNF-α, IL-6 and IL-18 in TG	(Shi, et al., 2020)
Maternal pain *PD-L1*	Mouse	Prevents pain	Increased PD-L1 level in late pregnancy and decreased PD-L1 level after delivery	(H. Tan, et al., 2021)
Bone cancer pain *PD-L1*	Rat	Reduces pain	Reduces DRG neurons excitability and EPSC in spinal cord neurons	(G. Chen, et al., 2017)
Bone cancer pain *PD-L1*	Mouse	Reduces pain	Downregulate TRPV1 in DRG neurons and decreases neuronal excitability	(B. L. Liu, et al., 2020)
Melanoma cancer pain *Anti-PD-1/PD-L1*	Mouse	Unmasks pain	Increases spontaneous discharges in nerve fibers and induce spontaneous pain	(G. Chen, et al., 2017)
Bone cancer pain *Anti-PD-1*	Mouse	Reduces pain	Suppresses osteoclastogenesis and protects against bone destruction and bone fracture	(K. Wang, et al., 2020)
Knee osteoarthritis PD-1	Human	Unknown	Exercise relieves knee pain and increases serum PD-1	(J. Liu, et al., 2019)
Enterocolitis *Anti-PD-1*	Human	Induces pain	Increases abdominal pain	(Kurokawa, et al., 2021)
Epididymo-orchitis *Anti-PD-1*	Human	Induces headache	Amplifies the inflammatory manifestations	(Quach, et al., 2019)