# Chapter 9
# Immunotherapy and Pain


**Junli Zhao, Alexus Roberts, Yul Huh, and Ru-Rong Ji**

**Abstract** Immunotherapy was initially developed as a method to treat cancer through the use of the host's immune system. Now, immunotherapy is used as a treatment for a wide variety of diseases. The connection between the nervous system and the immune system in chronic pain and neurological disease has given a new facet to immunotherapy research. This chapter provides an overview of the most common forms of immunotherapy and the emerging potential of immunotherapy in the treatment and management of various neurological diseases, including brain tumors, Alzheimer's disease, multiple sclerosis, stroke, spinal cord injury, and pain. We will particularly highlight pain-related immunotherapy mechanisms that target the programmed cell death protein 1 (PD-1) and stimulator of interferon gene (STING) pathways, as well as cytokine pathways, immune cell ablation, and adoptive cell transfer.

**Keywords** Adoptive cell transfer · Bone cancer pain · Cytokines · PD-1 · PD-L1 · Immune checkpoint inhibitor · Immune cell ablation · Immunotherapy · Macrophages · Osteoclast · type-I interferons

## 9.1 Introduction

Immunotherapy is often perceived to be a relatively recent medical advancement despite its historical background across several cultures. The prevalence of disease in human populations has been a problem across time and efforts to prevent various diseases emerged early in human history. One of the first recorded instances of a possible immunotherapy treatment occurred in the third century BC China, during the Qin dynasty, where inoculation with the variola minor virus prevented smallpox

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infection (Decker et al. 2017; Dobosz and Dzieciatkowski 2019). This chapter will cover modern advancements in immunotherapy, with a particular focus on cancer treatment research from the initial studies through to the discovery of cancer immunotherapy by James P. Allison and Tasuku Honjo, who were awarded the Nobel Prize in 2018 (Fig. 9.1).

"Immunotherapy" as a term encompasses a wide variety of methods and therapies, including cytokines, vaccines, oncolytic viruses, adoptive cell therapy, and antibody-based immunotherapy. Cytokines are small proteins produced and secreted by immune cells and are essential for immune cell signaling. Cytokines were initially recognized as systemic soluble factors that regulate lymphocyte function and inflammatory responses and were recognized as "non-specific immunotherapies" (Berraondo et al. 2019). The first cytokine type I interferon (IFN) was discovered in 1957 (Isaacs and Lindenmann 1957). The FDA approved the use of type I interferon

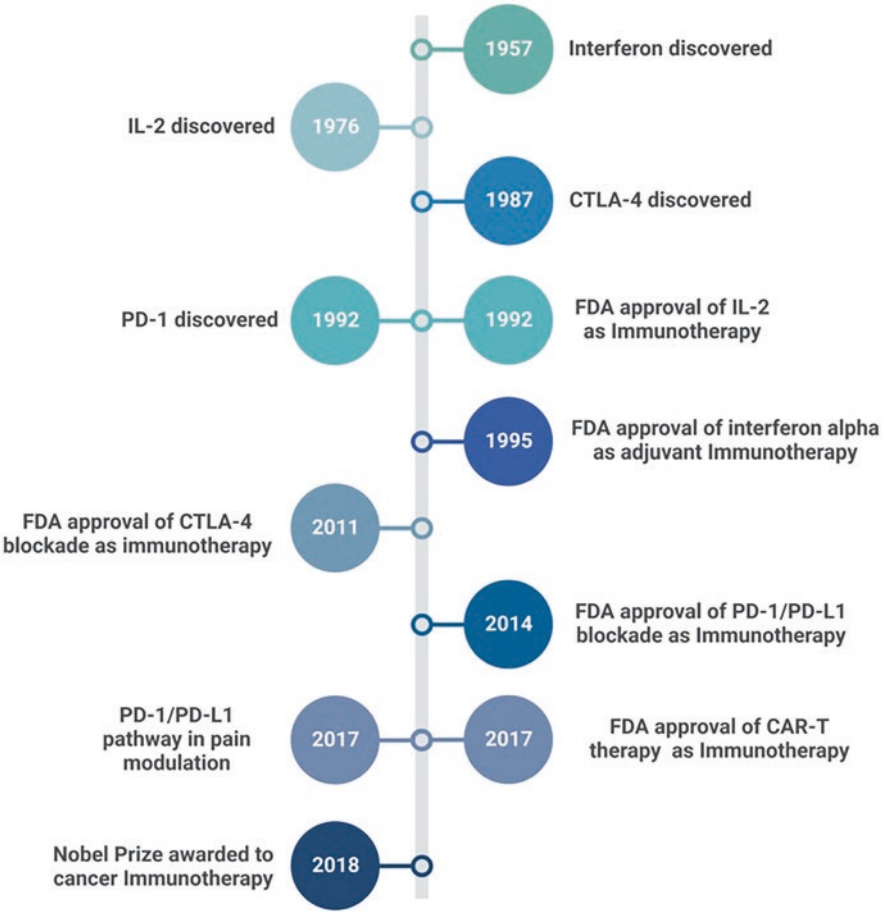


**Fig. 9.1** Timeline for major events leading to the development of immunotherapy

as an adjuvant immunotherapy in 1995. The T-cell growth factor interleukin 2 (IL-2) was discovered in 1976. IL-2 is a key cytokine with pleiotropic effects on the immune system and is considered as an immunostimulatory cytokine (Morgan et al. 1976). The discovery of IL-2 revolutionized the fields of basic immunology, immunotherapy for human cancers since IL-2 was an early candidate for cancer immunotherapy, and FDA approved it for the treatment of metastatic renal cell carcinoma in 1992 and metastatic melanoma in 1998. In addition to these two cytokines, other pro-inflammatory cytokines including IL-1β and tumor necrosis factor α (TNFα) and anti-inflammatory cytokines such as IL-10 and IL-6 have also been used in immunotherapy.

Antibodies to immune checkpoint molecules have become the most promising form of immunotherapy for the treatment of cancer due to their low toxicity profile and the ease by which they can be prepared and administered to patients. The first immune checkpoint molecule cytotoxic T-lymphocyte antigen number 4 (CTLA-4) was discovered in 1987 (Brunet et al. 1987). The function of CTLA-4 as a crucial immune checkpoint and target for anticancer therapy was discovered in 1995, after which the first anti-CTLA-4 antibody was immediately developed and tested in animal models in 1996 (Krummel and Allison 1995; Leach et al. 1996). The first checkpoint inhibitor used in cancer patients was ipilimumab, which was approved by the FDA in 2011 for the advanced melanoma treatment. Another very notable immune checkpoint molecule is programmed cell death protein 1 (PD-1), which was discovered by Dr. Tasuku Honjo's group at Kyoto University in 1992 (Ishida et al. 1992). After many clinical trials, the FDA approved the first anti-PD-1 inhibitor, nivolumab, in 2014.

Even though immunotherapy is primarily known as a cancer treatment, it has significant potential for the treatment of a variety of additional diseases and conditions (Fig. 9.2). This potential has become the focus of immunotherapy research. The role of the immune system in chronic and neuropathic pain has been well-documented in the literature, but the implications of these findings are still being studied. Significant pain augmentation or reduction immunotherapy regimens have been demonstrated across numerous molecular mechanisms, including immune checkpoint blockade, adoptive immunotherapy, and various cytokines. These examples illustrate the breadth of research topics within immunotherapy, which is bound to expand further. Notably, many immunotherapy treatments have not been studied in the context of pain management. Thus, future research efforts hold great promise for the development of novel immunotherapy-based clinical treatments for chronic pain.

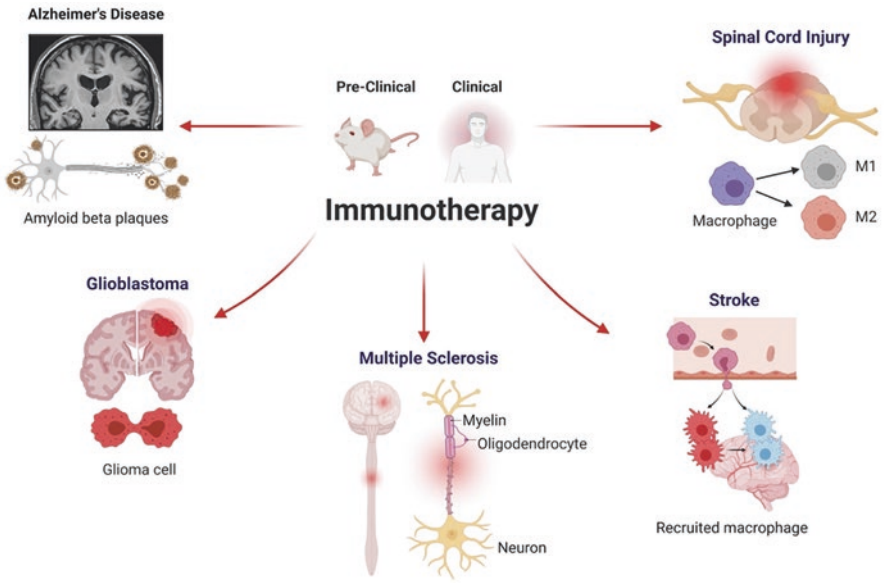


**Fig. 9.2** Immunotherapy in CNS diseases. Immunotherapy is widely used in various CNS disorders in both animal models and patients, including Alzheimer's disease, glioblastoma, multiple sclerosis, stroke, and spinal cord injury

## 9.2 Immunotherapy for Neurological Disease

### *9.2.1 Immunotherapy in Brain Tumors and Brain Metastases*

Gliomas are the most common type of primary brain tumors and are categorized based on their cell of origin, which can include astrocytes, oligodendrocytes, and ependymal cells (Gladson et al. 2010). Gliomas are further graded from grade I to IV based on the malignancy of the tumor as determined by WHO guidelines (Louis et al. 2016). Glioblastoma multiforme (GBM) has been a central focus of current research efforts due to its aggressive nature, high lethality, and the fact that it is the most common malignant brain tumor diagnosed in adults. GBM is a grade IV glioma that forms from astrocytes, which are a type of glial cell found in the central nervous system.

Recent research into treating GBM has focused primarily on immune checkpoint blockade, in which anti-PD-1 therapy induces a pro-inflammatory environment to increase the infiltration of immune cells into the tumor (Wang et al. 2021b). However, clinical studies have yet to show consistent and efficient results from treatment due to challenges posed by the nature of GBM tumors. The main complication of GBM treatment is the blood-brain barrier (BBB) which prevents the successful trafficking of anti-PD-1 drugs to the tumor site, and recent research has focused on methods to overcome the obstruction posed by the BBB through the use

of peptide shuttles (Cavaco et al. 2020). Additionally, the immunosuppressive microenvironment of GBM tumors poses another hurdle for anti-PD-1 therapy, which likely contributes to the inconsistent outcomes of clinical studies (Sampson et al. 2020).

Chimeric antigen receptor-T, or CAR-T, cell immunotherapy is a form of adoptive immunotherapy that takes T-cells from patients and modifies them to add the chimeric antigen receptor, which allows these engineered T-cells to bind to and attack cancer cells (Sterner and Sterner 2021). This form of immunotherapy has successfully treated blood cancers and is currently being explored as a potential treatment for GBM. Although clinical studies have shown promising results, complications remain when treating solid tumors, with particular concerns about T-cell trafficking, tumor infiltration, and the immunosuppressive microenvironment of GBM tumors.

### *9.2.2 Immunotherapy in Alzheimer's Disease*

Alzheimer's disease (AD) is a common neurodegenerative disease primarily found in older individuals, and it is the most common cause of dementia worldwide. The clinical symptoms of AD include a decline in cognitive abilities in two or more areas, such as memory, language, and behavior. The cellular mechanisms of this disorder have been a central focus of research, with two mechanisms garnering the most interest, namely, the extracellular accumulation of β-amyloid (Aβ) plaques and the formation of neurofibrillary tangles, which are composed of hyperphosphorylated tau proteins (Weller and Budson 2018). The Aβ plaques have been studied extensively as a potential point of intervention for treatments under development.

The PD-1/PD-L1 pathway has been an area of interest in Alzheimer's research, though studies have shown mixed results. Alzheimer's patients have been observed to have lower expression of PD-1 on T-cells and lower expression of PD-L1 on monocytes and macrophages. These findings indicate the clinical significance of the PD-1/PD-L1 pathway in the development of Alzheimer's disease (Saresella et al. 2012).

The efficacy of anti-PD-1 treatments in the reduction of AD symptoms and pathology has been well demonstrated with the mechanisms of action well-documented. In a study published by Rosenzweig et al. and supported by additional studies by Baruch et al., anti-PD-1 treatment was found to improve memory and led to increased Aβ plaque clearance (Baruch et al. 2016; Rosenzweig et al. 2019). PD-1/PD-L1 blockade boosts immune cell activity with the mobilization of monocyte-derived macrophages to the brain, which results in the reduction of Aβ plaque loads.

PD-1 signaling has also been associated with the production of IL-10, which has been found to inhibit inflammatory responses and reduce AD pathology in animal models (Guillot-Sestier et al. 2015; Koronyo-Hamaoui et al. 2009). This indicates that increasing PD-1 expression in AD patients may have a positive effect through re-establishing immune homeostasis.

### 9.2.3 Immunotherapy in Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease of the CNS that is characterized by lesions of the brain and spinal cord due to the degradation of myelin, which is the protective covering of nerves and particularly the axons. The physical symptoms of MS include neuropathic pain, bladder dysfunction, and fatigue, and patients experience episodes that worsen over time. MS is the most common cause of disability in young adults, and its incidence and prevalence are increasing (Dobson and Giovannoni 2019).

Research examining the expression of a wide variety of co-stimulatory molecules in MS patients found a significant increase in cells expressing PD-1 (Trabattoni et al. 2009), which indicated the potential for the treatment of MS through the PD-1/PD-L1 pathway. Animal studies found that anti-PD-1 treatment or deletion of the *Pdcd1* gene worsened MS pathology due to alterations of cytokine expression by T-cells (IFN-γ, IL-17) and B-cells (IL-10), suggesting the possibility of an MS treatment based on the enhancement of PD-1/PD-L1 signaling (Carter et al. 2007; Salama et al. 2003).

The use of interferon beta (IFN-β) to treat relapsing-remitting multiple sclerosis has been for over 20 years and remains an important treatment despite a lack of understanding of its mechanisms (Jakimovski et al. 2018). One mechanism discovered through clinical studies is the apparent suppression of certain pro-inflammatory cytokines, specifically interleukin-17 (IL-17) and interleukin-23 (IL-23) (Kurtuncu et al. 2012).

The STING (stimulator of interferon gene) agonist cGAMP was also reported as a therapy for MS. Studies showed that cGAMP mitigated MS by stimulating type I interferon dependent and independent immune-regulatory pathways. cGAMP induces IL-10 expression in both APCs and $CD4^+$ T-cells in a process that is ERK and CREB dependent. IL-10 induction by cGAMP is primarily IL-27 dependent, and cGAMP induction of IL-10 and IL-27 is crucial for protection against MS (Johnson et al. 2021). Meanwhile, splenic myeloid DCs may be another pivotal cell population that senses ingested DNA and cGAMP to generate robust tolerogenic responses to prevent MS progression in animal models (Lemos et al. 2020).

### 9.2.4 Immunotherapy in Stroke

Stroke is a severe neurological event characterized by a disruption in the flow of blood to the brain, which results in cell death and brain damage. The initial clinical symptoms of stroke include difficulty with speech and speech comprehension, paralysis, numbness, and loss of coordination. In the acute phase of stroke, there is a significant increase in neuroinflammation, which has certain beneficial effects but also significant detrimental effects.

PD-1 is expressed by activated microglia and macrophages after stroke. PD-1 knockout leads to larger brain infarcts and exacerbated neurological deficits. PD-1 expression by B-cells can lead to the inhibition of inflammatory responses of other immune effector cells. B-cells can also produce IL-10 and increase PD-1 expression by T-cells, providing neuroprotection against stroke (Bodhankar et al. 2013; Ren et al. 2011a; Ren et al. 2011b). T regulatory cells could lead to the inhibition of neutrophils through PD-1/PD-L1 signaling and protect the BBB by suppressing the expression of matrix metalloproteinase-9 (MMP-9). Thus, activation of the PD-1/PD-L1 pathway can serve a protective role during a stroke (Qin et al. 2019; Ren et al. 2011a).

Inflammatory processes that occur after the initial onset of the event worsen the negative impacts of a stroke. This suggests that the upregulation of anti-inflammatory cytokines could prove beneficial in decreasing long-term negative effects following a stroke. The connection between expression of anti-inflammatory cytokines and positive stroke outcomes has been the focus of several studies, in which upregulating specific interferons, especially IFN-β, has been shown to reduce neuroinflammation in the brain after stroke. Studies show that systemically administrated IFN-β could attenuate brain infarct progression after stroke (Veldhuis et al. 2003). Immune cells like mast cells, macrophages, and neutrophils from the circulation release the inflammatory cytokines after stroke, including IL-6, IL-4, IL-1β, IL-23p9, and TNFα, which lead to CNS inflammation and result in infarct formation in the brain. IFN-β treatment may suppress these overexpressed inflammatory cytokines and reduce brain infarcts caused by strokes (Inacio et al. 2015; Kuo et al. 2016). Meanwhile, microglia switch from a resting to a reactive state during a stroke, and this change of phenotype leads to the release of inflammatory cytokines. IFN-β treatment may inhibit microglia activation and protect the brain from inflammatory cytokines after stroke (Kuo et al. 2016).

### *9.2.5 Immunotherapy in Spinal Cord Injury*

Spinal cord injury (SCI) is a debilitating condition where significant damage to the spinal cord occurs from a traumatic or nontraumatic injury. Traumatic SCI has a primary and secondary stage of injury. The primary stage includes the physical injury to the spinal cord, and the secondary stage occurs in response to the injury event of the primary stage. This secondary stage response is characterized by inflammation and inflammatory cascades (Zha et al. 2014). The inflammatory response is the stage of SCI that can be addressed and treated with immunotherapy treatment, with anti-PD-1 therapies and IFN-β among the most well researched.

It was found that PD-1 expression is significantly upregulated in chronic SCI, which then impairs T-cell cytokine production. The use of anti-PD-1 therapy could potentially ameliorate these changes and rescue T-cell function in the spinal cord (Zha et al. 2014). PD-1 expression also plays an important role in the modulation of macrophage and microglial phenotypes after SCI. There are two primary

polarization types: the M1 "classically activated" phenotype and the M2 "alternatively activated" phenotype. The M1 phenotype promotes neuroinflammation through an increase in pro-inflammatory cytokines while the M2 phenotype suppresses neuroinflammation and encourages axonal regeneration. Upregulation of PD-1 signaling promotes the M2 phenotype after SCI, which in turn leads to better disease outcomes (Yao et al. 2014).

IFN-β has been reported to have potential therapeutic effects in acute SCI. Administration of IFN-β after SCI reduces myeloperoxidase activity, lipid peroxidation, and expression of inflammatory cytokines (mainly IL-6), with improved motor recovery (Gok et al. 2007; Sandrow-Feinberg et al. 2010). Nishimura et al. engineered neural stem cells (NSC) to constitutively secrete large amounts of IFN-β within the spinal cord injury site (Nishimura et al. 2013). Animals treated with these IFN-β-secreting neural stem cells had a significant reduction in astrocyte proliferation and enhanced preservation of axons, ultimately resulting in improved motor performance after SCI. Thus, IFN-β is beneficial in reducing SCI-related tissue damage and injury.

## 9.3 PD-1-Based Immunotherapy and Pain

### *9.3.1 Immunotherapy Targeting PD-1/PD-L1 in Physiological and Pathological Pain*

Immune checkpoint mechanisms and their blockade are one of the most well-studied immunotherapy treatments. The primary immune checkpoint explored in this chapter is the PD-1/PD-L1 axis, which consists of the cell surface receptor PD-1 and its corresponding ligand PD-L1. This pathway inhibits the function of T-cells, so the disruption or blockade of these pathways leads to a stronger immune response, which has been utilized extensively in cancer treatments. Recent research has demonstrated a strong link between PD-1/PD-L1 axis and acute and chronic pain (Zhao et al. 2021).

"No pain, no gain" is true with anti-PD-1 immunotherapy. PD-1/PD-L1 expression has been shown to inhibit nociceptive neuron excitability, producing significant analgesic effects in both mouse and human studies. Conversely, blocking of the PD-1/PD-L1 pathway activation induces spontaneous pain and hypersensitivity. PD-1/PD-L1 pathway suppresses neuronal excitability in both mouse and human DRG neurons through the modulation of sodium and potassium channels (Chen et al. 2017). Furthermore, PD-1/PD-L1 signaling potentiates the TREK2 potassium channel. These modifications of sodium and potassium channels are regulated by SHP-1, which is activated by PD-L1 in DRG neurons via phosphorylation. Thus, the PD-1/PD-L1 pathway produces antinociception through neuromodulation (Fig. 9.3).

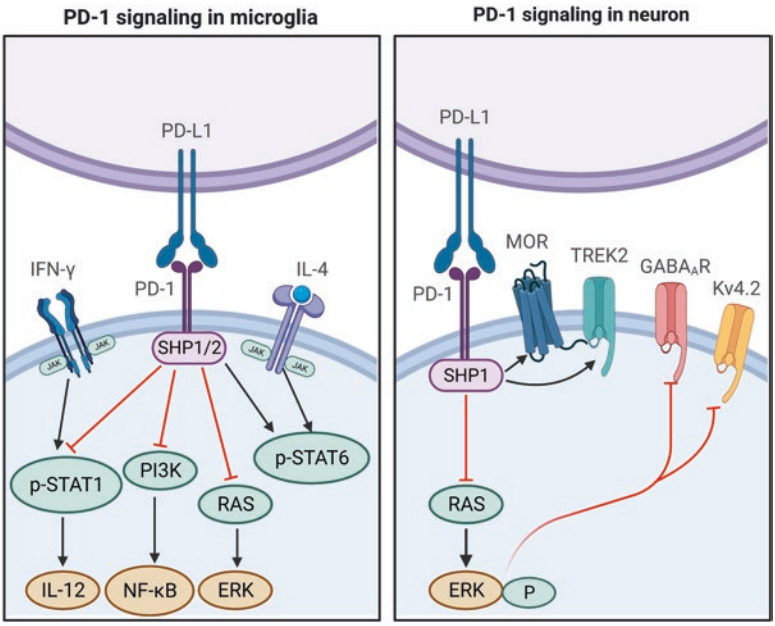


**Fig. 9.3** PD-1 signaling in microglia and neurons. Black arrows indicate positive regulation and red lines with bars represent inhibitory regulation. Abbreviations: $GABA_AR$, gamma-aminobutyric acid A receptor; Kv4.2, potassium voltage-gated channel subfamily D member 2; MOR, mu-opioid receptor; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand; RAS, a small GTPase encoding RAS (retrovirus-associated DNA sequences); SHP, Src homology 2 domain-containing protein tyrosine phosphatases; TREK2, TWIK-related potassium channel-2

### *9.3.2 Immunotherapy Targeting PD-1 in Melanoma*

Immunotherapies targeting PD-1 have revolutionized the clinical treatment of melanoma (Carlino et al. 2021). Given the important role of PD-1/PD-L1 signaling in melanoma, Chen et al. examined the contribution of PD-1/PD-L1 signaling to pain sensitivity in a mouse model of melanoma (Chen et al. 2017). The authors used several approaches, including pharmacological (soluble PD-1), genetic therapy (PD-1 siRNA), and anti-PD-1 antibody (nivolumab) treatments as means to block the PD-1/PD-L1 pathway in a melanoma animal model. The treatments elicited marked spontaneous pain and mechanical allodynia. *In vivo* recordings of mouse sciatic nerve showed that nivolumab treatment significantly increased spontaneous firing of nerve fibers, indicating that anti-PD-1 treatment can unmask pain by increasing the excitability of primary afferent fibers. Even though PD-1 blockade increased pain sensitivity in melanoma-bearing mice, the increased levels of mRNAs encoding T-cell markers (CD2, CD3), a macrophage marker (CD68), and inflammatory cytokine markers (TNF, IL-1β, IL-6, IFN-γ, CCL2) did not change, indicating that blocking PD-1/PD-L1 signaling induces pain via nonimmune modulation in the acute phase (first 3 hours).

### 9.3.3 Immunotherapy Targeting PD-1 in Morphine Analgesia

PD-1 co-localizes with opioid receptors in DRG sensory neurons in mouse and human DRG tissues. PD-1 receptor and opioid receptor interaction modulates the function of opioid receptors in DRG sensory neurons (Wang et al. 2020b). PD-1 knockout or blockade by anti-PD-1 antibody could impair morphine-mediated analgesia in both rodents and nonhuman primates. Morphine could produce antinociception via suppression of calcium currents in DRG neurons and synaptic transmission in the spinal cord, which could be reversed by PD-1 knockout or blockade. Additionally, PD-1 deficiency enhances opioid-induced hyperalgesia, tolerance, and long-term potentiation in the spinal cord.

### 9.3.4 Immunotherapy Targeting PD-1 in Bone Cancer Pain

Bone cancer pain usually results from tumor metastases reaching the bone from late-stage metastatic cancers, which form osteolytic bone lesions and fractures. The evidence of potent effects of anti-PD-1 immunotherapy in reducing metastatic tumors led Wang et al. to investigate whether anti-PD-1 blockade can reduce primary or metastatic bone cancer pain. They used a bone cancer pain animal model that received an inoculation of Lewis lung cancer cells (LLC) into the intramedullary canal of the femur (Wang et al. 2020a). PD-1 knockout mice or WT mice undergoing a PD-1 blockade by repeated administration of anti-PD-1 antibody (nivolumab) exhibited remarkable protection against bone destruction in the mentioned pain model. Mechanistically, PD-L1 promoted RANKL-induced osteoclastogenesis through JNK activation and chemokine C-C motif ligand 2 (CCL2) secretion. Moreover, PD-L1 can also activate SHP-1 to downregulate TRPV1 in DRG neurons and delay the development of bone cancer pain in mice. Thus, immunotherapy targeting PD-1/PD-L1 signaling could produce long-term benefits by preserving the bone structure and alleviating bone cancer pain through the suppression of osteoclastogenesis (Fig. 9.4).

Notably, anti-PD-1 treatment with nivolumab initially (early phase) causes an increase in bone cancer pain due to neuronal modulation in the animal model (Wang et al. 2020a). In contrast, nivolumab reduced bone cancer pain in the late phase of treatment through modulation of osteoclasts and protection from bone destruction. While the PD-1/PD-L1 pathway produces acute antinociception through neuromodulation, the delayed effects of this pathway may also depend on immunomodulation (Wang et al. 2020a). Thus, anti-PD-1 treatment's initial increase of cancer pain before the later phase reduction of cancer pain is a result of both neuromodulation and immunomodulation.

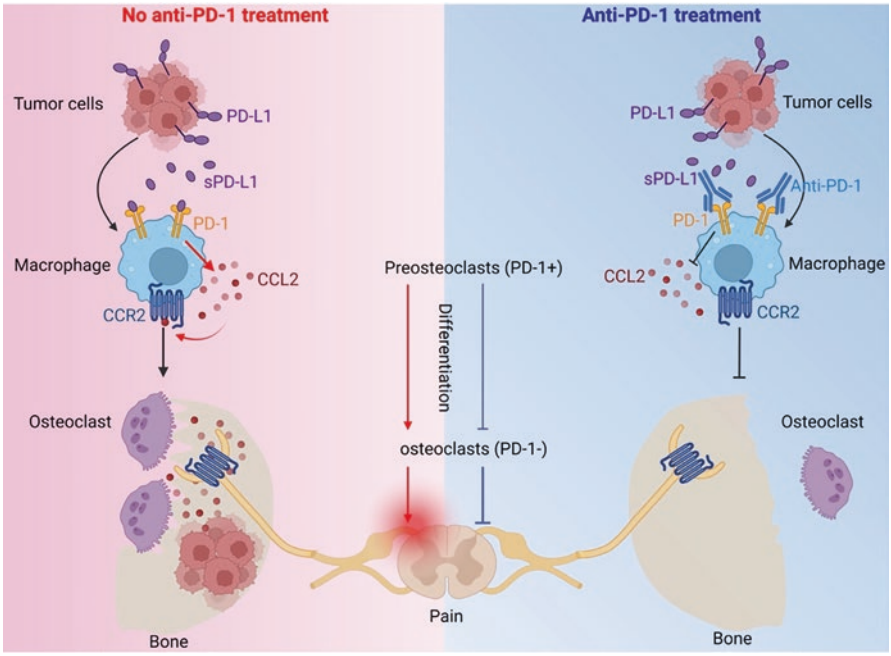


**Fig. 9.4** Neuroimmune interactions mediated by the PD-L1 and PD-1 axis in bone cancer pain. Activation of this immune checkpoint pathway results in osteoclast differentiation, bone destruction, and bone cancer pain. Immunotherapy with anti-PD-1 treatment (nivolumab) can inhibit the differentiation of preosteoclasts into osteoclasts, thus protecting against bone destruction and cancer pain

## 9.4 Interferon-Based Immunotherapy and Pain

### *9.4.1 Immunotherapy Targeting IFN-β in Pain*

Increasing evidence suggests that type-I interferons (IFNs) regulate pain via neuroimmune and neuro-glial interactions (Tan et al. 2021). Intrathecal injection of IFN-β increases paw withdrawal threshold in naïve mice and provides analgesia in inflammatory and neuropathic pain animal models. IFN-β treatment relieves mechanical allodynia induced by intrathecal injection of TLR2 or TLR4 ligands (Stokes et al. 2013). A single intrathecal IFN-β administration attenuates nerve injury-induced mechanical allodynia for several days in mice, which may be mediated by an inhibition of MAPK activation and the induction of interferon-stimulated gene 15 (ISG-15) (Liu et al. 2020). Intrathecal injection of IFN-β also showed a significant transient dose-dependent inhibition of CFA-induced inflammatory pain and this analgesic effect is reversed by intrathecal naloxone, suggesting that IFN-β analgesia occurs through central opioid receptor-mediated signaling (Liu et al. 2021).

### 9.4.2 Immunotherapy Targeting STING in Physiological and Neuropathic Pain

STING, as an innate immune regulator, is a critical sensor of self and pathogen-derived DNA. DNA sensed by STING leads to the induction of type-I interferons and other cytokines, which promote immune cell-mediated eradication of pathogens and neoplastic cells (Ishikawa and Barber 2008; Woo et al. 2014). In addition to the important role of STING in the immune system, STING has been shown to be a critical regulator of nociception through IFN-I signaling in DRG sensory neurons. Donnelly et al. demonstrated that administration of synthetic (DMXAA and ADU-S100) or biological (cGAMP) STING agonists can increase mechanical pain thresholds in both naïve and neuropathic pain model mice. More importantly, STING agonists produce analgesia in nonhuman primates. In contrast, mice lacking STING, including global (*Sting1*$^{gt/gt}$) and sensory neuron-selective (*Sting1*$^{fl/fl}$; *Nav1.8-Cre*) knockout mice, showed enhanced pain hypersensitivity and nociceptor excitability (Donnelly et al. 2021).

Activation of STING drives the production of IFN-I family members IFN-α and IFN-β. Mice lacking IFNAR1, including global (*Ifnar1*$^{gt/gt}$) and sensory neuron-selective (*Ifnar1*$^{fl/fl}$; *Nav1.8-Cre*) knockout mice, exhibited robust hypersensitivity to mechanical and cold stimuli as well as nociceptive activity. Thus, STING signaling with IFN-I serves as a critical regulator of physiological nociception and a promising target for treating neuropathic pain (Donnelly et al. 2021).

Another study showed that the spinal cord microglial STING/TBK1/NF-κB pathway contributes to pain initiation via IL-6 signaling. Pharmacological blockade of STING with the antagonist C-176 may be a promising target in preventing or limiting the initiation of neuropathic pain (Sun et al. 2022).

### 9.4.3 Immunotherapy Targeting STING in Bone Cancer Pain

STING is a robust driver of anti-tumor immunity, which has led to the development of STING activators and small-molecule agonists as adjuvants for cancer immunotherapy (Kwon and Bakhoum 2020). Activation of the STING pathway by the synthetic agonists DMXAA or ADU-S100 potently enhances anti-tumor immunity and promotes bone formation in a murine bone autoimmune disease model (Baum et al. 2017; Kwon et al. 2019). In addition, STING agonists can also serve as a therapeutic strategy for metastatic bone cancer pain and its comorbidities, including tumor-induced bone destruction and functional impairment. Wang et al. demonstrated that STING-mediated IFN-I signaling has direct effects on bone cancer pain in several different animal models via direct suppression of nociceptive excitability (neuromodulation). In addition, the potent analgesic effects of STING agonists are likely due to a combination of their direct effects on DRG sensory neurons (neuromodulation) and suppression of tumor burden and bone destruction (immune modulation) (Wang et al. 2021a).

## 9.5 Immunotherapy Targeting Pro-Inflammatory Cytokines in Pain

Cytokines are the main signaling molecules of immune system activation and have been shown to facilitate and increase pain. Cytokines are grouped into either pro-inflammatory or anti-inflammatory. The pro-inflammatory cytokines, including TNFα, IL-1β, IL-6, and IL-17, have been found to be elevated in pain animal models. Meanwhile, anti-inflammatory cytokines, including IL-4, IL-10, and TGF-β, are associated with a reduction in pain symptoms. Current studies have shown that anti-cytokine immunotherapies in the clinic were focused on pro-inflammatory cytokines and their receptors (Kalpachidou et al. 2022), and the following will serve as an introduction to these cytokines.

Tumor necrosis factor α (TNFα) was discovered in 1975 by Carswell et al. and the initial studies on TNFα primarily focused on its potential as a treatment for cancer (Carswell et al. 1975). However, anti-TNFα treatments have also been extensively explored in the context of neuropathic pain. Several studies have shown a correlation between neuropathic pain and TNFα upregulation (Leung and Cahill 2010; Wagner and Myers 1996). This correlation was also confirmed in humans through clinical studies in which elevated levels of TNFα were observed in patients with chronic neuropathic pain conditions (Alexander et al. 2005; Brisby et al. 2002). These findings suggest a clinical benefit to reducing the expression of TNFα, which was validated in animal models and clinical studies that found anti-TNFα treatment reduced neuropathic pain (Monaco et al. 2015). TNFα inhibitors, including infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab, are currently FDA-approved for painful disorders such as inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (Hung et al. 2017). With its safety profile and tolerability with long-term use, TNFα blockade may have significant value in the clinical treatment of chronic pain.

Interleukin 1β (IL-1β) is another pro-inflammatory cytokine that lowers pain thresholds, which has been explored as a potential target to reduce pain. The expression and upregulation of IL-1β have been extensively documented in various neuropathic pain conditions. Treatment with exogenous IL-1β has been shown to induce both mechanical and thermal hyperalgesia (Xiang et al. 2019; Zelenka et al. 2005). Treatment with anti-IL-1β antibody can reduce pain symptoms in animal models (Schafers et al. 2001). The mechanisms behind the hyperalgesia effects of IL-1β were studied in a variety of clinical studies and animal models. One important mechanism is the pro-inflammatory cascade, in which other pronociceptive mediators are significantly upregulated in response to IL-1β expression. IL-1β acts on both the peripheral and central nervous system, establishing the importance of IL-1β as a pro-inflammatory cytokine as well as an attractive target for anti-cytokine therapies developed to reduce neuropathic pain. Three IL-1-targeting agents have been approved for the treatment of inflammatory diseases: the IL-1 receptor antagonist anakinra for rheumatoid arthritis, the soluble decoy receptor rilonacept for cryopyrin-associated periodic syndromes, and the monoclonal anti-IL-1β antibody

canakinumab for systemic juvenile idiopathic arthritis (Alten et al. 2011; Botsios et al. 2007; Norheim et al. 2012). Several other drugs targeting IL-1β are in clinical trials. These anti-IL-1β treatments will need more studies with regard to pain conditions.

As a pro-inflammatory cytokine, IL-17 is upregulated in several animal pain models. IL-17 levels also increase with time during the development of chronic pain (Kim and Moalem-Taylor 2011; Meng et al. 2013; Noma et al. 2011). Exogenous IL-17 injection can induce neuropathic pain while anti-IL-17 antibody or IL-17 genetic knockout can decrease pain (Day et al. 2014). The mechanism underlying IL-17 involvement in neuropathic pain is related to the increased activity of transient receptor protein vanilloid 4 (TRPV4), an ion channel that has been found to mediate mechanical allodynia (Segond von Banchet et al. 2013). IL-17 also regulates neuron-glial interactions and synaptic transmission in neuropathic pain (Luo et al. 2019). The IL-23/IL-17A/TRPV1 axis plays an important role in neuropathic pain via macrophage-sensory neuron interactions (Luo et al. 2021). Currently, there are two IL-17A antibodies secukinumab and ixekizumab which are approved for the treatment of plaque psoriasis and also in clinical trials for other inflammatory diseases (Zwicky et al. 2020).

## 9.6 Immunotherapy to Ablate Immune Cell Populations in Pain

The immune system includes the innate immune system and the adaptive immune system. The innate immune system (T-cells, macrophages, neutrophils, microglia) and pro-inflammatory cytokines contribute to the pain transition from acute to chronic phase (Baral et al. 2019; Ji et al. 2016). Recent studies are pointing toward a potential role of immune cells in pain management.

T-cells are the main regulators of the immune response that contribute to the initiation and resolution of pain. T-cells can be divided into several subsets based on the pattern of cytokine production and specific expression of characteristic transcription factors (Zhu and Paul 2008). Thus, different subsets of T-cells may play different roles in pain. Many studies evaluated the contribution of T-cells to pain by comparing pain behaviors in WT mice and different types of T-cell deficiency mice, including *Rag1*$^{-/-}$, *Rag2*$^{-/-}$, nude, and SCID mice, as well as the mice reconstituted with specific populations of T-cells. At baseline, there is no significant difference in pain sensitivity between WT and T-cell-deficient mice (Cao and DeLeo 2008; Moalem et al. 2004; Vicuna et al. 2015). In different pain animal models, researchers did find varying contributions from different subsets of T-cells to the transition from acute to chronic pain. In neuropathic pain models, T-cells infiltrated the nervous system after nerve injury, mainly in DRGs, and contributed to pain hypersensitivity (Austin et al. 2012; Du et al. 2018). Ablation of T-cells in neuropathic pain models (CCI, SNI, and PSNL) reduced pain sensitivity compared with control mice (Costigan et al. 2009; Kleinschnitz et al. 2006; Kobayashi et al. 2015). The

development of pain hypersensitivity was completely prevented in *Rag1*$^{-/-}$ or *Rag2*$^{-/-}$ mice in the SNI model and the reintroduction of T-cells was able to reverse the results, which indicate a detrimental role for T-cells in chronic pain induced by nerve injury (Cao and DeLeo 2008; Costigan et al. 2009; Vicuna et al. 2015). Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment and is often associated with pain (Krukowski et al. 2016). In the CIPN model induced by injection of paclitaxel or cisplatin, *Rag1*$^{-/-}$ or *Rag2*$^{-/-}$ mice had similar pain hypersensitivity as WT mice but their resolution of pain was significantly delayed (Krukowski et al. 2016; Laumet et al. 2019). Reconstitution of CD8$^{+}$ T-cells restored pain resolution in these T-cell-deficient CIPN model mice. In an inflammatory pain model induced by injection of Complete Freund's Adjuvant (CFA), the severity of mechanical allodynia was identical in WT and several different subsets of T-cell-deficient mice, including nude, *Tcrb*$^{-/-}$, *Tcrd*$^{-/-}$, *Rag1*$^{-/-}$, and *Rag2*$^{-/-}$ mice (Ghasemlou et al. 2015; Laumet et al. 2018; Petrovic et al. 2019; Sorge et al. 2015). However, pain resolution was significantly delayed in these T-cell-deficient mice, and reconstitution with wild-type T-cells was able to restore pain resolution (Basso et al. 2016). In summary, T-cells are evidently detrimental in nerve injury models and beneficial in CIPN and CFA models. This differentiation may be derived from the engagement of different T-cell subsets. Thus, immunotherapy targeting T-cells should select for different T-cell subsets in different pain conditions.

Crosstalk between microglia and infiltrating macrophages or tissue-resident macrophages with primary afferent neurons contributes to the induction and maintenance of different chronic pain conditions (Bang et al. 2018; Chen et al. 2018). Macrophage number is significantly increased after nerve injury, indicating pronociceptive neurons and macrophages interact during pain. The effects of macrophages on pain modulation were examined by pharmacological and genetic ablations of macrophages in neuropathic pain models. Studies showed that clodronate ablation of DRG macrophages reduced mechanical allodynia in a nerve injury model and CIPN model (Cobos et al. 2018; Old et al. 2014). CSF1R inhibitors have the ability to cross the BBB and deplete CNS microglia and macrophages. As a result, blocking CSF1R signaling effectively attenuates injury-triggered neuropathic pain behavior. In addition, transgenic mouse lines that express a drug-inducible suicide gene, for example, herpes simplex virus type 1 thymidine kinase (CD11b-TK) or diphtheria toxin receptor (CD11b-DTR, LysM-DTR, and Cx3cr1-DTR) in both microglia and macrophages, or *Cx3cr1* global knockout mice, can be used to ablate microglia and macrophages. Thus, the ablation of microglia and macrophages can attenuate the allodynia and pain hypersensitivity from neuropathic pain.

## 9.7 Adoptive Immunotherapy in Pain

This section will cover the adoptive transfer of macrophages and T-cells for resolution of inflammatory pain, neuropathic pain, and infection-induced pain. The role of bone marrow stromal (stem) cells in pain control will be covered in Chap. 10.

### 9.7.1 *Adoptive Transfer of Macrophages for the Resolution of Pain*

Even though the mechanisms of pain induction have been extensively studied, the mechanisms of pain resolution are still not fully understood. Macrophages have been reported as key players in the resolution of pain. One study pointed toward macrophages as key players in the resolution of pain whose activity is blunted during nerve injury based on data from single-cell RNA sequencing (Niehaus et al. 2021). They demonstrated that the macrophages from superficially injured animals had increased expression of the anti-inflammatory mediator CD163 and alleviated nociceptive hypersensitivity via the cytokine IL-10. The hypersensitivity could be reduced in nerve injury animal models by increasing macrophage CD163 expression.

GPR37 expressed in macrophages is also a critical contributor to the resolution of inflammatory pain and infection-induced pain. Bang et al. demonstrated that GPR37 knockout (*Gpr37*$^{-/-}$) mice exhibited deficits in macrophage phagocytic activity, dysregulation of pro- or anti-inflammatory cytokines, and delayed resolution of zymosan-induced inflammatory pain (Bang et al. 2018). Macrophage depletion delays the resolution of inflammatory pain while the adoptive transfer of macrophages from WT mice promotes the resolution of inflammatory pain. Neuroprotectin D1 (NPD1) and artesunate (ARU) act as ligands of GPR37. Activation of GPR37 by NPD1 and ARU promotes the resolution of inflammatory and bacterial infection-induced pain. In addition, the adoptive transfer of macrophages primed with GPR37 activators could confer protection against malaria and listeria infection (Bang et al. 2021; Bang et al. 2018). Thus, specific targeting of macrophage-bound GPR37 by NPD1 or ARU could help promote inflammatory pain resolution and alleviate other inflammation-related disorders (Fig. 9.5).

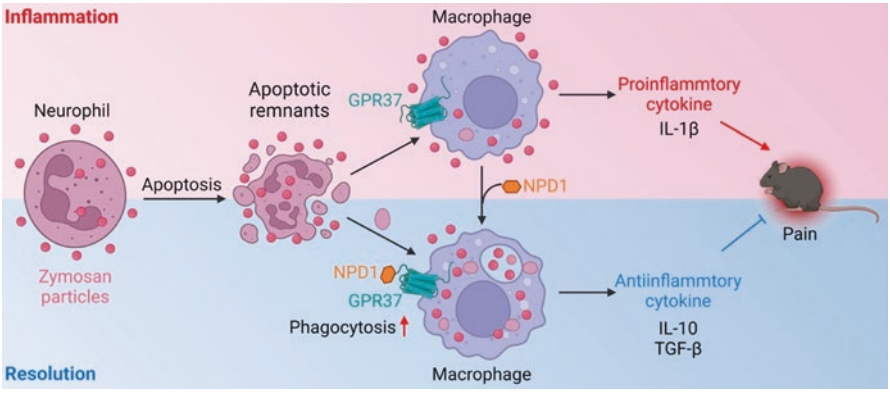


**Fig. 9.5** GPR37 regulates macrophage phenotype and phagocytosis in the resolution of inflammatory pain. Neuroprotectin D1 (NPD1) treatment can increase the phagocytosis of macrophages and thus relieve pain

Furthermore, recent research efforts into inflammatory pain resolution point toward macrophage mitochondrial transfer as a major mechanism. Vlist et al. found that macrophages actively control the resolution of inflammatory pain outside of the site of inflammation by transferring mitochondria to sensory neurons (van der Vlist et al. 2022). During inflammatory pain resolution, M2-like macrophages infiltrate the DRG containing the somata of sensory neurons, correlating with the recovery of oxidative phosphorylation in sensory neurons. The resolution of pain by mitochondrial transfer requires the expression of the CD200 receptor (CD200R) on macrophages and the non-canonical CD200R-ligand iSec1 on sensory neurons (van der Vlist et al. 2022). Thus, the restoration of mitochondrial homeostasis in neurons and perhaps enhanced mitochondria transferred from macrophages could be a novel therapeutic strategy for chronic pain resolution.

### *9.7.2 Adoptive Transfer of T-Cells for the Resolution of Pain*

Adoptive transfer of T-cells, either from the patient or from other sources, to treat various conditions is known as adoptive immunotherapy. Although this treatment was initially developed as a cancer treatment, it has been found to be useful in treating neurological diseases and more recently in pain management. In the context of pain management, a recent clinical study demonstrated the effectiveness of adoptive immunotherapy to reduce pain in advanced cancer patients. One recent study showed that transfusion of immune cells was reportedly associated with reductions in opioid consumption and pain intensity among patients with advanced cancer and suggested increased production of endogenous opioids due to the activation of $CD4^+$ T-lymphocytes (Zhou et al. 2020).

The administration of mesenchymal stem cells (MSCs) or bone marrow stromal cells (BMSCs) is another strategy to relieve bone cancer pain, neuropathic pain, or osteoarthritis. Injection of autologous MSCs into the joint alleviated pain in patients with osteoarthritis (Harrell et al. 2019). Intrathecal injection of BMSCs has been shown to exert antinociceptive effects in animal models of bone cancer pain and neuropathic pain (Chen et al. 2015; Huh et al. 2017; Sun et al. 2017). BMSC transplantation may have the potential to treat painful diseases in patients. Thus, cell-based pain therapies will represent a promising strategy to treat chronic pain.

## 9.8 Concluding Remarks

Although immunotherapy is perceived to be a recent medical advancement in clinical cancer therapy, increasing evidence highlights the emerging role of immunotherapy in treating a range of diseases, including pain. The mechanisms of pain induction and resolution are complex, and the potential of immunotherapy as a novel approach to pain management will be a research area of increasing interest to

address the multifaceted mechanisms of chronic pain. Ongoing and future research in connecting immunotherapy and the treatment of pain will thus hold promise in novel clinical applications.

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