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REVIEW ARTICLE

A Review of the Role of Lymphocytes in Chronic Neuropathic Pain: A Clinical Perspective

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ABSTRACT

Chronic neuropathic pain is one of the most common morbidities in the developed world. It has a lifetime incidence of 80% with females being affected more than males. Chronic neuropathic pain pathogenesis and its associated “sickness syndrome” has been poorly understood but recent research has shown a neuroimmune basis. Many studies performed to date have been pre-clinical or animal-based with a lack of human studies in chronic neuropathic pain.

Background: We performed a review of literature with emphasis on clinical and human studies. The numbers of such studies are low due to limitations with ethical approval, recruitment and heterogeneity of humans. We aimed to investigate the most recent studies as well as important seminal research in this area.

Methods: Literature search was performed using Stella search engine, Pubmed and National Library of Medicine search engines. Pre-clinical, animal and human studies were included.

Conclusion: The immune system, in particular the adaptive immune system, regulates the initiation, progression and resolution of chronic neuropathic pain in humans. The exact “switch” which mediates initiation, upregulation and downregulation of the components of the immune system is not known. Further research in this area is needed but the challenge of recruiting patients for CNP studies remains. Study sample sizes tend to be small. However, clinically relevant findings although small can offer important information to further our understanding of CNP.

Introduction

Autoimmune and inflammatory disorders are caused by physiologically inappropriate activation of the autoimmune system mediated by activation of T, B and natural killer (NK) cells. These disorders are associated with acute inflammatory episodes which do not cease completely leading to chronicity, dysregulation and may result in chronic neuropathy with neuropathic pain as a major symptom. An effective immune response requires an inflammatory response. How this response is mediated depends on the pathogen or injury presented.¹

Chronic pain is the most common morbidity in the developed world and third most common morbidity in the developing world. Chronic neuropathic pain (CNP) has a point prevalence of 8% with a lifetime incidence of almost 80%.² CNP is pain caused by a primary lesion or disease of the somatosensory level, which has been present for more than 3 months.³ CNP adversely affects a patient's quality of life, reduces their ability to perform daily activities, reduces normal functioning, mental health issues may be amplified and socioeconomic difficulties such as work absenteeism may occur.⁴ A "sickness syndrome" is observed in these patients with co-existing anxiety, depression and drug abuse, all of which have a central immune basis.⁵ These issues are compounded by resistance of CNP to conservative pain therapies and inconsistent results. Advanced pain therapies available include medications with growing interest in monoclonal antibody therapy, interventional pain procedures and neuromodulation. Medications have low efficacy with numbers needed to treat numbers needed to harm ratios (NNT: NNH) high, various adverse effects such as difficulty with tolerability, addiction, sedation and accidental overdose are seen. Interventional pain procedures are effective but costly. Additionally, availability of these procedures is heterogeneous.⁶ Neuromodulation is an advanced and costly pain treatment which requires surgical placement of an implantable device. This device provides moderate analgesia for specific neuropathic pain conditions such as failed back surgery syndrome and Complex regional pain syndrome (CRPS).^{7,8}

The exact pathogenesis of CNP remains to be definitively elucidated however there is growing clinical evidence that chronic neuropathic pain, fibromyalgia and chronic widespread pain are neuroinflammatory disorders associated with changes in the neuroimmune interface.⁹⁻¹¹ Advancements in knowledge of pathways involved

in chronic pain pathogenesis would allow novel therapies to be developed as well as offer alternative therapies to those currently available. There is a paucity of knowledge in the pathogenesis of CNP. Immune cells have been shown to play a role in both the pathogenesis and resolution of chronic neuropathic pain. Intrinsic components of the immune system such as neutrophils, macrophages, and mast cells are activated by proinflammatory mediators and initiate acute pain at site of injury peripherally. Centrally, activation of microglia, astrocytes and macrophages occur in the dorsal horn dorsal root ganglion promoting chronic neuroinflammation. These cells have been shown to be involved in the transition from acute to chronic pain and its maintenance. Adaptive immune cells such as T and B cells are mainly involved in the initiation of chronic pain with T cells contributing to pain resolution.^{12,13}

Peripherally, T cells are directly regulated by sensory neurons of the dorsal root ganglion (DRG) and trigeminal ganglion. Local T cell activity is affected by release of neurotransmitters and neuropeptides (such as glutamate and calcitonin gene-related peptides) from sensory neurons. It has been shown that dendritic cells activate T cells through antigen presentation and promote T cell differentiation into T-helper 1 cells (Th1). Th1 cells accumulate and infiltrate at the site of injury and the distal end of the nerve and then DRG, where interferon-gamma (IFN- γ) is secreted by Th1 cells. IFN- γ then activates glial cells and initiates chronic pain.¹⁴

T cells also appear to play a role in pain suppression and resolution. Subsets of T-cells produce mediators such as endogenous opioids and cytokines which can suppress or resolve pain.^{15,16}

B cells produce antibodies in response to a foreign antigen and also present antigens to T cells. This mediates the release of CXCL1 which is a pro-inflammatory chemokine which activates neuronal nociceptors in the DRG, further mediating development of inflammation and pain.¹⁷

Characteristic alterations in neuronally-activated immune cells such as T and B cells causing direct activation of pathways are seen in both activation and resolution of pain. Both peripherally activated and centrally activated immune cells promote a chronic neuroinflammatory state which promotes pain chronicity and resolution.

Inhibiting the pain-promoting functions of T and B cells or modulating the beneficial effects of pro-resolution T cells may offer new disease-

modifying strategies for the treatment of chronic pain.

Lymphocytes in humans

T cells

T cell progenitors are made in bone marrow, acting as naïve, immature lymph cells. They are transported to the thymus for maturation, selection and ultimately transport to the periphery. Upon activation by antigen presentation in the periphery, they proliferate in effector cell subtypes such as T-1, T-2, t-helper and T-regulatory cells (all CD4+) CD8+ cells differentiate in cytotoxic T cells or suppressor/regulatory cells. The majority of these cells short-lived but a portion remain as memory cells. Memory cells are important components of long-term immunity in the human.¹⁸

In a typical healthy central nervous system, activated CNS-specific T cells are in a quiescent state. In this state, they patrol the CNS and become activated for maintenance and repair on discovery of injury to tissue. Disruption of this role is contributory to the pathogenesis of neurodegenerative diseases such as Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis and Multiple Sclerosis.^{19,20} Overactivity of these cells may also result in over-production of pro-inflammatory mediators resulting in a pathological rather than protective state.²¹

T cells infiltrate the CNS in many neuroinflammatory disorders, in which their activation plays a critical role on microglial activation and consequent neuroinflammation. The immune cell content of healthy CSF is estimated to consist of approximately 90% T cells, 5% B cells, 5% monocytes, and <1% dendritic cells.²² Studies have shown that, during nerve injury, peripheral dendritic cells activate T cells via antigen presentation and promote T cell differentiation into T-helper (Th1) cells. Th1 cells accumulate at the site of injury and the distal end of the nerve, then the DRG, where IFN- γ is secreted by Th1 cells. Finally, IFN- γ activates glial cells centrally, which can initiate chronic neuropathic pain.²³

B cells

B cells and the antibodies (mediated by immunoglobulins) they produce when activated make up the adaptive immune system. Newly formed transitional B cells with an intact B cell receptor (BCR) emigrate from bone marrow into peripheral circulation and secondary lymphoid organs. They can encounter and respond to T cell-dependent foreign antigens bound to follicular

dendritic cells, proliferate, and either differentiate into plasma cells or enter germinal centre reactions. When B cells are activated, they produce antibodies in addition to presenting antigens to T cells and causing a cytokine response. T cells can activate B cells, which mature into plasma cells and secrete antibodies. This may be part of peripheral sensitisation. After an initial exposure, memory B cells remain in the circulation. After repeat exposure, an antibody response, mediated by these memory B cells, is quicker and prolonged. B cells can also function as cytokine-producing effector cells that influence T-cell differentiation.²⁴⁻²⁶

B cells play a role in many autoimmune diseases such as MS, Myasthenia Gravis, SLE, NMO and others and are therapeutic targets for the future.^{27,28} Injection of anti-citrullinated protein antibodies (ACPA) from RA patients or arthritic mice into healthy mice was found to cause persistent pain and increase their nociceptive sensitivity. This is mediated via expression of CXCL1 (a chemokine associated with injured tissue and nociception), causing an associated increase in excitability and sensitivity of nociceptive neurons via receptor CCR2.²⁹

B cells causing impairment or suppression of immune reactions are known as "regulatory" B cells.³⁰ It has been shown that these regulatory B-cells inhibit excessive inflammation. Specific B reg cells produce IL-10, a potent anti-inflammatory interleukin. B reg lacking mice demonstrated excessive inflammation and a persistently activated immune system with a decrease in number and function of B-reg suppressor cells. The role of B cell activity in chronic neuropathic pain remains to be elucidated in vivo.

Natural Killer Cells

NK cells are a third distinct subset of lymphocytes. They were originally thought to become activated by a pathogen or pathological process without needing prior exposure (a natural killing response). It is now understood the effect of NK cells is mediated by a complex system of cytotoxicity and cytokine production.³¹ This response plays a critical role in development of both innate and acquired immunity in various chronic disease states, such as Systemic Lupus Erythematosus, T1 Diabetes Mellitus, Sjogrens syndrome and systemic sclerosis, identifying them as a link between adaptive and innate immune system. It has been shown that NK cells have a regulatory effect on T cell modulation and function. Early production of IFN- γ by NK cells can

modulate antigen-presenting cell function and promote direct differentiation of Th1 cells and indirectly inhibit Th2 cell and Th17 cell differentiation. NK cell dysregulation may result in failure of controlled T cell responses via dysfunction of cytokine dysfunction and cytotoxicity.³²

Clinically, NK-derived cytokines and their cytotoxic functions through induction of apoptosis can take part in regulation of the immune responses and may contribute to pathogenesis of many immune-mediated diseases including ankylosing spondylitis, Bechet's disease, multiple sclerosis, rheumatoid arthritis, psoriasis and type-1 diabetes. A recent study showed that CD56+ NK cells may contribute to SLE development.³³

Many unanswered questions remain regarding the specific role NK cells play in the pathogenesis of autoimmune disease. Further elucidation of the role NK cells play in initiation, progression and possible resolution of these diseases may prove valuable in developing new therapeutic interventions.

Dorsal Root Ganglion

Dorsal root ganglia (DRG) have unique physiological and anatomical features. Although separate from the central nervous system (CNS), they are covered in meninges and are surrounded by cerebrospinal fluid but remain outside the blood-brain barrier. Each DRG possess nociceptive molecules such as ion channels, glial cells and neuropeptides. They have the ability to sequester pain-associated antibodies, allowing for induction of immune-mediated hyperalgesia. Essentially, they facilitate modulation of neuro-immune crosstalk.³⁴

Each DRG houses both small and large sensory nerve fibre cell bodies. DRGs have rich, fenestrated blood supply and are robustly encapsulated by immunologically active glial cells. DRGs have a "pseudo-unipolar" structure consisting of a single axon projecting from the cell body in a distal direction and is responsible for afferent signalling. The proximal portion of the axon extends into the CNS and shows multiple branches spreading into the spinal cord in the distribution of multiple anatomical dermatomes. DRG are in direct connection with the sympathetic nerve chain via communicating nerves³⁵

At a cellular level, macrophages and lymphocytes populate DRGs. T cell level have been shown to increase at corresponding DRG shortly after a lesion occurs. Macrophages play a role in the initiation and propagation of

mechanical hypersensitivity seen in neuropathic pain. At the time of peripheral injury, macrophages proliferate at the corresponding sensory DRG. DRGs contain particular Na⁺ channels (Nav1.8 and TPRV1) which are activated and produce pro-nociceptive mediators resulting in pain and inflammation.³⁶

Cellular Phenotype in Chronic Pain

Acute injury results in local infiltration of lymphocytes and macrophages and this response leads to oedema, colour change and pain. Macrophages in particular have shown an important role in initiation, maintenance and resolution of acute inflammation. After neural tissue damage, macrophages peripherally and microglia centrally in the spinal cord produce inflammatory mediators including interleukin-1 β (IL1 β), tumour necrosis factor (TNF), bradykinin, and nerve growth factor. These mediators contribute to acute pain by activating nociceptive neurons peripherally.³⁷

Activation of macrophages peripherally after a distal axonal injury is a key feature of Wallerian degeneration. A similar picture is seen with microglia in the dorsal horn of the spinal cord with microglial activation (and overactivation) occurring in adjacent injured axons. This neuro-immune crosstalk causes gradual production and release of immune mediators via complement cascade (C1q and C3b complement cascade proteins) which initiate and play a role in the development of chronic neuropathic pain by altering neuronal function.³⁸

Healthy and injured neurons send different signals that determine neuroprotective or neurotoxic microglial activities. Activated microglia produce pro- and anti-inflammatory cytokines including TNF- α , IL-1 β , IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IFN- α , IFN- γ , TGF- β , M-CSF, and GM-CSF; chemokines (IL-8, Gro α , IP-10, MIP-1 α , MIP-1 β); growth factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF); reactive oxygen species (ROS); ; inflammatory markers (C-reactive protein, serum amyloid P); proteases (α -antitrypsin, α -antichemotrypsin); and complement system protein.³⁹

T cells

Circulating levels of total T cells in patients with chronic have provided little diagnostic information this far however T cell subsets have

been shown to be more informative. A study investigating peripheral blood in patients with migrainous headaches showed a significantly lower percentage of blood CD3+CD4+ helper T cells and CD4+CD25+ regulatory T cells, compared to controls.⁴⁰ Other recent studies have shown imbalances in Th1/Th2 and Treg/Th17 in patients with chronic neuropathic pain. In a 2010 study quantifying CD4+ sub-populations (Th1 and Th2) in patients with drug-induced peripheral neuropathy, an imbalance in Th1/Th2 ratio with a shift towards Th2 and associated significant increase of pro-inflammatory IL-6 levels were shown.⁴¹ A study in 2014 investigated T cell subsets in patients with chronic non-specific low back pain and showed significantly increased anti-inflammatory Tregs and decreased pro-inflammatory Th17 cells in these patients as compared to healthy controls.⁴² A study investigating the autoimmune pathogenesis of Complex regional Pain syndrome (CRPS) showed expansion and activation of distinct populations of central memory T lymphocyte in peripheral blood in patients with CRPS. The number of central memory CD8+ T cells was increased 2.15-fold compared to healthy controls. Central memory CD4+ T lymphocytes such as number of Th1 and Treg cells was increased 4.98-fold and 2.18-fold.⁴³ A similar study showed decreased numbers of pro-inflammatory Th17 cells in patients with CRPS as compared to healthy volunteers.⁴⁴

Interestingly, the phenotype and function of T cells expressed in patients using particular analgesics is also affected. In long-term opioid use, T-cell function, expression of cytokines, suppression of T-cell apoptosis and T-cell differentiation are affected. When administered, morphine binds to μ receptors on T-cells and drives T-cell proliferation towards Th-2 phenotype. This intracellular switch towards pro-inflammatory Th2 phenotype may predispose functionally to immune suppression.⁴⁵

Tricyclic antidepressants are first-line pharmacological therapy for chronic neuropathic pain. A study from our group investigated the effect of tricyclic antidepressants on T cell phenotype in vitro. Cellular quantification of T cell phenotype 24 and 48 hours post treatment with either amitriptyline, nortriptyline or both was performed. No cell death occurred post treatment in either group. There were significantly lower frequencies of CD8+ T-cells after treatment with amitriptyline, nortriptyline and a combination of both compared to control ($p < 0.001$). The frequencies of naive CD8+CD45RA+ cells were

significantly lower after amitriptyline, nortriptyline and a combination of both ($p < 0.001$). The frequencies of CD27+CD4+ and CD27+CD8+ T-cells were also significantly lower following combination drug treatment, suggesting reduction of activated effector T cells. Significantly lower frequencies of pro-inflammatory IFN- γ -producing CD8+ T-cells were observed with all treatment combinations ($p < 0.05$) and frequencies of IL-17-producing CD4+ and CD8+ T-cells were significantly lower following amitriptyline treatment ($p < 0.05$). Frequencies of Natural Killer T-cells were significantly higher following treatment with nortriptyline ($p < 0.05$).⁴⁶

Pulsed radiofrequency (PRF) to dorsal root ganglion (DRG) in patients with lumbar radicular pain has been demonstrated clinically to result in cellular and proteomic response post PRF with reduced total TNF- α concentration and CD3+ count in CSF. CD4+/CD8+ ratio in patients with CNP was lower than historical controls (1.4 versus 3.0–4.2). The majority of CD3+ cells in the CNP patients were activated effector memory cells (80%) versus the surveillance central memory cells (85%) seen in healthy controls suggesting immune activation.⁴⁷

A mouse study investigating the collaborative role acetylcholine and T cell mediation play in pain signalling showed both cholinergic signalling and T lymphocytes have established roles in modulating pain phenotypes, and it is not cholinergic signalling initiated by T lymphocytes that drive this.⁴⁸ This further suggests a neuroimmune crosstalk as main player in pain perception and signalling.

B cells

The role played by B cells in chronic neuropathic pain is unclear. In other autoimmune diseases, B cells have been shown to play a role. It has been shown that virus-specific IgG is increased in patients with herpes zoster. Based on this, it is possible that formation of IgG-antigen complex (mediated by B cells) on the nociceptive neurons is involved in chronic herpetic pain.⁴⁹ Very limited clinical research on phenotype and role played by B cells in neuropathic pain is available.

A study looking at immunohistochemical quantification of infiltrating B-cells in epithelium of patients with interstitial cystitis showed a clonal expansion of B cells as a consequence of local immune response.⁵⁰

A more recent study investigated the role of B cells in CSF of patients with multiple sclerosis, an autoimmune disease which includes neuropathic

pain as a symptom. It is thought B cells and more specifically oligoclonal bands and immunoglobulins play a large role in MS but the contribution to pathogenesis and progression of B cells is unknown. CSF of patients with MS was analysed and showed significant differences in the CSF B cell subsets between MS subtypes and patients with other neurological diseases, but CSF B cells had no predictive role for disease and end stage of disease progression or conversion to different sub-types of MS (relapsing remitting, primary progressive etc).⁵¹

Autoantibodies from mice with RA injected into healthy mice produced pain and increased nociceptive receptor sensitivity. This is mediated by release of chemokine CXCL1 (similar to pronociceptive IL-8 in humans) which acts as a pronociceptor.⁵² In an animal model of CRPS, wild-type mice lacking B cells were given IgM with a resulting pronociceptive effect on a fractured limb possibly mediated by complement C5 and downstream pro-inflammatory cytokine release.^{53,54}

Rituximab is a monoclonal antibody which targets B cells by binding to cell surface receptor CD 20 (a B-cell specific antibody) and increases success rate of NK cells for killing B cells. It has been used to successfully treat Rheumatoid arthritis with a significant improvement in their pain.⁵⁵

Despite what is known about the activity of B cells, the exact role they in the pathogenesis of chronic neuropathic pain is unknown with very little available in the literature.

NK cells

A paper investigating the phenotype of NK cells in patients with neuropathic pain performed flow cytometry on 41 patients with chronic neuropathic pain. Cerebrospinal fluid of 41 patients (10 herpes zoster and 31 Polyneuropathy) was analysed by flow cytometry identifying lymphocyte subsets. Results showed a negative correlation between the frequency of NK cells and mechanical allodynia suggesting central sensitisation. A high frequency of NK cells correlated with lower reported levels of allodynia suggesting reduced central sensitisation. NK cells appear to play a protective role in the neuroinflammatory cascade and may be used as a marker for pain chronicity.⁵⁶

Neuropathic pain models

Rodent models

There are significant ethical restrictions regarding investigation of chronic neuropathic pain

in vivo despite it being a common clinical problem. Many pre-clinical models of chronic neuropathic pain have been developed to provide information on this condition the most common being the sciatic nerve transection model. This was mostly used for investigation of acute nociceptive pain as only hypersensitivity and response to noxious painful stimuli were assessed^{57,58}

Chronic constriction injuries (CCI) in rodent models produced a peripheral mononeuropathy. These injury models assessed longer term effects of injury and assessed the behavioural, physiological and electrical alterations which occurred over time.⁵⁹

Partial sciatic nerve ligation (PSL) rodent models have shown behavioural alterations such as cold allodynia and mechanical hyperalgesia as little a one-week post injury.⁶⁰

From the physiological point of view, immune changes occur quite early post nerve injury. Complement system can be activated as soon as 6 hours after peripheral nerve injury.⁶¹

Upregulation of C3 expression (component of complement system) following peripheral nerve injury corresponded with a reduced expression of cell surface inhibitor of C3, decay accelerating factor (DAF), a natural regulator of complement activation in naïve animals.⁶²

Dorsal root ganglia of injured nerves have also demonstrated increased complement components after injury. On the ipsilateral DRG, increased C3b expression is predominantly located on satellite glial cells and infiltrating macrophages, whilst there is decreased DAF expression on the surface of neurons, increasing their susceptibility complement modulation.⁶³

Spinal cord activation of complement components has also been seen in many neuropathic pain models in particular C5a and its receptor C5aR. Complement activation has been associated with macrophage and microglial activation, as well as regulation of T cell responses, during both induction and effector phases of the immune response.

Animal models of chronic constriction injury (CCI), spinal nerve transection (SNT), complete Freund's adjuvant (CFA) and partial sciatic nerve ligation show decreased pain intensity in rodents with genetically altered T-cell phenotype (usually T-cell lacking or reduced, wild type). In CCI rodent models, T cell infiltration was observed were observed at 7 days and peaked at 21 days at proximal and distal sites of the injury. Regulatory T cells (Treg) identified as CD4+ FoxP3+ T cells was shown to suppress neuropathic pain induced

by peripheral nerve ligation and inflammatory pain in a model of neuritis.⁶⁴

Clinical Evidence in Pain

Cellular Composition of Healthy CSF

Flow cytometric and cellular quantification of cerebrospinal fluid (CSF) has been performed on normal CSF. A seminal paper by Svenningsson in 1995 investigated the lymphocyte phenotype and quantified the cellular subset distribution in normal cerebrospinal fluid of healthy CSF in volunteers. This paper showed a predominance of T lymphocytes and an almost total lack of B lymphocytes, an increased CD4:CD8 ratio with more predominant CD45RO-stained activated memory cells compared to lower proportion of naïve T cells, suggesting preferential recruitment of memory T cells to CSF.⁵⁹ A later paper showed that normal CSF is predominantly composed of CD4+ T lymphocytes, mostly with a central memory phenotype, and in addition contains very low frequencies of B lymphocytes, NK cells, and NKT lymphocytes.^{65,66}

Chemotherapy induced peripheral neuropathy

Paclitaxel is well-known chemotherapeutic agent which causes chemotherapy-induced peripheral neuropathic pain (CIPN). The mechanism of pathogenesis is unclear. Studies have investigated the T cell subsets and ratios after exposure to chemotherapeutic agents. Liu reported that intrathecal anti-CD8 reduced mechanical allodynia on day 5 and 6 after paclitaxel. This study also showed that intrathecal injection of CD8+ T cells worsened pain hypersensitivity, while injection of Treg cells briefly reduced mechanical allodynia.⁶⁷

Comparatively, resolution of chemotherapy-induced mechanical allodynia post cisplatin exposure was significantly delayed in the absence of T cells.^{68,69} Reconstitution with CD8+ T cells restored the resolution of mechanical allodynia. A similar response was not seen with reintroduction of CD4+ T cells. Transfer of exogenous CD8+ T cells did not produce similar resolution of pain, suggesting prior exposure of CD8+ T cells to cisplatin is required for pain resolution.⁷⁰

Vincristine in another chemotherapeutic agent which causes CIPN. Rodent studies have shown SIRT1 activity and expression were significantly lower in the sciatic nerve, spinal cord, and DRG of rats in the Vincristine group vs naive group.⁷¹

A study in 2016 investigating minocycline for prevention of paclitaxel-induced neuropathy in breast cancer patients showed minocycline did not reduce the incidence of chemotherapy-induced peripheral neuropathy but a reduction in acute pain syndrome quantified by reduced daily use of opioid was shown.⁷²

Diabetic Neuropathy

An immunohistochemical study examined 20 sural nerve biopsies from patients with a diagnosis of diabetic neuropathy. Results showed a lymphocytic infiltration in each tissue section with a significant increase in the number of lymphocytes present. These T cells were mostly CD8+ cells which expressed immunoreactive cytokines and MHC-II antigens, suggestive of activated effector T cells. This suggests T cell infiltration may participate in diabetic neuropathy.⁷³

A recent review article investigated the role Sirtuins play in chronic neuropathic pain pathogenesis. Sirtuins (in particular SIRT1) are a class of nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases that participate in many important cellular biological processes. SIRT1 directly colocalizes with Foxp3 and mediates its deacetylation.⁷⁴ As noted above, Foxp3 is one of the main regulators of Treg differentiation.^{75,76} In vitro data show that removal of SIRT1 in human CD4+ T cells induces Treg differentiation and increased Foxp3 mRNA expression, indicating that a decrease in SIRT1 expression contributes to an increase in Treg cells in patients with neuropathic pain.⁷⁷ These studies indicate that SIRT1 may exert its effects on neuropathic pain by regulating Treg induction.

Studies investigating the role SIRT1 plays in diabetic neuropathy also have performed. Levels of SIRT1 protein, mRNA, and their activity levels are lower in the spinal cord of diabetic neuropathic pain rats also.⁷⁸ These studies suggest Sirtuins and in particular SIRT1 may be potential therapeutic target for treatment in the future.

SPRINT Trial

SPRINT trial was published in 2017. It was a phase 2, multicentre, double-blinded, placebo-controlled study evaluating the efficacy and safety of five neublentin doses for treatment for radicular lower limb pain with radiological or electromyographic evidence of lower lumbar nerve root irritation. Neublentin was a first-in-class glial cell-derived neurotrophic factor. The smallest dose of neublentin showed a statistically significant differences from placebo in radicular lower limb

pain at weeks 1, 3, and 5, and in axial back pain at week 1. Further analysis suggested the greatest reductions overall were for radicular lower limb pain, with significant differences from placebo at weeks 1 and 3. Follow-up extended for 56 days after last dose. These results further highlight the neuroimmune role glial cells and other immune cells play in pain resolution.⁷⁹

An exploratory, multicentre, double-blind, placebo-controlled, two-period, cross-over trial was undertaken to evaluate the effect of diltapimod, a selective p38 MAPK inhibitor, on neuropathic pain symptoms and signs. P38 MAPK is a mediator involved in regulation and synthesis of inflammatory mediators. Patients with nerve trauma, radiculopathy or carpal tunnel syndrome were randomised to receive diltapimod or placebo. After 2 weeks, a statistically significant reduction in average daily pain scores using NRS (numerical rating scale) was noted.⁸⁰

LIPS Study

A study looking at low-dose IVIG therapy in the treatment of long standing Complex Regional Pain Syndrome (CRPS) showed low-dose immunoglobulin was not effective in relieving pain in patients with moderate to severe CRPS of 1–5 years' duration.⁸¹ Although this was a negative study, the need for further studies investigating other immune therapies in neuropathic pain is needed.

PD-1

PD-1 is a cell surface protein found on activated T and B lymphocytes. Its ligand PD-L1 is commonly found on macrophages and dendritic cells. When PD-1 binds PD-L1, the resulting complex reduces the efficacy of T cells in an effort to ensure the immune system is activated at a specific time only. This reduces the initiation of the chronic inflammatory pathway. In particular cancers such as non-small cell lung cancer and malignant melanoma, tumours over express PD-L1, resulting in the binding of PD-1 + T cells and the subsequent deactivation of the T cell. This allows development of the tumour unopposed and can result in late detection and diagnosis of cancer in the patient. Painless progression of cancer is seen in these cases which highlights the potential role by a novel pain pathway involving ligand-bound PD-1 and analgesia, activated PD-1/PD-L1 pathway may play in nociception.

A mouse study showed blocking PD-L1 or PD-1 elicits spontaneous pain and allodynia in melanoma-bearing mice. This suggests a previously

unrecognised role of PD-1 as an endogenous pain inhibitor and a neuromodulator.⁸²

B-cells in neuropathic pain models

B cells and the antibodies they produce when activated make up the adaptive immune system. T cells can activate B cells, which mature into plasma cells and secrete antibodies. This may be part of peripheral sensitisation. After an initial exposure, memory B cells remain in the circulation. After repeat exposure the antibody response is faster and more prolonged. The role B cells plays in chronic neuropathic pain is unclear. A study examining the immunohistochemical quantification of infiltrating B-cells in the epithelium of patients with interstitial cystitis showed a clonal expansion of B cells as a consequence of local immune response.

In an animal model of CRPS, wild-type mice lacking B cells were given IgM with a resulting pronociceptive effect on a fractured limb possibly mediated by complement C5 and downstream pro-inflammatory cytokine release.⁸³

Opioids and the Immune System

Analgesic effects of T cell-producing endogenous opioids have been investigated in models of chronic pain as infiltrating T cells and other leukocytes in the damaged nerve produce and release opioid peptides.⁸⁴ It has been suggested anti-inflammatory IL-4 production is mediated by opioid exposure such as fentanyl and methadone inducing a substantial response IL-4 production by T cells. On the contrary, lowered levels of IL-4 are produced with morphine and buprenorphine.⁸⁵ Long-term morphine exposure on the circulating T cell population dynamics in rhesus monkeys showed numbers of circulating Treg cells and the functional activity of Th17 cells significantly increased with chronic morphine administration. The functional result of these immune alterations needs further investigation.⁸⁶

T cells for Resolution of Pain

T cells also promote resolution of pain and prevent the transition from acute to chronic pain. The pathways involving T cells to resolve pain are not fully known, but some mechanisms have been investigated. Subsets of Treg cells, Th2 cells, and suppressor CD8+ T cells have been shown to reduce or resolve pain. This is likely through their capacity to switch to an anti-inflammatory environment.⁸⁷⁻⁸⁹ Many neuroprotective and pain resolving effects of these T-cells could be recreated by IL-10 administration and are absent

in mice lacking IL-10, pointing to IL-10 as a major player in the pain resolution effects of T cells.⁹⁰ The exact mechanism of IL-10 production is not known but it is thought T cells mediate production of IL-10 by activation of other CNS-resident cells.⁹

Conclusion

Our knowledge regarding the pathogenesis of chronic neuropathic pain has evolved over the last 2 decades. It is now accepted that T lymphocyte differentiation, activation and subset ratio alteration contributes to chronic neuropathic pain initiation and maintenance. T lymphocytes also appear to play a major role in pain resolution. The role played by B cells is less clear but appears clinically relevant. B-cell targeted therapies such as rituximab are in clinical use already for inflammatory arthropathies. Further investigation in the area of B cells and CNP are needed also. T cells also appear to have an anti-inflammatory effect, in particular Treg cells. Tregs contribute to resolution of neuropathic pain, but mechanism of

initiation and eventual resolution is unknown. Potential targets for novel therapeutic agents based on T cells and pain resolution is an area needing further investigation. Advanced understating of T cell and B cell subset alterations and behaviours in response to injury to the central nervous system will allow identification of the “switch event” which results in the chronicity of CNP.

Another area needing further studies is the dorsal root ganglion. Investigation of changes occurring at this location pre and post interventional procedures will allow us to identify a target for treatment.

A challenging area of in vivo studies is the difficulty recruiting patients for CNP studies. For this reason, the sample sizes tend to be small. However, clinically relevant findings although small can offer important information to further our understanding of CNP.

References

1. Headland SE, Norling LV. The resolution of inflammation: Principles and challenges. *Semin Immunol.* 2015;27(3):149-160. doi:10.1016/j.smim.2015.03.014
2. Rice ASC, Smith BH, Blyth FM. Pain and the global burden of disease. *Pain.* 2016;157(4):791-796. doi:10.1097/j.pain.0000000000000454
3. International Association for the Study of Pain. IASP Taxonomy. Pain terms. Neuropathic pain. Updated 2017 Dec 14. www.iasp-pain.org/Taxonomy#Neuropathicpain [cited 2018 May 1]
4. Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: results of a French nationwide survey. *Pain.* 2011 Dec;152(12):2836-2843. DOI: 10.1016/j.pain.2011.09.014. PMID: 22019149.
5. Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. *Nature reviews. Immunology.* 2014 Apr;14(4):217-231. DOI: 10.1038/nri3621. PMID: 24577438; PMCID: PMC5525062.
6. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162-173. doi:10.1016/S1474-4422(14)70251-0
7. Deer TR, Grider JS, Lamer TJ, et al. A Systematic Literature Review of Spine Neurostimulation Therapies for the Treatment of Pain [published correction appears in *Pain Med.* 2021 Feb 4;22(1):236]. *Pain Med.* 2020;21(7):1421-1432. doi:10.1093/pm/pnz353
8. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain.* 2007;132(1-2):179-188. doi:10.1016/j.pain.2007.07.028
9. Albrecht DS, Ahmed SU, Kettner NW, et al. Neuroinflammation of the spinal cord and nerve roots in chronic radicular pain patients. *Pain.* 2018;159(5):968-977. doi:10.1097/j.pain.0000000000001171
10. Hundehage P, Fernandez-Orth J, Römer P, et al. Targeting Voltage-Dependent Calcium Channels with Pregabalin Exerts a Direct Neuroprotective Effect in an Animal Model of Multiple Sclerosis. *Neurosignals.* 2018;26(1):77-93. doi:10.1159/000495425
11. Szepanowski F, Winkelhausen M, Steubing RD, Mausberg AK, Kleinschnitz C, Stettner M. LPA₁ signaling drives Schwann cell dedifferentiation in experimental autoimmune neuritis. *J Neuroinflammation.* 2021;18(1):293. Published 2021 Dec 17. doi:10.1186/s12974-021-02350-5
12. Duan Y-W, Chen S-X, Li Q-Y, Zang Y. Neuroimmune Mechanisms Underlying Neuropathic Pain: The Potential Role of TNF- α -Necroptosis Pathway. *International Journal of Molecular Sciences.* 2022; 23(13):7191. <https://doi.org/10.3390/ijms23137191>
13. Royds J, McCrory C. Neuroimmunity and chronic pain. *BJA Educ.* 2018;18(12):377-383. doi:10.1016/j.bjae.2018.09.003
14. Kavelaars A, Heijnen CJ. Immune regulation of pain: Friend and foe. *Sci Transl Med.* 2021;13(619):eabj7152. doi:10.1126/scitranslmed.abj7152
15. Kavelaars A, Heijnen CJ. T Cells as Guardians of Pain Resolution. *Trends Mol Med.* 2021;27(4):302-313. doi:10.1016/j.molmed.2020.12.007
16. Liu, X., Yang, W., Zhu, C. et al. Toll-like receptors and their role in neuropathic pain and migraine. *Mol Brain* 15, 73 (2022). <https://doi.org/10.1186/s13041-022-00960-5>
17. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature.* 2008;454(7203):445-454. doi:10.1038/nature07204
18. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 2015;14(4):388-405. doi:10.1016/S1474-4422(15)70016-5
19. Morales I, Guzmán-Martínez L, Cerda-Troncoso C, Farías GA, Maccioni RB. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. *Front Cell Neurosci.* 2014;8:112. Published 2014 Apr 22. doi:10.3389/fncel.2014.00112
20. Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. *N Engl J Med.* 2006;354(9):942-955. doi:10.1056/NEJMra052130
21. Lim SL, Rodriguez-Ortiz CJ, Kitazawa M. Infection, systemic inflammation, and Alzheimer's disease. *Microbes Infect.* 2015;17(8):549-556. doi:10.1016/j.micinf.2015.04.004
22. Lun MP, Monuki ES, Lehtinen MK. Development and functions of the choroid plexus-

- cerebrospinal fluid system. *Nat Rev Neurosci*. 2015;16(8):445-457. doi:10.1038/nrn3921
23. Laumet G, Ma J, Robison AJ, Kumari S, Heijnen CJ, Kavelaars A. T Cells as an Emerging Target for Chronic Pain Therapy. *Front Mol Neurosci*. 2019;12:216. Published 2019 Sep 11. doi:10.3389/fnmol.2019.00216
24. Anolik JH, Looney RJ, Lund FE, Randall TD, Sanz I. Insights into the heterogeneity of human B cells: diverse functions, roles in autoimmunity, and use as therapeutic targets. *Immunol Res*. 2009;45(2-3):144-158. doi:10.1007/s12026-009-8096-7
25. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. *Nat Immunol*. 2002;3(10):944-950. doi:10.1038/ni833
26. Lee, D.S.W., Rojas, O.L. & Gommerman, J.L. B cell depletion therapies in autoimmune disease: advances and mechanistic insights. *Nat Rev Drug Discov* **20**, 179–199 (2021). <https://doi.org/10.1038/s41573-020-00092-2>
27. Catrina AI, Svensson CI, Malmström V, Schett G, Klareskog L. Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. *Nat Rev Rheumatol*. 2017;13(2):79-86. doi:10.1038/nrrheum.2016.200
28. Mauri C, Basma A. Immune regulatory function of B cells. *Annu Rev Immunol*. 2012;30:221-241. doi:10.1146/annurev-immunol-020711-074934
29. Kaminski DA, Wei C, Qian Y, Rosenberg AF, Sanz I. Advances in human B cell phenotypic profiling. *Front Immunol*. 2012;3:302. Published 2012 Oct 10. doi:10.3389/fimmu.2012.00302
30. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med*. 2004;350(25):2572-2581. doi:10.1056/NEJMoa032534
31. Lassen J, Stürner KH, Gierthmühlen J, et al. Protective role of natural killer cells in neuropathic pain conditions. *Pain*. 2021;162(9):2366-2375. doi:10.1097/j.pain.0000000000002274
32. Lin SJ, Kuo ML, Hsiao HS, et al. Cytotoxic Function and Cytokine Production of Natural Killer Cells and Natural Killer T-Like Cells in Systemic Lupus Erythematosus Regulation with Interleukin-15. *Mediators Inflamm*. 2019;2019:4236562. Published 2019 Mar 31. doi:10.1155/2019/4236562
33. Hudspeth K, Wang S, Wang J, et al. Natural killer cell expression of Ki67 is associated with elevated serum IL-15, disease activity and nephritis in systemic lupus erythematosus. *Clin Exp Immunol*. 2019;196(2):226-236. doi:10.1111/cei.13263
34. Vega-Avelaira D, Géranton SM, Fitzgerald M. Differential regulation of immune responses and macrophage/neuron interactions in the dorsal root ganglion in young and adult rats following nerve injury. *Mol Pain*. 2009;5:70. Published 2009 Dec 10. doi:10.1186/1744-8069-5-70
35. Martínez-Lavín M. Dorsal root ganglia: fibromyalgia pain factory?. *Clin Rheumatol*. 2021;40(2):783-787. doi:10.1007/s10067-020-05528-z
36. Liu JA, Yu J, Cheung CW. Immune Actions on the Peripheral Nervous System in Pain. *Int J Mol Sci*. 2021;22(3):1448. Published 2021 Feb 1. doi:10.3390/ijms22031448
37. Watanabe S, Alexander M, Misharin AV, Budinger GRS. The role of macrophages in the resolution of inflammation. *J Clin Invest*. 2019;129(7):2619-2628. Published 2019 May 20. doi:10.1172/JCI124615
38. Gaudet, A.D., Popovich, P.G. & Ramer, M.S. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. *J Neuroinflammation* **8**, 110 (2011). <https://doi.org/10.1186/1742-2094-8-110>
39. Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med*. 2015;3(10):136. doi:10.3978/j.issn.2305-5839.2015.03.49
40. Li, H., Fu, Q., Philips, K. et al. Leukocyte inflammatory phenotype and function in migraine patients compared with matched non-migraine volunteers: a pilot study. *BMC Neurol* **22**, 278 (2022). <https://doi.org/10.1186/s12883-022-02781-4>
41. Mangiacavalli S, Corso A, De Amici M, et al. Emergent T-helper 2 profile with high interleukin-6 levels correlates with the appearance of bortezomib-induced neuropathic pain. *Br J Haematol*. 2010;149(6):916-918. doi:10.1111/j.1365-2141.2010.08138.x
42. Luchting B, Rachinger-Adam B, Zeitler J, et al. Disrupted TH17/Treg balance in patients with chronic low back pain. *PLoS One*. 2014;9(8):e104883. Published 2014 Aug 14. doi:10.1371/journal.pone.0104883
43. Russo, M.A., Fiore, N.T., van Vreden, C. et al. Expansion and activation of distinct central memory T lymphocyte subsets in complex regional pain syndrome. *J Neuroinflammation* **16**, 63

- (2019). <https://doi.org/10.1186/s12974-019-1449-9>
44. Heyn, J., Azad, S.C. & Luchting, B. Altered regulation of the T-cell system in patients with CRPS. *Inflamm. Res.* **68**, 1–6 (2019). <https://doi.org/10.1007/s00011-018-1182-3>
45. Plein LM, Rittner HL. Opioids and the immune system - friend or foe. *Br J Pharmacol.* 2018;175(14):2717-2725. doi:10.1111/bph.13750
46. Royds J, Cassidy H, Conroy MJ, Dunne MR, Lysaght J, McCrory C. Examination and characterisation of the effect of amitriptyline therapy for chronic neuropathic pain on neuropeptide and proteomic constituents of human cerebrospinal fluid. *Brain Behav Immun Health.* 2020;10:100184. Published 2020 Dec 7. doi:10.1016/j.bbih.2020.100184
47. Moore D, Galvin D, Conroy MJ, et al. Characterisation of the effects of pulsed radio frequency treatment of the dorsal root ganglion on cerebrospinal fluid cellular and peptide constituents in patients with chronic radicular pain: A randomised, triple-blinded, controlled trial. *J Neuroimmunol.* 2020;343:577219. doi:10.1016/j.jneuroim.2020.577219
48. Halievski K, Sengar AS, Hicks J, Haight J, Salter MW, Steinberg BE. Cholinergic modulation is independent of T lymphocytes in a mouse model of neuropathic pain. *Mol Pain.* 2022;18:17448069221076634. doi:10.1177/17448069221076634
49. Hayward A, Levin M, Wolf W, Angelova G, Gilden D. Varicella-zoster virus-specific immunity after herpes zoster. *J Infect Dis.* 1991;163(4):873-875. doi:10.1093/infdis/163.4.873
50. Maeda D, Akiyama Y, Morikawa T, et al. Hunner-Type (Classic) Interstitial Cystitis: A Distinct Inflammatory Disorder Characterized by Pancystitis, with Frequent Expansion of Clonal B-Cells and Epithelial Denudation. *PLoS One.* 2015;10(11):e0143316. Published 2015 Nov 20. doi:10.1371/journal.pone.0143316
51. Wurth S, Kuenz B, Bsteh G, et al. Cerebrospinal fluid B cells and disease progression in multiple sclerosis - A longitudinal prospective study. *PLoS One.* 2017;12(8):e0182462. Published 2017 Aug 4. doi:10.1371/journal.pone.0182462
52. Wigerblad G, Bas DB, Fernades-Cerqueira C et al. Autoantibodies to citrullinated proteins may induce joint pain independent of inflammation. *Annals of the rheumatic diseases.* 2016; 75(4), 730-738.
53. Li M, Peake PW, Charlesworth JA, Tracey DJ, Moalem-Taylor G. Complement activation contributes to leukocyte recruitment and neuropathic pain following peripheral nerve injury in rats. *Eur J Neurosci.* 2007;26(12):3486-3500. doi:10.1111/j.1460-9568.2007.05971.x
54. Levin ME, Jin JG, Ji RR, et al. Complement activation in the peripheral nervous system following the spinal nerve ligation model of neuropathic pain. *Pain.* 2008;137(1):182-201. doi:10.1016/j.pain.2007.11.005
55. Atzeni F, Doria A, Turiel M et al. What is the role of rituximab in the treatment of rheumatoid arthritis? *Autoimmun Rev.* 2007; 6:553–8. doi:10.1016/j.autrev.2007.02.004
56. Lassen J, Stürner KH, Gierthmühlen J, et al. Protective role of natural killer cells in neuropathic pain conditions. *Pain.* 2021;162(9):2366-2375. doi:10.1097/j.pain.0000000000002274
57. Wall PD, Gutnick M. Properties of afferent nerve impulses originating from a neuroma. *Nature.* 1974;248(5451):740-743. doi:10.1038/248740a0
58. Wall PD, Devor M, Inbal R, et al. Autotomy following peripheral nerve lesions: experimental anaesthesia dolorosa. *Pain.* 1979;7(2):103-113. doi:10.1016/0304-3959(79)90002-2
59. Gabay E, Tal M. Pain behavior and nerve electrophysiology in the CCI model of neuropathic pain. *Pain.* 2004;110(1-2):354-360. doi:10.1016/j.pain.2004.04.021
60. De Vry J, Kuhl E, Franken-Kunkel P, Eckel G. Pharmacological characterization of the chronic constriction injury model of neuropathic pain. *Eur J Pharmacol.* 2004;491(2-3):137-148. doi:10.1016/j.ejphar.2004.03.051
61. Dowdall T, Robinson I, Meert TF. Comparison of five different rat models of peripheral nerve injury. *Pharmacol Biochem Behav.* 2005;80(1):93-108. doi:10.1016/j.pbb.2004.10.016
62. Li M, Peake PW, Charlesworth JA, Tracey DJ, Moalem-Taylor G. Complement activation contributes to leukocyte recruitment and neuropathic pain following peripheral nerve injury in rats. *Eur J Neurosci.* 2007;26(12):3486-3500. doi:10.1111/j.1460-9568.2007.05971.x
63. Levin ME, Jin JG, Ji RR, et al. Complement activation in the peripheral nervous system following the spinal nerve ligation model of neuropathic pain. *Pain.* 2008;137(1):182-201. doi:10.1016/j.pain.2007.11.005

64. Dailey AT, Avellino AM, Benthem L et al. Complement depletion reduces macrophage infiltration and activation during Wallerian degeneration and axonal regeneration. *Journal of Neuroscience*. 1998; 18(17), 6713-6722.
65. de Graaf MT, de Jongste AH, Kraan J, Boonstra JG, Sillevs Smitt PA, Gratama JW. Flow cytometric characterization of cerebrospinal fluid cells. *Cytometry B Clin Cytom*. 2011;80(5):271-281. doi:10.1002/cyto.b.20603
66. Svenningsson A, Andersen O, Hansson GK, Stemme S. Reduced frequency of memory CD8+ T lymphocytes in cerebrospinal fluid and blood of patients with multiple sclerosis. *Autoimmunity*. 1995;21(4):231-239. doi:10.3109/08916939509001941
67. Liu XJ, Zhang Y, Liu T, et al. Nociceptive neurons regulate innate and adaptive immunity and neuropathic pain through MyD88 adapter. *Cell Res*. 2014;24(11):1374-1377. doi:10.1038/cr.2014.106
68. Krukowski K, Eijkelkamp N, Laumet G et al. CD8+ T cells and endogenous IL-10 are required for resolution of chemotherapy-induced neuropathic pain. *J. Neurosci*. 2016; 36, 11074–11083. doi: 10.1523/JNEUROSCI.3708-15.2016
69. Laumet G, Dantzer R, Krukowski K et al. N. T lymphocytes are required for resolution of inflammatory pain and depression-like behavior. *Brain Behav. Immun*. 2016; 57, e5–e6. doi: 10.1016/j.bbi.2016.07.022
70. Laumet G, Edralin JD, Dantzer R, Heijnen CJ, Kavelaars A. Cisplatin educates CD8+ T cells to prevent and resolve chemotherapy-induced peripheral neuropathy in mice. *Pain*. 2019;160(6):1459-1468. doi:10.1097/j.pain.0000000000001512
71. Zhang XL, Zhang JJ, Chen ZH, et al. Difference of pain vulnerability in adult and juvenile rodents: the role of SIRT1-mediated CIC-3 trafficking in sensory neurons. *Pain*. 2021;162(6):1882-1896. doi:10.1097/j.pain.0000000000002176
72. Pachman DR, Dockter T, Zekan PJ, et al. A pilot study of minocycline for the prevention of paclitaxel-associated neuropathy: ACCRU study RU221408I. *Support Care Cancer*. 2017;25(11):3407-3416. doi:10.1007/s00520-017-3760-2
73. Younger DS. Diabetic neuropathy: a clinical and neuropathological study of 107 patients. *Neurol Res Int*. 2010;2010:140379. doi:10.1155/2010/140379
74. Zhang Y, Chi D. Overexpression of SIRT2 Alleviates Neuropathic Pain and Neuroinflammation Through Deacetylation of Transcription Factor Nuclear Factor-Kappa B. *Inflammation*. 2018;41(2):569-578. doi:10.1007/s10753-017-0713-3
75. Beier UH, Akimova T, Liu Y, Wang L, Hancock WW. Histone/protein deacetylases control Foxp3 expression and the heat shock response of T-regulatory cells. *Curr Opin Immunol*. 2011;23(5):670-678. doi:10.1016/j.coi.2011.07.002
76. van Loosdregt J, Brunen D, Fleskens V, Pals CE, Lam EW, Coffey PJ. Rapid temporal control of Foxp3 protein degradation by sirtuin-1. *PLoS One*. 2011;6(4):e19047. Published 2011 Apr 20. doi:10.1371/journal.pone.0019047
77. Heyn J, Luchting B, Hinske LC, Hübner M, Azad SC, Kreth S. miR-124a and miR-155 enhance differentiation of regulatory T cells in patients with neuropathic pain. *J Neuroinflammation*. 2016;13(1):248. Published 2016 Sep 20. doi:10.1186/s12974-016-0712-6
78. Oza MJ, Kulkarni YA. Formononetin Ameliorates Diabetic Neuropathy by Increasing Expression of SIRT1 and NGF. *Chem Biodivers*. 2020;17(6):e2000162. doi:10.1002/cbdv.202000162
79. Backonja M, Williams L, Miao X, Katz N, Chen C. Safety and efficacy of neublentin in painful lumbosacral radiculopathy: a randomized, double-blinded, placebo-controlled phase 2 trial using Bayesian adaptive design (the SPRINT trial). *Pain*. 2017;158(9):1802-1812. doi:10.1097/j.pain.0000000000000983
80. Anand P, Shenoy R, Palmer JE, et al. Clinical trial of the p38 MAP kinase inhibitor diltapimod in neuropathic pain following nerve injury. *Eur J Pain*. 2011;15(10):1040-1048. doi:10.1016/j.ejpain.2011.04.005
81. Goebel A, Bisla J, Carganillo R, et al. A randomised placebo-controlled Phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial). Southampton (UK): NIHR Journals Library; November 2017.
82. Chen G, Kim YH, Li H, et al. PD-L1 inhibits acute and chronic pain by suppressing nociceptive neuron activity via PD-1 [published correction appears in *Nat Neurosci*. 2019 Mar;22(3):503]. *Nat Neurosci*. 2017;20(7):917-926. doi:10.1038/nn.4571
83. Li M, Peake PW, Charlesworth JA, Tracey DJ, Moalem-Taylor G. Complement activation contributes to leukocyte recruitment and neuropathic pain following peripheral nerve injury

- in rats. *Eur J Neurosci.* 2007;26(12):3486-3500. doi:10.1111/j.1460-9568.2007.05971.x
84. Labuz D, Schmidt Y, Schreier A, Rittner HL, Mousa SA, Machelska H. Immune cell-derived opioids protect against neuropathic pain in mice [published correction appears in *J Clin Invest.* 2009 Apr;119(4):1051]. *J Clin Invest.* 2009;119(2):278-286. doi:10.1172/JCI36246
85. Börner C, Lanciotti S, Koch T, Höllt V, Kraus J. μ opioid receptor agonist-selective regulation of interleukin-4 in T lymphocytes. *J Neuroimmunol.* 2013;263(1-2):35-42. doi:10.1016/j.jneuroim.2013.07.012
86. Cornwell WD, Lewis MG, Fan X, Rappaport J, Rogers TJ. Effect of chronic morphine administration on circulating T cell population dynamics in rhesus macaques. *J Neuroimmunol.* 2013;265(1-2):43-50. doi:10.1016/j.jneuroim.2013.09.013
87. Moalem G, Xu K, Yu L. T lymphocytes play a role in neuropathic pain following peripheral nerve injury in rats. *Neuroscience.* 2004;129(3):767-777. doi:10.1016/j.neuroscience.2004.08.035
88. Austin PJ, Kim CF, Perera CJ, Moalem-Taylor G. Regulatory T cells attenuate neuropathic pain following peripheral nerve injury and experimental autoimmune neuritis. *Pain.* 2012;153(9):1916-1931. doi:10.1016/j.pain.2012.06.005
89. Baddack-Werncke U, Busch-Dienstfertig M, González-Rodríguez S, et al. Cytotoxic T cells modulate inflammation and endogenous opioid analgesia in chronic arthritis. *J Neuroinflammation.* 2017;14(1):30. Published 2017 Feb 6. doi:10.1186/s12974-017-0804-y
90. Duffy SS, Keating BA, Moalem-Taylor G. Adoptive Transfer of Regulatory T Cells as a Promising Immunotherapy for the Treatment of Multiple Sclerosis. *Front Neurosci.* 2019;13:1107. Published 2019 Oct 15. doi:10.3389/fnins.2019.01107
91. Laumet G, Edralin JD, Chiang AC, Dantzer R, Heijnen CJ, Kavelaars A. Resolution of inflammation-induced depression requires T lymphocytes and endogenous brain interleukin-10 signaling. *Neuropsychopharmacology.* 2018;43(13):2597-2605. doi:10.1038/s41386-018-0154-1