Title

The therapeutic potential of natural killer cells in neuropathic pain

Authors

Hyoung Woo Kim[1], Shuaiwei Wang[2], Alexander J Davies[2†], Seog Bae Oh[1*]

[1]Department of Neurobiology and Physiology, School of Dentistry, and Dental Research Institute, Seoul National University, Seoul, Republic of Korea

[2]Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Correspondence

[†]alexander.davies@ndcn.ox.ac.uk

[*]odolbae@snu.ac.kr

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Abstract

Novel, disease-modifying treatments for neuropathic pain are urgently required. The cellular immune response to nerve injury represents a promising target for therapeutic development. Recently, the role of natural killer (NK) cells in both the central and peripheral nervous system disease has been the subject of growing interest. In this opinion piece, we set out the case for NK cell-based intervention as a promising avenue for development in the management of neuropathic pain. We explore the potential cellular and molecular targets of NK cells in the peripheral nervous system by contrasting with their reported functional roles in central nervous system diseases, and suggest strategies for utilizing the beneficial functions of NK cells and immune-based therapeutics in the context of neuropathic pain.

Main text

In need of new approaches to neuropathic pain

Neuropathic pain is caused by lesion or disease of the somatosensory nervous system resulting from pathological conditions as diverse as trauma, diabetes, chemotherapy and viral infection. Peripheral neuropathies are a leading cause of chronic pain with a strong negative impact on quality of life [1]. Current therapeutic drugs including anticonvulsants, antidepressants and opioids act by silencing pain pathways but do not address the pathophysiological mechanisms underlying neuropathic pain, and can produce serious adverse narcotic effects [2]. According to the US Center for Disease Control and Prevention (CDC), during 1999–2020 more than 564,000 people in the US died from an opioid overdose driven in large part by a dependency on prescription opioid analgesics [3]. As nociceptive pain has protective function, molecules and signaling pathways responsible for nociceptive pain might not be suitable therapeutic targets for persistent and chronic neuropathic pain. Due to the heterogeneity of disease etiology and the diversity of pathophysiological mechanisms underlying neuropathic pain, combination therapies, rather than a single drug target, have been recently suggested for future therapeutic development [2, 4]. However, in order to successfully manage neuropathic pain in the long-term, and most effectively combat the opioid crisis, novel and disease-modifying therapeutic approaches with high analgesic potency and low risk of abuse are urgently required [5].

The involvement of innate and adaptive immune responses in various chronic pain conditions, and the demonstration that neuropathic pain manifests with some features of chronic neuroinflammatory disease in the nervous system [6], has generated considerable interest in the immune system as a source of potential therapeutic intervention. Neuroinflammation in chronic pain involves interactions with non-neuronal cells throughout the neural pathways of pain; for example, activation of resident neuroglial cells such as

microglia and astrocytes within the brain and spinal cord of the central nervous system (CNS), alterations to resident glia and structural cells of the peripheral nervous system (PNS), as well as infiltration of circulating immune cells at all levels of the nervous system [7].

While traditionally seen solely as a driver of neuropathic pain development, recent evidence has revealed potential cellular immune mechanisms underlying the natural *resolution* of neuropathic pain [8-14]. In this opinion piece, we explore the possibility of harnessing one such immune cell, natural killer (NK) cells, as a novel therapeutic strategy for the treatment of chronic neuropathic pain and discuss the potential benefits and pitfalls of this approach.

NK cells represent 5-20 % of total circulating lymphocytes in the body and are known primarily as killers of unwanted cells (e.g. tumor cells, virus infected cells) by introducing cytolytic proteases, such as granzymes, via perforin pores into the target cell cytoplasm. Additional distinct subsets of NK cells preferentially perform an immunomodulatory role by releasing inflammatory cytokines [15]. NK cell cytotoxicity against a target cell is controlled by the ability to detect germline-encoded, major histocompatibility (MHC) I-like activating and inhibitory ligands on the target cell surface and unlike adaptive T cells do not require prior sensitization [15] (see **Box 1**). Recent evidence points to the role of cytotoxic NK cells in response to nerve injury, the function of which can in turn affect pain outcomes [8, 16].

Natural pain killers?

Early reports into the neuronal regulation of NK cell cytotoxicity provided a link to acute pain. Within 30 min of acutely painful electric stimulation in humans, both NK cell cytotoxicity, as measured by the specific lysis of the K652 tumor cell line, and the proportion of $CD56^+$ cells in peripheral blood, were significantly increased [17]. In a later report, acute heat shock pain in mice was shown to cause a similar increase in the cytotoxicity of splenic

NK cells [18].

Conversely, studies of NK cells in *chronic* pain conditions suggest an association with *decreased* numbers and/or cytotoxic function of systemic NK cells. Both inherited and infectious arthritis patients showed a decrease in the frequency of perforin-expressing cytotoxic NK cells in the blood, while there was an increase in regulatory NK cells expressing TNFα [19]. NK cell frequency was negatively correlated with mechanical pain sensitivity in herpes zoster neuralgia and polyneuropathy patients [20], and significantly decreased in patients with fibromyalgia – a chronic pain condition of unknown etiology - compared to healthy controls [21, 22]; furthermore, NK cells in the blood of people with fibromyalgia expressed higher level of degranulation marker $CD107a^{+}$ and inhibitory receptor TIGIT, implying recent NK cell activity followed by a state of exhaustion [22]. A study of CD56 bright and dim NK cell populations (see **Box 1**) in people with heterogeneous chronic pain conditions showed no correlation with pain scores [23], suggesting that NK cell modulation is not necessarily a ubiquitous feature across all pain syndromes. Further study of NK cell responses in specific diseases will require consideration of the heterogeneity of NK cell subsets across different tissues [24].

Investigations relating NK cells to chronic pain outcomes point to a potential benefit in NK cell gain-of-function after injury. In preclinical studies systemic administration of interleukin (IL)-2 prevented chronic pain-like hypersensitivity after sciatic nerve crush injury that was dependent on the presence of endogenous NK cells despite the pleiotropic action of this cytokine *in vivo* [8]. Analogously, the analgesic effect of electro-acupuncture in rats with chronic constriction injury correlated with a regulation of IL-2 levels, and was again dependent on NK cell activity [25]. People with spinal cord injury showed lower levels of NK cell-related genes in whole blood compared to uninjured controls [26], and whole blood RNA sequencing of people with low back pain revealed a dynamic increase in NK cell frequency

in the group whose pain resolved after three months compared to those that did not [9, 27].

The apparent inverse relationship between NK cell activity and chronic pain observed in clinical studies may be related to stress hormone-mediated changes in the immune function [28]. Acute stress hormones (e.g. catecholamine) tend to increase NK cell numbers [29], while chronic stress hormones (i.e. corticosteroids) impair NK cell cytotoxicity [30]. Nociceptive pain may activate the sympathetic nervous system as an acute stressor, and chronic pathological pain is associated with activation of the hypothalamus-pituitary-adrenal (HPA) axis, upon which chronic pain may act as a long-term stressor [31].

Overall, growing pre-clinical and clinical research suggest a potential therapeutic benefit to restoring NK cell function in various chronic pain diseases. However, further mechanistic studies are required to distinguish the causative and correlative changes in NK cell properties in clinical pain conditions.

Finding the motive for NK cells in the peripheral nervous system

How might NK cells function after nerve injury aid the resolution of neuropathic pain? Axons expressing the self-antigen retinoic acid early protein 1 (RAE1), a membrane-bound stress ligand encoded by the *Raet1* gene family in mice, also known as the UL16 binding protein (*ULBP)* gene family in humans, are targeted for pruning by NK cells expressing the cytotoxicity receptor Natural Killer group 2D (NKG2D) [8]. Ligand-specific engagement of sensory neurons by cytotoxic NK cells – leading to direct axonal degeneration – appeared to be restricted to an injury context [8]. ULBP ligands have also been identified in epidermal nerve fibers of fibromyalgia patients with CD56+ cells shown in close apposition [22], suggesting a homologous mechanism may occur in humans [27].

While the regulation of stress ligands in sensory neurons after nerve injury remains

unknown, we do know that the expression of the RAE1 in other tissues can be upregulated by Ras [32] and PI3K signaling [33] pathways, which are crucial to axonal guidance and neuronal survival via growth factor receptor signaling [34]. Activation of the PI3K-AKT-mTOR cascade in chronic inflammation was identified as a key risk factor for neuronal hyperexcitability by promoting elongation and collateral branching of the nerve terminals [35]. Thus, stress-ligand expression could indicate ongoing aberrant neuronal activity in sensory axons.

Recent evidence suggests that misdirected reinnervation after traumatic nerve injury contributes significantly to the neuropathic phenotype in mice [36]. Such 'miswired' sensory neurons might therefore be a target for NK cell-mediated pruning [8]. The analgesic efficacy of the genetic ablation of these nociceptive afferents [36] suggests the potential for cytotoxic NK cells to offer a form of 'cellular neurosurgery' for chronic neuropathic pain, akin to the 'molecular neurosurgery' of chemical neuro-ablation [37, 38]. Knowledge of the sensory neuron subtypes targeted by NK cell receptor-ligand interactions will be essential in the design of any potential cellular therapies for targeted neuro-ablation.

Cellular senescence - a pause in the life cycle of a cell by stressors such as tissue injury [39] – is another potential target for immune surveillance by cytotoxic NK cells [40]. Senescence-like processes are increasingly recognized in neuroinflammatory diseases, including peripheral neuropathies [41]. After nerve crush injury in rats, senescence-associated genes and β-galactosidase (SA-β-gal) expression increase in the sciatic nerves [42]. Interestingly, the number of SA-β-gal positive cells declined around two weeks, suggesting the majority are removed or transition out of a senescence-like state [42]. Schwann cells adopt a senescence-like phenotype after peripheral nerve injury in aged and chronically de-innervated mice. Elimination of senescent Schwann cells by the senolytic drug ABT-263 reduces neuroinflammation, and improves reinnervation and sensory recovery [43].

Like sensory neurons after peripheral nerve injury [8], recruitment of NK cells to senescent fibroblasts is driven by the expression of NKG2D ligands [44]. The failure of senescence elimination may lead to chronic inflammation and fibrosis [39, 44, 45], both of which are significant risk factors for neuropathic pain in humans [46, 47].

NK cells are also capable of immune modulation, either indirectly via cytokine or chemokine release, or direct killing of other immune cells [48]. Recently, RNA sequencing of the mouse sciatic nerve after crush injury revealed pathways of potential cross-talk between infiltrating NK cells and dendritic cells (DC), which may in turn affect DC migration and function [49]. NK cells were also shown to reduce fibrosis and inflammation after skeletal muscle injury by contact-mediated apoptosis of infiltrating neutrophils [50]. This capability of NK cells to modulate the inflammatory response of DCs, neutrophils, as well as macrophages [51], is therefore likely to influence functional outcomes owing to the role of these cells in the immune response to peripheral nerve injury [52, 53].

In summary, NK cell function could in theory result in the resolution of neuropathic pain in the context of peripheral nerve injury by directed cytotoxicity against a number of pathological cellular targets (**Figure 1**, **Key Figure**). The outcome of indirect immune modulation by NK cells, while clearly a possibility within the inflammatory milieu of an injured nerve, remains more complex to predict (see **Box 2**).

What can we learn from NK cells in the central nervous system?

Numerous lines of evidence have shown the involvement of NK cells in the brain and spinal cord in health and disease [54] (**Figure 2**). Current knowledge of the molecular mechanisms underlying NK cell function in the CNS provides important insights into the potential roles of NK cells in PNS diseases, and may help guide the development of NK-

based immunotherapies for neuropathic pain.

Like immature sensory neurons of the PNS [55], neural stem cells (NSCs) in mice express high levels of the NK activating ligand RAE1, suggesting a direct interaction between NK cells and resident cells in the CNS [56]. In adults, NSCs sustain their self-tolerance against NK cells through co-expression of the inhibitory CD94/NKG2A receptor ligand Qa1 [56]. A reduction in Qa1 expression at the late stage of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, leads to the loss of self-tolerance and the elimination of NSCs by NK cells, limiting the recovery from brain inflammation [56]. Neural progenitor cells (NPCs) also express RAE1, promoting their elimination, and diminish the survival of neurons in NPC allografts [57, 58]. Cytotoxic NK cells are also capable of targeting motor neurons expressing ligands for both NKG2D and DNAM-1 receptors in the motor cortex of amyotrophic lateral sclerosis (ALS) patients and mouse models [59], as well as human oligodendrocytes by NKG2D receptor activation in multiple sclerosis (MS) [60]. NK cells in the cerebrospinal fluid (CSF) of patients with Alzheimer's Disease (AD) express high levels of cytotoxicity-related genes *NKG7* and *GNLY* [61], and the NK cells in the brain tissues from triple-transgenic AD mouse model (3xTg-AD) show higher mRNA level of granzyme B [62]. NK cell-deficient mice showed enhanced neurogenesis and improved cognitive function [62]. Together these data indicate a potential direct neurodegenerative role of cytotoxic NK cells in the CNS in the context of underlying genetic or immune risk factors (see **Figure 2**).

NK cells also regulate CNS diseases by producing immune mediators. NK cells enhance the migration of pathogenic $CD4^+$ T cells into the CNS by providing IFN-γ in the early stage of EAE [63]. In AD, circulating NK cells may contribute to derangement by overproduction of IFN-γ and TNFα [64]. On the other hand, NK cells may also act in an anti-inflammatory capacity by IFN-γ-induced astrocyte expression of TRAIL, thereby promoting

apoptosis of autoreactive $CD4^+$ T cells via death receptor DR5 signaling [65]. NK cells responding to the release of the chemokine CXCL12 are also reported to be protective in a minimally invasive photothrombotic model of ischemic brain injury [66], though a more severe brain infarction injury may result in direct NK cell-mediated neurotoxicity and exacerbate neurological deficits [67].

The varying functional outcomes of the NK cell response to CNS pathology may be due to the diversity of NK cell receptor repertoire and effector molecules, as well as the heterogeneity of targets in the CNS and PNS. Similar to catecholaminergic neurons in the CNS [68], administration of IFN-γ promotes PNS sensory neurons to express MHC-I [69], which affects the activation of NK cells. Like immature primary sensory neurons, as well as those after injury [8], NSCs and NPCs in the brain express the NKG2D ligand RAE1 [56-58], while motor neurons express NKG2D ligand MULT1 to regulate NK cells [59]. In the injured brain of a mouse stroke model, NK cells expressing the inhibitory receptor NKG2A outnumber NKG2D-expressing NK cells in the injured brain [70]. These findings suggest that stressed neurons in the CNS and PNS could signal to NK cells through the expression of distinct ligands. Whether parallel roles for NK cell receptor-ligand interactions identified in CNS diseases exists in the PNS remains to be explored.

NK cell therapy in pain: tilting the balance towards homeostasis.

The evidence discussed above suggests a double-edged sword function of NK cells in nervous system disease: Detrimental neurodegeneration by direct NK cytotoxicity in the CNS; and neuropathy-resolving degeneration of pathogenic sensory neurons in the PNS.

The beneficial reduction in neuropathic phenotype by peripheral axon degeneration is supported by experiments in mice which fail to undergo Wallerian degeneration and as a

consequence display a prolongation of neuropathic hypersensitivity after nerve injury [71]. Wallerian degeneration of axons is an integral part of the response to nerve injury, and is likely better tolerated in the PNS due to its regenerative capacity. Recent evidence implicates two key cytotoxic immune mediators, perforin and granzyme, in the inhibition of axon regeneration after nerve injury [72, 73]. It is possible that cytotoxic immune cell-mediated sensory neuron interactions leading to axon degeneration [8] and impaired regeneration [73] are two observations of the same underlying process (see **Box 2**). The context in which an NK cell-based intervention is made will therefore depend on the therapeutic outcome being sought; impaired regeneration may be desired when aberrant innervation leads to chronic pain, but it should be actively avoided when assistance with functional nerve repair is required with age.

Cellular senescence is a useful analogy for understanding the therapeutic potential of NK cells in neuropathic pain. Kale and colleagues have proposed that while senescent cells are beneficial in the short-term, the return of tissue homeostasis relies on their timely removal [45]. NK cells can distinguish stressed and healthy self [74], and naturally target pro-inflammatory senescent cells [45]. Thus, general NK cell stimulation may be useful in a post-injury pathology (see **Figure 2**).

Clearly the benefits of enhanced NK cell function must be balanced with the potential to exacerbate existing neurological or inflammatory disease. NK cell-based therapies for nerve injury-induced pain may be contraindicated with articular [75, 76], or intestinal [77] inflammation. The potential contribution of NK cells must be considered in other forms of peripheral neuropathy, such as chemotherapy-induced or inflammatory neuropathies [16]. For example, the efficacy of intravenous immunoglobulin (IVIg) treatment in chronic inflammatory neuropathy patients has been associated with suppression of NK cell cytotoxicity [78-81]. These findings suggest either the potential role for NK cells in disease

etiology, or that IVIg may achieve its benefit by conversion of NK cells to an inflammation resolving phenotype [82] (see **Figure 2**). Caution must also be exercised in interpreting NK cell dysfunction in painful peripheral neuropathies such as fibromyalgia [22] and whether axon dye-back is a response to, or cause of, the disease [16, 27]. A deeper understanding of NK cell function in disease states, in combination with accessible biomarkers, may help stratify patients ahead of treatment.

At present, therapies designed to induce a gain of immune function are typically reserved for the treatment of aggressive, chemotherapy-resistant cancers, where serious side-effects may nevertheless be tolerated. As a non-life threatening condition, treatments for neuropathic pain will necessarily require a wider therapeutic window, setting the bar higher than immunotherapies currently available. Early trials of NK cell stimulation *in vivo* using cytokines such as interleukin-2 resulted in off-target and non-specific side effects [83], precluding the approach taken in previous preclinical models [8]. Instead, an alternative to adoptive cell therapy is to harness antibody-dependent cellular cytotoxicity (ADCC) using multi-specific antibodies, known as NK cell ‘engagers’ [84], owing to their interaction with one or more NK cell activating receptors [85, 86]. Unlike T cells, NK cells operate independently of HLA presentation [87], and may be less prone to cytokine release syndrome [88], thereby offering the possibility of allogeneic, or “off-the-shelf” NK cells for a cellular immunotherapy for pain. Despite growing evidence, establishing an NK cell therapy for neuropathic pain presents the challenge of deciding on the appropriate neuronal, glial or structural cellular target. Advancing knowledge on the biological mechanisms will be critical to maximize the therapeutic efficacy of such specific engager molecules, as well as minimize their potential side effects. Recruitment of specific NK cell subsets (e.g., resident, infiltrating or memory cells) may also be required [48].

Concluding remarks

NK cells potentially target multiple critical cellular components implicated in neuropathic pain, acting via NK cells' direct cytotoxic and/or immunomodulatory effects in peripheral nerves (**Figure 1**). In terms of potential translational implications, so far, the best evidence for NK cell intervention lies in painful traumatic neuropathies, where preclinical studies indicate that the therapeutic effects may result from removal of abnormal sensory axons. It is important to remember, however, that NK cells will inevitably operate in concert with other immune cells to restore homeostasis in the microenvironment of injured peripheral nerves [49] (see **Box 2**). The design of therapeutic immune interventions should minimize the effects on reparative tissue re-modelling via phagocytic [89] and autophagic [90] mechanisms, which may be equally important in preventing pain chronification after nerve injury. To fully realize the therapeutic potential of NK cells for peripheral neuropathy and chronic pain, several important questions about the diverse neuroimmune interactions between NK cells, non-neuronal cells and sensory neurons should be addressed (see **Outstanding Questions**). Further translational and clinical research, along with mechanistic studies in preclinical models, will be required to assess whether NK cell immunotherapy is a realistic option for treatment of neuropathic pain.

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Declaration of interests

HWK, AJD and SBO are named inventors on a patent for the use of immune cells in the treatment of nerve injury.

Box 1. NK cells: classification, origin and function

NK cells derive from lymphoid progenitor cells common to B and T cells. NK cells are classified as one of five founding members of an expanded family of lymphocytes known as innate lymphoid cells (ILCs): NK, ILC1, ILC2, ILC3 and Lymphoid tissue inducer (LTi) [91]. NK cells were first characterized by their natural cytotoxicity against several types of tumor cells [92]; later, their cytokine-producing regulatory effector function was also recognized [93]. In humans NK cells are categorized into cytotoxic $CD56^{dim}CD16^{+}$ cells and regulatory $CD56^{bright}CD16^{neg}$, and in mice $CD27^{neg}$ $CD11b^{+}$ and $CD27^{+}CD11b^{neg}$ cells, respectively [94]. Around 90% of peripheral NK cells are $CD56^{dim}$ and $perforin^{+}$ cytotoxic NK cells, which are the matured form of the NK-lineage cells. Cytotoxic NK cells release lytic granules containing pore-forming perforin proteins and serine proteases such as the granzyme family to the target. This cytolytic activity is usually mediated by either the upregulation of “induced-self” activating ligands, or downregulation of inhibitory ligands (typically major histocompatibility class I molecules) in defective cells, known as “loss-of-self”. Cytotoxic NK cells also possess direct cytolytic activity against other effector cells in an NK receptor-ligand interaction-dependent manner [95-97], preventing immune-mediated damage to the host. For example, NK cells may eliminate both activated $CD4^{+}$ and $CD8^{+}$ T cells as well as LPS-activated inflammatory macrophages [98], and accelerate neutrophil apoptosis via activating NK cell receptor NKp46 and the Fas pathway [99], which may have implications for the resolution of inflammation. The immature $CD56^{bright}CD16^{neg}$ population regulates maturation of other immune cells, which is essential for modulating adaptive immune responses [93, 100, 101]. $CD56^{bright}$ NK cells are usually fewer than 10% of total blood NK cells, and are generally enriched in secondary lymphoid organs. This regulatory NK cell subset secretes a host of signaling molecules including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNFα) and colony-stimulating factor 2 (CSF2) [15]. IFN-γ from NK cells may promote T_H1 cell

responses [102, 103], and with TNFα may also mature dendritic cells (DC) [104] leading to the induction of a cytotoxic $CD8^+$ T cell response [103]. In addition to the conventional NK cells, they can also be found highly localized in non-lymphoid organs including liver [105], lung [106], gut [107], and uterus [108]. Uterine NK cells, for example, uniquely promote vascular remodeling in early pregnancy [109, 110]. The expression of distinct phenotypic markers related to organ-specific niches further emphasize the unconventional roles played by these tissue-resident NK cells [111].

Box 2. Lymphocytes other than NK cells with similar roles

CD8$^+$, γδ T and NKT cells have a similar cytotoxic capacity to NK cells with the additional requirement of antigen-specific co-stimulation of a corresponding T cell receptor. In the murine CNS, CD8$^+$ T cells appear to exacerbate neurological deficits after traumatic brain injury by targeting neurons at chronic time points [112]. In addition, in humans cytotoxic CD8$^+$ and γδ T cells are capable of killing oligodendrocytes through NKG2D receptor-ligand interactions, which can promote demyelination and neuroinflammation [60]. In the feline PNS, CD8$^+$ T cells have been shown to cause direct injury to lentivirus-infected DRG neurons via co-stimulator receptor CD40 [113] and infiltrate the peripheral nerve in a model of spontaneous chronic peripheral neuritis [114]. NKG2D is a key costimulatory receptor for CD8$^+$ T cells [115] suggesting that expression of RAE1 by sensory neurons [8] may additionally trigger sensory neuroimmune interactions with CD8$^+$ T cells after nerve injury. Indeed, CD8$^+$ T cells were recently shown to interact with sensory neurons after injury in an MHC-I dependent manner, though the exact molecular interaction remains unclear [73]. CD8$^+$ T cells may also play an indirect role in peripheral nerve function, for example by secreting IL-13 and thereby promoting IL-10 production by macrophages, contributing to neuropathic pain resolution [11, 12].

Innate lymphocyte cells (ILCs) are tissue resident cells involved in the rapid response to tissue damage and its repair by TCR-independent stimulation [91]. ILC1s partially share a receptor repertoire with NK cells, including NKG2D, and molecular secretions including IFN-γ and granzymes [116]. NKp46$^+$ ILC3s also express NKG2D and may therefore be involved in the interaction with sensory neurons in the context of nerve injury [8]. ILC2s might also be involved in resolving neuropathic pain by producing IL-4 and IL-13 [12, 117, 118]. It remains to be clarified whether other ILC subsets are present after peripheral nerve injury, and if so, what are their roles.

Other lymphocytes have been shown to be protective in neuropathic pain [14]. For example, $CD4^+$ regulatory T (Treg) cells, which are immunosuppressive and capable of limiting tissue inflammation [119], promote the recovery of neuropathic pain by activation of the transmembrane receptor tumor necrosis factor receptor 2 (TNFR2)-mediated [13]. Moreover, Treg cells are a source of the anti-inflammatory cytokine IL-10, which may contribute to chronic pain resolution via the IL-10 receptor expressed by sensory neurons [10]. For further reading in this area we recommend an excellent recent review by Kavelaars and Heijnen [120].

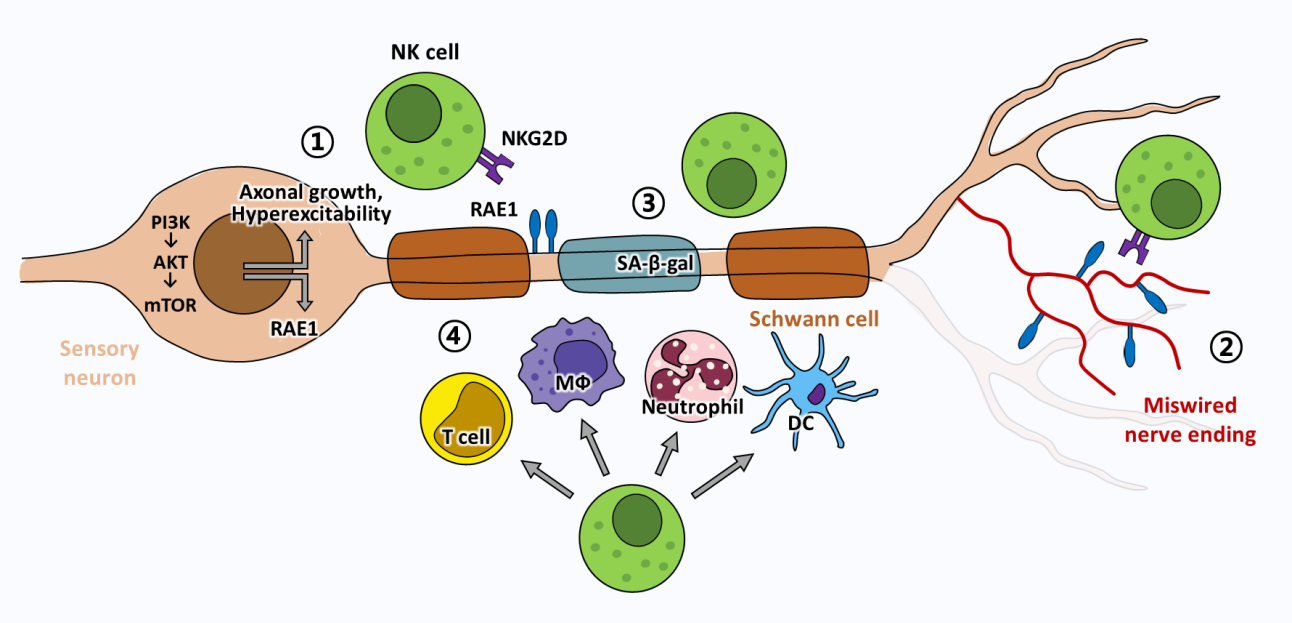

Figure 1. Potential targets for NK cells in the context of neuropathic pain.

(1) Nerve injury upregulates the NKG2D receptor ligand RAE1, as well as the activation of the PI3K-AKT-mTOR pathway, which promotes collateral axonal growth, neuronal hyperexcitability and potential neuropathic pain. Hyperexcitable neurons expressing RAE1 therefore represent a potential target for NK cells to eliminate via receptor recognition. (2) Misdirected sensory nerve innervation contributes to neuropathic pain and may also be a target for NK cell-mediated pruning. By eliminating these miswired nerve endings, NK cells may help restore normal sensory function and reduce pain. (3) Senescence-associated genes are upregulated in cells within the nerve after injury. NK cells are capable of eliminating senescent cells, including senescent Schwann cells. NK cells may improve reinnervation and sensory recovery by eliminating senescent Schwann cells or other structural cells, which may help to reduce neuropathic pain. (4) NK cells may inhibit the activity of inflammatory immune cells by direct interactions, which can aid in the resolution of inflammation. NK cells can also activate cytotoxic immune cells via cytokine release, promoting target cell killing and further reducing neuropathic pain.

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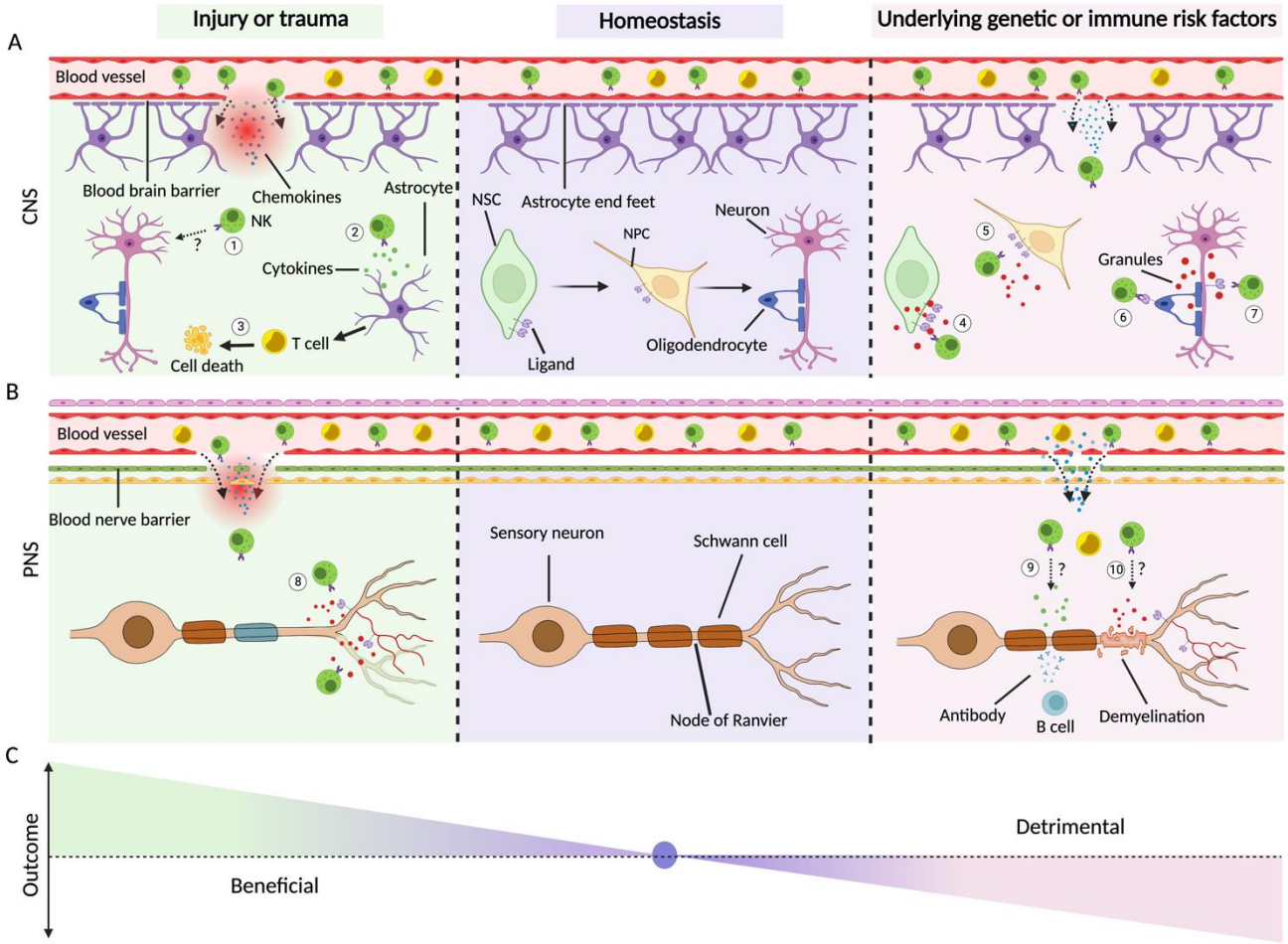

Figure 2. CNS and PNS disorders recruit NK cells affecting neurons and the surrounding cells.

A) During CNS homeostasis, the presence of the blood-brain barrier prevents the direct communication of peripheral NK cells with NSCs, NPCs and mature neurons. Thrombotic stroke injury recruits NK cells into the brain parenchyma by chemotaxis with anti-inflammatory outcome [66] (1). IFN-γ produced by NK cells may also attenuate inflammation via TRAIL induction in astrocytes and promoting apoptosis of autoreactive $CD4^+$ T cells [65] (2 and 3). Elevated permeability of the blood-brain barrier in inflammatory disease also enables the recruitment of NK cells to the CNS. Regulation of cytotoxicity receptor ligands in NSC and NPC in mouse model EAE leads to loss of NK cell tolerance and cell death (4 and 5). Oligodendrocytes (6) and motor neurons (7) expressing activatory ligands become a target

for NK cytotoxicity in MS and ALS, respectively [59, 60]. **B**) During homeostasis the peripheral nerve is largely devoid of NK cells [114]. Peripheral nerve injury recruits NK cells that interact with sensory neurons and a network of resident and infiltrating immune cells [49]. Cytotoxic granules and cytokines produced by NK cells regulate the degeneration and regeneration of injured sensory neurons (8) [8, 73], attenuating the development of neuropathic pain. Where peripheral neuropathies may be underlined by genetic or immune risk factors, such as CIDP and GBS, NK cells along with cytotoxic T cells [114] may themselves participate in detrimental neuroinflammation within the nerve (9 and 10) [79-81]. **C**) When tissue homeostasis is disturbed, NK cell function in the central and peripheral nervous systems may result in physiologically beneficial or detrimental outcomes depending on the underlying disease context. Abbreviations: ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; EAE, experimental autoimmune encephalitis; GBS, Guillain-Barré syndrome; NPCs, neural precursor cells; NSC, neural stem cells; PNS, peripheral nervous system; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand. Figure created with BioRender (BioRender.com).

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