Pathophysiology of Peripheral Neuropathic Pain: Immune Cells and Molecules

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Damage to the peripheral nervous system often leads to chronic neuropathic pain characterized by spontaneous pain and an exaggerated response to painful and/or innocuous stimuli. This pain condition is extremely debilitating and usually difficult to treat. Although inflammatory and neuropathic pain syndromes are often considered distinct entities, emerging evidence belies this strict dichotomy. Inflammation is a well-characterized phenomenon, which involves a cascade of different immune cell types, such as mast cells, neutrophils, macrophages, and T lymphocytes. In addition, these cells release numerous compounds that contribute to pain. Recent evidence suggests that immune cells play a role in neuropathic pain in the periphery. In this review we identify the different immune cell types that contribute to neuropathic pain in the periphery and release factors that are crucial in this particular condition.

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Several types of immune cells have been implicated in the pathogenesis and altered nociceptive processing characteristic of peripheral neuropathic pain. Although their relative contribution and the timing of their appearance have not been completely elucidated, they seem to be coincident with inflammation (Fig. 1). Here we review the contribution of a number of immune cell types in the periphery and some of the key inflammatory mediators they release.

IMMUNE CELLS

Mast Cells

Mast cells are crucial players in allergic reactions and important initiators of innate immunity (1). After a partial ligation of the sciatic nerve (PNL), the resident population of mast cells in the peripheral nerve are activated and degranulated at the site of nerve damage (2). They release proinflammatory mediators, including histamine, serotonin, cytokines and proteases (1,3). Histamine seems to be a key mast cell mediator, having sensitizing effects on nociceptors (4–6), and is capable of inducing severe burning pain when applied to the skin of patients suffering from postherpetic neuralgia (7). In addition, neuronal histamine receptors are upregulated after a crush injury to the sciatic nerve (8).

Stabilization of mast cells by sodium cromoglycate attenuates the development of allodynia, and reduces neutrophil and monocyte/macrophage infiltration at the site of nerve injury after PNL (2). Furthermore, treatment with histamine receptor antagonists suppresses mechanical allodynia in neuropathic rats (2). However, the antiallodynic effect of these antagonists was less effective than sodium cromoglycate treatment, suggesting that other mast-cell-derived mediators (i.e., neurotrophins, prostaglandins, proteases and cytokines) may be involved in the generation of neuropathic pain.

These studies suggest that activated mast cells contribute directly to neuropathic pain by releasing algogenic mediators after degranulation. Mast cells may also contribute indirectly by enhancing the recruitment of other key immune cell types which, in turn, release pronociceptive mediators (Fig. 2).

Neutrophils

Neutrophils (or polymorphonuclear leukocytes) are normally the earliest inflammatory cells to infiltrate damaged tissue and dominate the acute inflammatory stage (9,10). As well as being capable of phagocytosis, they release a variety of proinflammatory factors, including cytokines and chemokines, which, in turn, activate and attract other inflammatory cell types, most notably macrophages (9,10).

The role of neutrophils in the production of inflammatory pain is well documented (11,12). Several studies suggest that they may also contribute to the mechanisms of neuropathic pain. Neutrophils are almost absent in the intact, uninjured nerve. Significant infiltration of neutrophils has been observed at the site of nerve lesion in a number of rodent neuropathy models, including PNL (2), sciatic nerve crush (13), and chronic constriction

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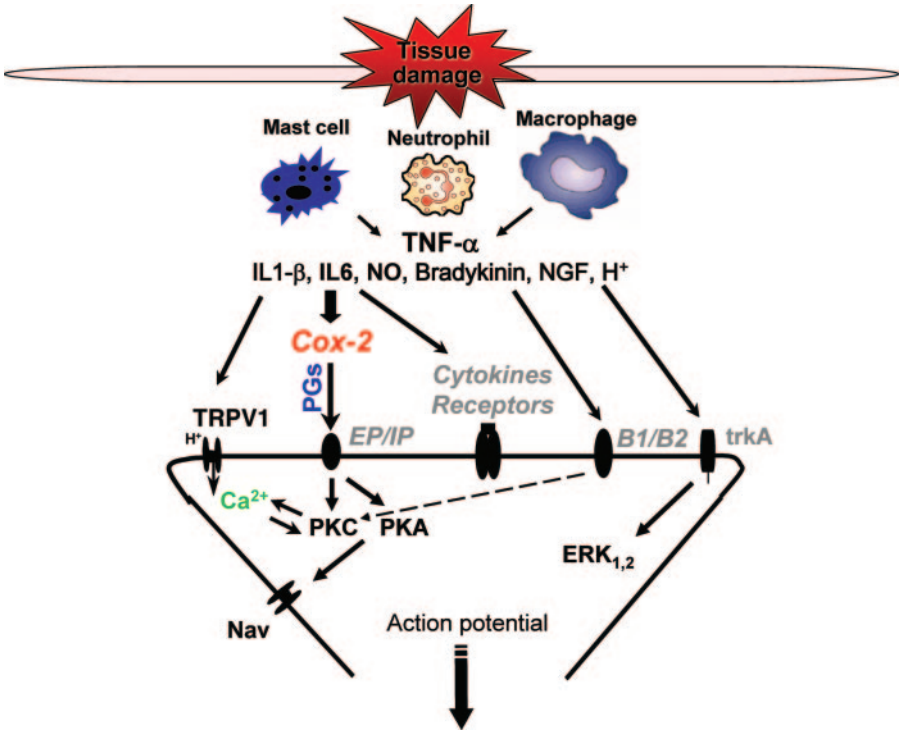

Figure 1. Inflammatory pain. After tissue damage, mast cells and macrophages are activated and some blood-born immune cells including neutrophils are recruited. A variety of immune mediators are released, which exert algesic actions by acting directly on nociceptors, or indirectly via the release of other mediators, most notably prostanoids. There is increasing knowledge of the intracellular cascades that are activated in nociceptors by these mediators, which ultimately either activate or sensitize these neurons. TNF-α, tumor necrosis factor α, IL-1β; interleukin-1β; IL-6, interlekin-6; NO, nitric oxide; PGs, prostaglandins; NGF, nerve growth factor; Cox-2, cyclooxygenase 2.

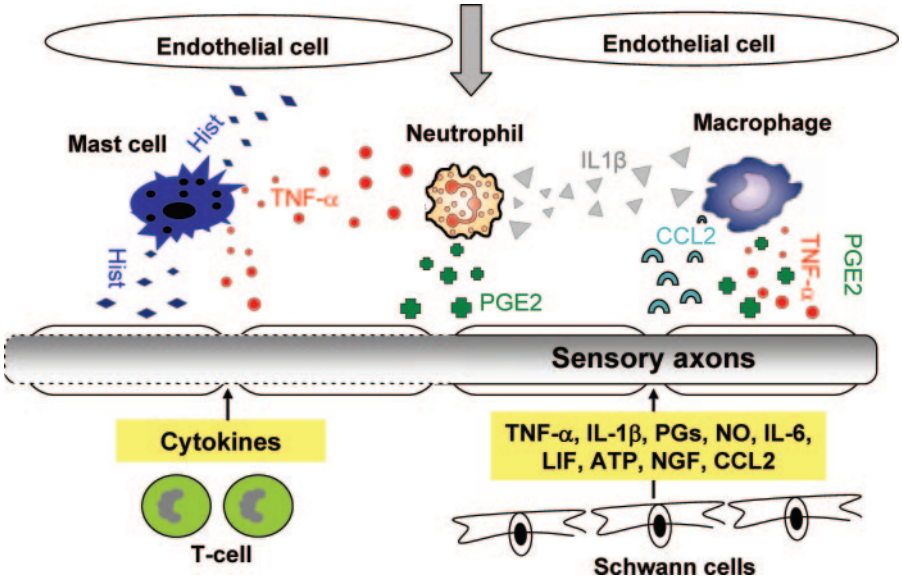

Figure 2. After peripheral nerve injury, the site of damage is typified by the activation of resident immune cells and recruitment and proliferation of non-neuronal elements (such as Schwann cells, mast cells, neutrophils, macrophages and T-cells), which release factors (e.g., TNF-α, IL-1β, IL-6, CCL2, histamine, PGE2, and NGF) that initiate and maintain sensory abnormalities after injury. These factors may either induce activity in axons or are transported retrogradely to cell bodies in the dorsal root ganglia, where they may alter gene expression of the neurons. Mast cells, residing in the nerve, are the first cells to be activated and contribute to the recruitment of neutrophils and macrophages. These initial events promote the recruitment of T-cells, which reinforce and maintain inflammatory reactions. Hist, histamine; TNF-α, tumor necrosis factor α, IL-1β; interleukin-1β; IL-6, interlekin-6; NO, nitric oxide; ATP, adenosine triphosphate; PGs, prostaglandins; PGE2, prostaglandin E2; NGF, nerve growth factor; CCL2, C-chemokine ligand 2.

injury (CCI) (14). Perkins and Tracey have shown substantial endoneurial neutrophil invasion at the site of a partial transection of the sciatic nerve, peaking at 24 h (15). Because there are epineurial neutrophils in sham animals, the endoneurial invasion seems more likely to be involved in hyperalgesia. These authors also demonstrated that preventive, rather than curative, depletion of circulating neutrophils, after systemic administration of a selective cytotoxic antibody, reduced the development of thermal hyperalgesia. Thus, neutrophils may be important during the early stages of neuropathic pain development, releasing mediators such as chemokines at the injury site that initiate macrophage infiltration and activation (16). It is noteworthy, however, that several

authors report that the neutrophil response in peripheral nerves after injury is extremely limited in both time and extent (17–20). It is likely that other leukocyte populations (i.e., eosinophils and basophils) are involved in the early events after nerve injury, but little is known about their potential role in the production of neuropathic pain.

Macrophages

Macrophages are the key immune and phagocytic cell in the peripheral nerve. They are recruited in response to peripheral nerve injury, such as inflammation of and/or loss of axons, myelin, or both. Their main function is to phagocytose foreign material, microbes, and other leukocytes as well as to play a critical role in removing injured and dying tissue debris during Wallerian degeneration (13,21). The macrophage population in the peripheral nerve consists of resident cells and hematogenously derived macrophages, only seen after tissue damage (17).

In contrast to other tissue systems, resident macrophages do not require the activation of precursor cells (19), and respond extremely rapidly to nerve damage (13,17,22). They are joined by circulating macrophages that flood across the leaky blood–nerve barrier, a process that can occur for 2–3 days after damage (17). Recruited macrophages quickly outnumber the resident cells and are thought to be vital for successful degeneration, and subsequent regeneration, of the nerve (19). The recruitment and activation of macrophages within the peripheral nerve is an extremely specific and well-modulated mechanism, involving several proinflammatory mediators and other cell types (17).

Macrophage function has been examined in various models of neuropathic pain, including CCI (23–25), PNL (25,26), and spinal nerve ligation (SNL) (27). A reduction in neuropathic pain behaviors correlating with an attenuation of macrophage recruitment into the damaged nerve has been demonstrated by several groups. For example, in the C57BL/Wld mouse, which has delayed recruitment of nonresident macrophages and retardation of Wallerian degeneration after nerve injury (28,29), there is a lack of thermal hyperalgesia after CCI (23,24).

Liu et al. were able to correlate alleviation of PNL-induced thermal hyperalgesia with a reduction in macrophage number in the injured nerve using a novel strategy (26). They used IV administration of liposome-encapsulated clodronate to deplete circulating monocytes/macrophages. The authors note that this treatment protected both myelinated and unmyelinated fibers against degeneration. This strategy is also able to attenuate mechanical hyperalgesia after PNL (30). However, several groups report a failure to relieve mechanical allodynia using the same treatment (27,30). These inconsistencies may reflect differences in the involvement of macrophages in the mechanisms underlying hyperalgesia versus allodynia, or discrepancy between the study methodologies.

Taken together, these studies suggest that macrophages may play an important role in the generation of neuropathic pain. It is likely that they contribute through several mechanisms, including the release of pronociceptive mediators. Their unique position, sitting at the "crossroads" between the adaptive inflammatory response and the immune system, makes them an obvious target when attempting to establish the neuroimmune interactions that lead to neuropathic pain.

Schwann Cells

Cell types not usually classified as immune cells may be important in the production of pain from damaged peripheral nerves. The role of Schwann cells as "immune cells" has been discussed for several years. They have been shown to possess immune molecules *in vitro*, constitutively expressing major histocompatibility complex (MHC) class I but not class II molecules on their cell membrane (31). Stimulation with interferon-γ or coculture with T lymphocytes results in both an up-regulation of MHC I and *de novo* expression of MHC II molecules, an effect further enhanced in the presence of tumor necrosis factor α (TNF-α) (32,33). More importantly, there is evidence to suggest that similar responses occur *in vivo* (34).

Schwann cells are in intimate contact with all sensory neurons. During Wallerian degeneration, the Schwann cells that envelope degenerating axons undergo remarkable reactive changes, begin to phagocytose myelin debris (35), and synthesize a range of potent biological molecules, including nerve growth factor (NGF) (36,37), TNF-α (38–40), interleukin-1β (IL-1β) (33,40), interleukin-6 (IL-6) (38,41) and adenosine triphosphate (42). In partial nerve injuries, which are often associated with neuropathic pain, axons that remain intact distal to the lesion (so-called spared axons) are exposed to novel Schwann-cell-derived factors. The distal ends of damaged axons are also exposed to some of these factors at the site of injury. The upregulation of NGF by Schwann cells is driven largely by macrophage-derived IL-1β in the damaged nerve (36,43). We are still relatively ignorant of the factors regulating the release of other Schwann-cell-derived factors.

It has been more difficult to evaluate the role of Schwann cells because the strategy of removing these cells *in vivo* (e.g., in demyelinating lesions induced by lysolecithin or as seen in Guillain Barre Syndrome) can itself induce abnormal pain states. However, some *in vitro* studies provide good circumstantial evidence that Schwann cells may contribute to some neuropathic pain states, such as that associated with human immunodeficiency virus (44). More compelling evidence that Schwann cells are involved in the production of neuropathic pain comes from a series of studies by Campana et al., who were able to demonstrate

neuroprotective and antinociceptive effects of erythropoietin after both CCI (45) and crush-induced lesions (46,47). They successfully attenuated neuropathic pain behaviors by both local and systemic administration of recombinant human erythropoietin. Furthermore, they were able to correlate these findings with a reduction in levels of TNF-α immunoreactivity in Schwann cells (45). It is noteworthy that there was no change in macrophage TNF-α immunoreactivity, suggesting an important and selective role for Schwann-cell-derived TNF-α in the production of pain.

Further clarification of the exact role of Schwann cells in nociceptive processing is provided by the work of Chen et al., who used transgenic mice expressing a dominant negative ErbB receptor to establish the role of myelinating (48) and nonmyelinating (49) Schwann cells in sensory processing. ErbB is a tyrosine kinase receptor that binds neuregulin 1 and is important in axon–Schwann cell interactions. The authors were able to demonstrate alterations in the processing of noxious and nonnoxious information by selectively expressing the dominant negative ErbB in either myelinating or nonmyelinating Schwann cells (48,49). In both cases, normal Schwann cell–axon phenotypes were selectively affected. Using behavioral responses to assess alterations in sensory processing, Chen et al. were able to demonstrate specific alterations in sensory processing in transgenic animals compared with wild types. A selective loss of thermal sensitivity to both noxious heat and cold stimuli was observed when ErbB signaling was disrupted in nonmyelinating Schwann cells, with no alteration in the responses to mechanical stimuli (49). In contrast, transgenic mice with disruption of ErbB signaling in myelinating Schwann cells showed marked responses to low-threshold mechanical stimuli, that is, a mechanical allodynia, and no alteration in thermal, unmyelinated mediated responses (48). Together, these data suggest highly specific and important roles for different Schwann cell phenotypes in the signaling of noxious information.

Thus, although there is preliminary evidence supporting a role for Schwann cells as mediators of pain after nerve injury, further work remains to be undertaken.

T Cells

Lymphocytes are classified into two subpopulations: B lymphocytes, responsible for antibody production, and T lymphocytes, which are mediators of cellular immunity (T cells), or natural killer cells. The involvement of T cells in neuropathic pain was initially proposed after the identification of both T cells and natural killer cells at the site of nerve injury in several rodent models (25). A role for T cells in the generation of neuropathic pain was established by Moalem et al. They confirmed previous findings that T cells infiltrate injured sciatic nerves (50). More importantly, they demonstrated that both thermal and mechanical allodynia/hyperalgesia after CCI were attenuated in congenitally athymic nude rats, which lack mature T cells.

The T-cell population is very heterogeneous and is divided into two subpopulations, helper T cells ($CD4^+$) and cytotoxic T cells ($CD8^+$). In addition, each of these two subpopulations is further divided into Type 1 and Type 2 according to its cytokine expression profile. It has been demonstrated that the passive transfer of a T-cell population alters the susceptibility of nude rats to neuropathic pain (50). After CCI, transfer of Type 1 helper T cells (which produce proinflammatory cytokines) into nude rats increases their pain levels to that of their heterozygous littermates (50). In contrast, transfer of Type 2 helper T cells (which produce antiinflammatory cytokines) into nude rats produced a modest reduction of pain sensitivity compared with their heterozygous littermates (50). However, Tsai et al. failed to demonstrate a difference in splenocyte proliferation and natural killer cell activity between sham and CCI rats (51,52). Thus, it seems that the function and cytokine profile of a subpopulation of T cells may confer its ability to modulate nociceptive processing. As a large heterogeneous population, the contribution of specific subsets of T cells in neuropathic pain requires further study.

There is also evidence of macrophage and T-cell extravasations in the dorsal root ganglion (DRG). In naive DRG (which lack a blood–nerve barrier), there is a population of satellite glial cells, as well as cells expressing macrophage markers [e.g., MHC II (53)], and a small population of T cells that perform an immune surveillance function as in other tissues. After both sciatic and spinal nerve transection, increased MHC II cell density is observed in ipsilateral DRGs (53,54). The additional MHC II immunopositive cells in "lesioned" DRG are likely to be intrinsic satellite glial cells and/or hematogenous monocytes/macrophages. Increased T-cell density was also observed at early time points. The density of both types of immune cells is still significantly higher than control levels 11 wk after nerve transection. In addition, after transection of a spinal nerve, both cell types appear in the adjacent, uninjured DRG, although in lower numbers (54). The invasion of DRG is apparently triggered by retrograde signals from the peripheral nerve. Finally, sural nerve biopsies taken from neuropathic pain patients suggest that T-cell infiltration may be temporally correlated to hyperalgesia (55).

IMPORTANT INFLAMMATORY MEDIATORS

The above account has made reference to a number of immune cell-derived mediators of inflammation and/or pain. However, there is not a "one-to-one" relationship between cells and the products they upregulate/secrete. Here we discuss the evidence for several of these molecules in the production of neuropathic pain.

Cytokines/Chemokines

Cytokines are pivotal mediators in the multistep response that the host organizes to counteract xenobiotic insults. Several proinflammatory cytokines and chemokines have been implicated in altered nociceptive processing. Synthesized and released by a wide range of immune cell types, cytokines act synergistically, inducing the production of one another. Two main mechanisms have been proposed to explain the contribution of proinflammatory cytokines to neuropathic pain: first, direct action on primary afferent neurons; and second, indirect actions via activation of signaling pathways in immune cells.

Interleukin-1β

IL-1β is one of many pluripotent proinflammatory cytokines. It is produced and secreted by immune cells including macrophages (56), monocytes (57), and microglia (58,59) under conditions of stress. IL-1β has been identified as one of many algogenic agents that may play a role in neuropathic pain. In the periphery, IL-1β itself results in prolonged hyperalgesia and allodynia after intraplantar (60,61), intraperitoneal (62), and intraneural (63) administration.

There is an upregulation of IL-1β mRNA in the injured sciatic nerve after transection (40), crush (64), and CCI (65,66), as well as in a rodent model of Guillain Barre Syndrome (64). In addition, increases in spinal protein after peripheral neuropathy and inflammation have been demonstrated (67). More importantly, after CCI, neutralizing antibodies to the IL-1 Type 1 receptor reduce pain-associated behavior in neuropathic mice (68,69). However, the mechanism of action of IL-1β in the periphery is still unclear. Several studies indicate that binding of IL-1β to its receptor initiates the translocation of the transcription factor nuclear factor-κB to the nucleus (70), resulting in the transcription of genes involved in inflammation and nociception, and the production of agents including nitric oxide, bradykinin, prostaglandins, and proinflammatory cytokines (71,72). Some of these compounds may lead to changes in gene expression and modulate neuronal excitability in intact nociceptors (73,74). Electrophysiologic evidence also suggests that IL-1β may directly excite nociceptive fibers (75,76) and increase their responses to heat stimuli (77). Furthermore, there is evidence that IL-1β can modulate sensory neuron transmission via increased release of the nociceptive neuropeptides substance P (78,79) and calcitonin gene-related peptide (75,80).

Tumor Necrosis Factor α

TNF-α initiates the cascade of activation of several cytokines and growth factors. TNF-α has been shown to be directly involved in the production of pain in several models of nerve injury. Injury-induced increases in TNF-α mRNA (39) and protein expression (24,81) have been observed to correlate with the development of allodynia/hyperalgesia in several neuropathic pain models. In addition, enhanced expression of TNF-α receptors 1 and 2 occurs in the injured nerve after both CCI and sciatic crush injuries (82). Furthermore, the direct application of TNF-α to the sciatic nerve of naive rodents dose-dependently enhances ectopic firing in afferent fibers (83), and endoneurial injection of TNF-α produces neuropathic pain behaviors (84,85). In addition, impairment of TNF-α signaling attenuates hyperalgesia/allodynia after SNL (86), CCI (87–89), and partial transection of the sciatic nerve (88). Schafers et al. observed an increased sensitivity of injured and adjacent uninjured rat primary sensory neurons to exogenous TNF-α after SNL (86). It is noteworthy that only preemptive treatment with etanercept inhibited mechanical allodynia, suggesting that TNF-α is an "initiator" of neuropathic pain. They also confirmed previous findings by Shubayev and Myers (90) that TNF-α accumulated proximally to the injury site after CCI, suggesting that the major contributing source of TNF-α was the DRG (91). They found that endogenous TNF-α was exclusively increased in medium and large diameter DRG neurons (86). In contrast, after sciatic nerve crush Ohtori et al. observed an upregulation of TNF-α and TNF receptor 1 in GFAP immunoreactive DRG satellite cells, and TNF receptor 1 in neurons (92). The effect of TNF-α on DRG neurons seems to be mediated, directly and/or indirectly, by the phosphorylation of extracellular regulated kinase (93) and p38 mitogen activated protein kinase (86). The phosphorylation of p38 mitogen activated protein kinase may mediate mechanical allodynia via a modulation of tetrodotoxin-resistant Na^+ channels (94). Finally, Lindenlaub and Sommer have shown a correlation between TNF-α nerve content and serum TNF-α receptor 1, and painful neuropathy in humans (95). Thus, a growing body of evidence suggests that TNF-α has a critical influence on altered pain processing.

Interleukin-6

There is also compelling evidence that a third proinflammatory cytokine, IL-6 is involved in the mechanisms of neuropathic pain after both CCI (25,96) and PNL (25). A comparison of the CCI and PNL models of neuropathy revealed a correlation between mechanical allodynia and increased IL-6 immunoreactivity at the site of injury in both models (25). In addition, increased IL-6 mRNA levels are detected in the DRG after CCI (96). Importantly, IL-6 knockout mice exhibit an attenuation of thermal hyperalgesia and mechanical allodynia after CCI compared with wild-type mice (96). After SNL, the same group demonstrated delayed mechanical allodynia in IL-6 knockout mice, which correlated with decreased adrenergic sprouting (97). However, the same mice displayed no alterations in thermal allodynia. Having a direct excitatory effect on nociceptive neurons, IL-6-induced adrenergic sprouting could be another mechanism by which IL-6 contributes to the production of

neuropathic pain. In contrast, using both behavioral and electrophysiologic techniques, Flatters et al. demonstrated that peripheral IL-6 administration had antinociceptive effects (98). In addition, spinal application of IL-6 induces a dose-dependent inhibition of neuronal firing responses after SNL (99).

Leukemia Inhibitory Factor

Several studies suggest a role for leukemia inhibitory factor (LIF) in the generation of neuropathic pain. Banner and Patterson demonstrated the *de novo* expression of LIF by Schwann cells at the site of injury after sciatic nerve transection (100). Thompson et al. showed that subpopulations of nociceptive sensory fibers retrogradely transport and accumulate LIF in their cell bodies (101). Furthermore, approximately 60% of the LIF-accumulating cell bodies were immunopositive for trk-A, that is, responsive to NGF (101). Sugiura et al. established a critical role for LIF in the recruitment of macrophages and other immune cells into damaged nerves after a crush injury (102). Later work from the same group established a cascade of cytokines involving IL-6, LIF, and chemokine ligand 2 (CCL2) that resulted in the attraction of macrophages to the site of damage (103).

Chemokine Ligand 2

In addition to their ability to recruit immune cells into the peripheral nerves after damage, chemokines are thought to be involved in the mediation of neuropathic pain (104,105). Although the exact mechanisms of their action remain uncertain, several studies indicate that they have both direct and/or indirect effects in the production of neuropathic pain. Among a family of 50 members and 18 chemokine receptors (106), the most elaborate data concern CCL2 (MCP-1) and its receptor CCR2.

The CCL2/CCR2 system is expressed in several cell types within damaged peripheral nerves, including Schwann cells, macrophages, and neurons. The upregulation of CCL2 in non-neuronal cells is thought to involve a cascade of cytokines including TNFα, IL-1β, IL-6, and LIF (103). The exact signal for neuronal expression of CCL2 remains to be elucidated, although nuclear factor-κB is involved (107). Several findings suggested a role for CCL2 in animal models of neuropathic pain. CCL2 is upregulated by DRG cells after sciatic nerve axotomy (108,109) with preferential expression in small diameter nociceptive afferents (110). Tanaka et al. supported these findings, demonstrating CCL2 immunoreactivity in the DRG after PNL (111). Around the same time, Oh et al. demonstrated that dissociated embryonic DRG neurons with nociceptive properties expressed the receptors for, and were excited by, CCL2 (105).

The role of the CCL2/CCR2 system in neuropathic pain was established *in vivo* by Abbadie et al. (112). They demonstrated that neuropathic pain behaviors were significantly attenuated in null mutant CCR2 mice after PNL (112). They concluded that there was likely to be more than one site at which CCL2 activates its receptor, including nerve trunk, DRG, and spinal dorsal horn, and proposed that these interactions are likely to involve macrophages and microglia, respectively (112). Consistent with these suggestions is the finding that intraneural administration of CCL2 into the sciatic nerve produces a transient mechanical allodynia and thermal hyperalgesia that is both temporally and spatially correlated to the recruitment of macrophages into the nerve (113).

White et al. reported increases in CCR2 mRNA in both neuronal and non-neuronal cells in the DRG after a compression injury of the DRG itself (114). In addition, they found that *in vitro* application of CCL2 to the cell bodies of a previously compressed ganglion produced a potent excitatory effect not observed in uninjured ganglion (114). More recent reports demonstrate that CCL2 is able to excite cultured DRG nociceptive neurons (115) and reduces γ-aminobutyric acid currents in cultured spinal neurons (116). Together, these studies indicate an important peripheral role for the CCL2/CCR2 system in the generation of neuropathic pain.

Nerve Growth Factor

Neurotrophic factors regulate the long-term survival, growth or differentiated function of discrete populations of neurons. The prototypical neurotrophin is NGF. Critical evidence for a role of NGF in pain production was the identification of a mutation in the gene encoding trkA, the high-affinity receptor for NGF. This mutation in trkA leads to congenital insensitivity to pain (117) by disrupting NGF signaling and demonstrates its importance for normal nociceptive functioning. The mechanisms of NGF in pain signaling are now well understood. Small doses of NGF produce pain and hyperalgesia in adult animals and humans. In rodents, thermal and mechanical hyperalgesia develop after systemic NGF administration (118). In humans, IV injections of very small doses of NGF produce hyperalgesia at the injection site, as well as widespread aching pains in deep tissues (119). The rapid onset and location of these effects suggest that they arise, at least in part, from a local effect on the peripheral terminals of nociceptors; and indeed, this has been directly observed (120).

NGF produces sensitization of nociceptors both directly (after activation of trkA on nociceptors) and indirectly, mediated via other peripheral cell types. The direct mechanisms involve both altered gene expression and posttranslational regulation of receptors and ion channels, including TRPV1 (121) and tetrodotoxin-resistant Na^+ channels (122).

In addition to neuronal sensitization, NGF directly modulates a number of peripheral immune cell types. Mast cells express trkA (123,124) and

NGF can result in degranulation (124,125) and increased proliferation of these cells. In peritoneal mast cell cultures, NGF induced the expression of a number of cytokines (126). In addition, mast cell degranulators have been demonstrated to partially prevent the thermal hyperalgesia that occurs in response to NGF (127,128). NGF may also target eosinophils (129) and increase B- and T-cell proliferation (130), suggesting a role for NGF as an immunoregulatory factor. It has also been demonstrated that NGF may produce peripheral sensitization via activation of the 5-lipoxgenase pathway, leading to local neutrophil accumulation (12,131). Indeed, depletion of neutrophils in animals prevents NGF-induced thermal hyperalgesia, indicating that neutrophil accumulation may be critical for the sensitizing actions of NGF (12).

After nerve injury, sensory neurons become disconnected from their targets, and hence, the normal retrograde transport of NGF is reduced (36,132). As a result, a compensatory response is observed in the distal nerve stump, whereby nonneuronal cells express NGF mRNA. Two phases of increased NGF expression are detected: rapid (days) and long-term (weeks). The second peak of expression is mediated by the invasion of macrophages and the release of IL-1β (36), although the magnitude of this effect is inadequate to compensate for the loss of target-derived NGF. However, the provision of exogenous NGF after nerve injury has a neuroprotective effect on these damaged neurons. Many changes in gene expression within sensory neurons after nerve injury (e.g., axotomy-induced transcription factor 3) are reversed or partially reversed by exogenous NGF treatment (133).

In a clinical setting, the most common neuropathy is that associated with diabetes. Diabetic neuropathy is typically seen as a distal polyneuropathy, occurring as a consequence of the "dying back" of nerve terminals. In animals, NGF has been demonstrated to reverse a number of the changes seen during diabetic neuropathy (134). However, clinical trials of NGF for the treatment of diabetic neuropathy have proved disappointing, despite initial positive results (135). One reason for this failure may be the algogenic effects of NGF, which have required the use of very small doses in these trials. However, NGF has been reported to show some efficacy in the treatment of human immunodeficiency virus neuropathy (136).

Given the neuroprotective versus algogenic effects of NGF, would NGF itself, or an anti-NGF strategy be of functional use in the treatment of neuropathic pain? The use of NGF itself as a treatment for neuropathic pain may be of benefit because of the pathological conditions associated with the injured nerves. Indeed, a number of studies have observed benefits of NGF treatment on neuropathic pain. However, there is also logic for trying to treat neuropathic pain by blocking the actions of NGF. This theory is justified by the rationale that uninjured fibers have an increased availability of NGF, because they are competing with fewer fibers for any target-derived supply. In addition, reactive Schwann cells in the damaged nerve begin to synthesize large amounts of NGF. Indeed, NGF overexpressing mice display a marked hypersensitivity to both mechanical and thermal stimuli after CCI, suggesting that excess NGF may enhance neuropathic pain behaviors (137). Several groups have therefore tested the use of anti-NGF treatment in models of neuropathic pain. Anti-NGF antibodies are able to delay the development of neuropathic pain behaviors after both CCI (138), and SNL (139). In addition, in a rodent model of spinal cord injury, in which neuropathic pain behaviors developed bilaterally, anti-NGF attenuated both mechanical hyperalgesia and enhanced neuronal responses in the spinal cord (140). Despite the apparent success of anti-NGF treatment observed by a number of groups, neuroprotective effects have been reported using other neurotrophic factors. For example, exogenous glial cell line-derived neurotrophic factor administration attenuates both ectopic neuronal firing and neuropathic pain behaviors after SNL (141). It is therefore feasible that a combination of anti-NGF with glial cell line-derived neurotrophic factor would have additional efficacy in the treatment of neuropathic pain.

CONCLUSIONS

Many studies have provided evidence of a critical role for immune cells and proinflammatory mediators in the generation of neuropathic pain after injury of the peripheral nervous system. Although there is growing evidence for specific actions of individual molecules, the complex interactions of the cells and mediators involved are not fully established. The peripheral immune response may play a pivotal role in nerve injury-induced pain. Although important, these peripheral processes do not occur in isolation from central neuroinflammation. Together, these neuroimmune interactions seem essential for the production of neuropathic pain symptoms.

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