Neuroimmune mechanisms in cancer pain

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Purpose of review
The current review provides a summary of recent advances in our understanding of the neuroimmune interactions which influence the development of pain associated with cancer.

Recent findings
Common signalling pathways, mediators and immune cell types are involved in the generation of pain as a result of both cancer and its treatment. Distinct alterations in central and peripheral neuronal function occur in multiple forms of cancer pain. Other more unusual neuroimmune processes such as graft-versus-host disease may cause cancer pain.

Summary
Identification of the cellular processes which underlie the generation of cancer pain provide potential novel targets for drug development and may eventually lead to improved pain management for cancer patients.

Keywords
cancer, graft-versus-host disease, neuroimmune, pain

INTRODUCTION

The concept that interactions between the immune and nervous systems contribute to the development and maintenance of pain states is relatively novel. The blurring of the respective lines between these two distinct systems may initially seem alien. However, a wealth of evidence now supports the theory that in both the central and peripheral nervous systems, considerable influence is exerted on neuronal function by a variety of associated satellite and immune cells, including astrocytes, microglia and macrophages [1,2▪]. Not only do these neuroimmune interactions manifest themselves in the form of inflammatory and neuropathic pain but they also play a role in the pain state associated with cancer and its treatment.

Causes of pain in cancer

Major causes of pain in cancer include chemotherapy-induced peripheral neuropathy (CIPN), toxicity as a result of radiotherapy, persistent postsurgical pain and pain directly caused by the presence of disease. Immune cell-mediated processes play an important role in their respective pathophysiology. The current review will discuss the various forms of pain associated with cancer from a neuroimmune perspective, presenting a summary of our current understanding of the topic, discussing relevant areas of interest and providing an indication of potential future developments.

NEUROIMMUNE INTERACTIONS AND PAIN CAUSED BY PRIMARY TUMOURS

Traditional views on the causes of cancer pain focus on the physical effects of the growing tumour, both in the form of tissue destruction and the direct compression of nerve fibres present in the locality [3▪▪]. However, it is becoming increasingly apparent that cancer pain is an entity distinct from other pain states, admittedly possessing a number of their features but with a unique underlying pathophysiology.

The tumour and the tumour–host stroma

As a neoplasm develops, pain may arise through a number of distinct mechanisms related to the direct physical effects of the tumour and its biochemical interactions with its host environment, both near and distant. A tumour comprises not only the

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KEY POINTS

- Neuroimmune interactions play a fundamental role in the generation of pain associated with both primary tumours and their treatment.
- Common mediators are involved in the promotion of tumour growth and metastasis and in generating pain arising from the primary tumour.
- Understanding neuroimmune interactions in cancer pain may lead to the identification of novel therapeutic targets.

malignant cells but also an associated community of immune, mesenchymal and endothelial cells forming the host-derived stroma [4]. The host-derived stroma interfaces directly with the tumour, and communication and interaction between the two influences the on-going behaviour of the neoplasm [5,6]. Infiltration of the tumour itself by tumour infiltrating lymphocytes (TILs) is also a common occurrence, reflecting the potent immunogenicity of neoplasms [7]. Crosstalk between the tumour and neighbouring cells is facilitated by the signalling molecules produced by both the malignancy and stroma. These soluble mediators recruit additional cells to the site of the tumour and direct localized tissue remodelling – paving the way for tumour invasion and distant spread [8].

Release of mediators

Malignant cells, TILs and the cells of the tumour stroma synthesize a number of pain-modulating agents which are released into the tumour microenvironment [9]. The substances released include endothelins, tumor necrosis factor α (TNFα), prostaglandins, interleukin-1 and interleukin-6, transforming growth factor β (TGFβ) and hydrogen ions produced by cells present in the tumour's hypoxic core [10▪,11,12,13▪,14], all of which act either by sensitizing or by directly stimulating nociceptors (Fig. 1). Tumour cells present in a range of malignancies, including melanoma, prostate, thyroid, gastric, pancreatic, lung and colorectal cancer [15–20], release neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor and neurotrophins 3 and 4, which influence neuronal growth, guidance, transmitter release and plasticity in the proximity of the tumour [21]. Therefore, not only is the biochemical profile of the milieu present at the site of a tumour induced to the generation of pain, neurogenesis and neuromodulation occur, further amplifying the degree of pain arising from the tumour [22].

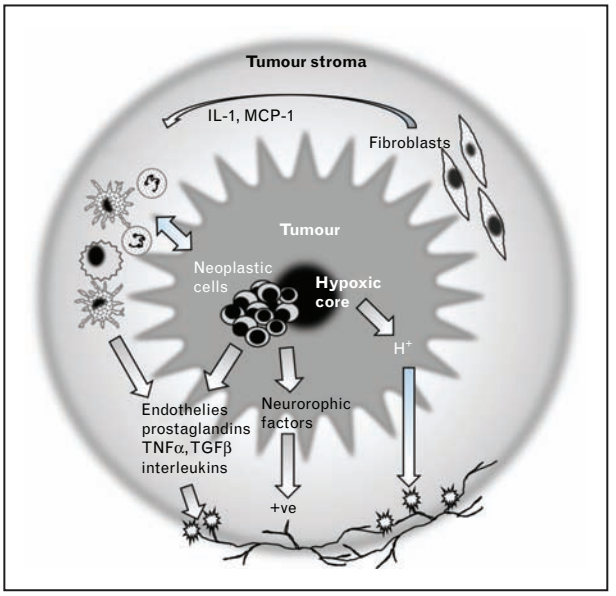

FIGURE 1. Overview of processes contributing to pain caused by tumours. Multiple factors are thought to contribute to the generation of pain by a tumour. Monocyte chemotactic protein 1 (MCP-1) recruits immune cells to the tumour site. Signalling molecules released by the tumour and the cells of the tumour stroma encourage nerve growth and sensitize fibres. These nerve fibres are in turn stimulated by mediators and hydrogen ions released by the neoplasm and by direct pressure from the growing tumour.

NEUROIMMUNE INFLUENCE ON PAIN ASSOCIATED WITH CANCER TREATMENT

Pain may arise in cancer patients due to a number of different treatment modalities for the disease. In this review, the neuroimmune influence on pain caused by surgery, chemotherapy and haematopoietic stem cell transplantation are described.

POSTSURGICAL PAIN

A variety of tumours can be treated surgically to achieve either a definitive cure or a period of disease control. Neuroimmune interactions contribute both to the acute pain associated with the initial surgical wound and with the development of persistent postsurgical pain – defined as pain present at 2 months following a surgical procedure and for which alternative causes have been excluded [23].

Acute pain

Surgery-associated tissue disruption triggers a complex, stereotyped cellular response which facilitates efficient wound healing [24]. Immune cells, such as mast cells, cutaneous dendritic cells, neutrophils and macrophages populating the surgical

microenvironment, produce and release a slew of pro-inflammatory mediators and signalling molecules. These mediators serve a number of roles, recruiting circulating cells to the wound site, driving cellular proliferation and contributing to the acute pain experienced following surgery [25]. The epidermis, dermis and deeper structures are innervated by an extensive array of nociceptive fibres, responding either to specific modalities such as cold or pressure or being activated by mechanical, thermal and chemical stimuli (polymodal nociceptors) [26]. These unmyelinated fibres act as peripheral afferent pain sensors stimulated by signalling molecules (TNFα, interleukin-1β and interleukin-6) present in the inflammatory milieu [27]. In addition, small fibres can directly perpetuate and amplify the cellular changes occurring at the surgical site by releasing neuropeptides such as substance P and calcitonin gene-related peptide, a process termed neurogenic inflammation [28]. Therefore, a somewhat circuitous situation exists whereby acute pain may be sensed, modulated and to a degree promoted by the interaction between the efferent and afferent functions of small nerve fibres and the immune cell population of the surgical wound (Fig. 2). Acute pain generally resolves as the wound heals and the immunocytic nidus at the surgical site dissipates; however, in a proportion of patients, resolution of pain does not occur leading to the phenomenon of persistent postsurgical pain.

Persistent postsurgical pain

The incidence of persistent postsurgical pain is variable and is influenced by a range of factors related to both the surgery and the patient. In the most high-risk procedures such as thoracotomy and amputation, persistent postsurgical pain may be greater than 50% [29]. The precise mechanisms that influence the transition from acute to persistent pain remain poorly understood [30]. What is clear is that the noxious stimulus of surgery results in peripheral and central nervous system modulation in which neuroimmune interactions play a fundamental role [31].

Central sensitization

Injury to sensory fibres accompanied by the shift to a more inflammatory profile at the surgical site results in localized neuronal sensitization and abnormal afferent signalling [32▪]. Repetitive aberrant input from these fibres leads to central sensitization in the spinal cord and the brain. Subsequent inputs from nociceptive and non-nociceptive sensory fibres are amplified [33], causing heightened perception of pain in the affected patient. Alterations in neuronal gene expression [34], occurring within a short period of the initial injury [35], promote increased synaptic coupling and communication between sensory neurones.

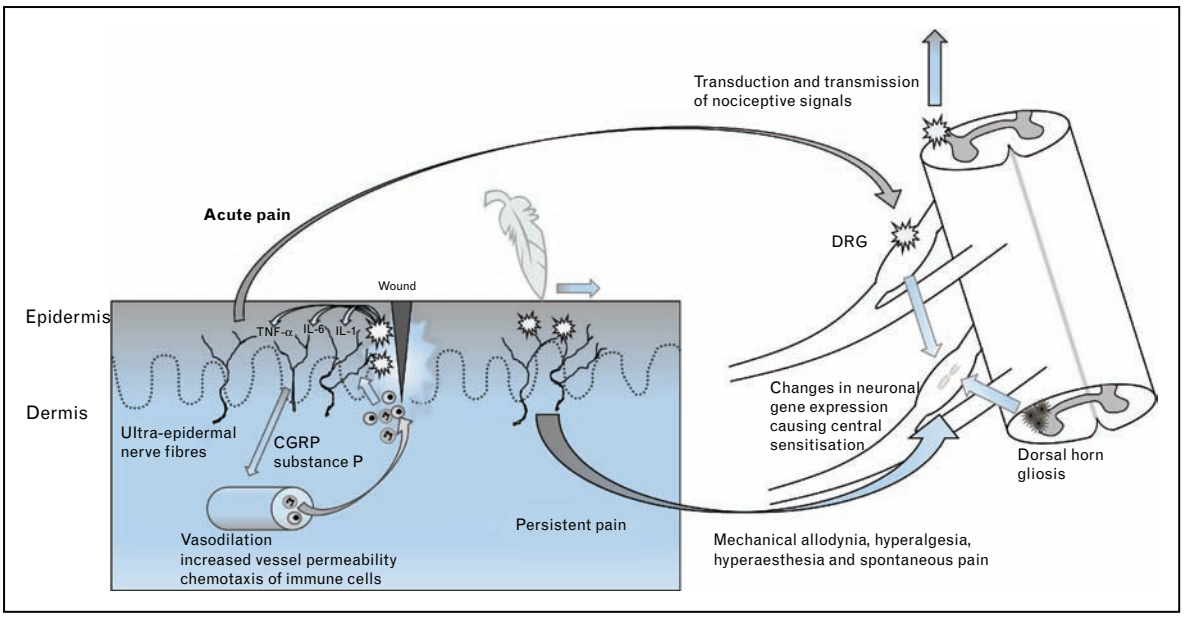

FIGURE 2. Neuroimmune influences on acute and persistent pain associated with cancer surgery. Acute pain is potentiated by neuroimmune interactions in the vicinity of the wound – mediators released by nerve cells in the periphery drive the inflammatory process, whilst centrally changes in gene expression occur. In a persistent pain state, alterations in the cellular population of the dorsal root ganglion (DRG) and the dorsal horn of the spinal cord result in adherent neuronal function and the sensory changes witnessed clinically. CGRP, calcitonin gene-related peptide.

Neuroimmune influences

Neuroinflammation plays an important role in the induction and maintenance of this central neuronal plasticity [36] with infiltration of immune cells and increased glial cell activity observed in the dorsal horn of the spinal cord following peripheral nerve and tissue injury [37,38]. Microglia, the resident macrophages of the central nervous system, communicate directly with neurones via a number of signalling pathways, including those involving neuregulin, metalloproteinase-9, CCL-2 and Toll-like receptors [39]. It has been suggested that remodelling of neuronal synaptic connections in the dorsal horn combined with pathological neuronal sprouting results in the formation of abnormal links between afferent fibres of differing modality (such as nociception and fine touch), the amplification of afferent signals and reductions in descending inhibitory inputs [40]. These proposed central changes, driven by neuroimmune interactions, may explain the clinical picture seen in persistent postsurgical pain of allodynia, hyperalgesia and hyperaesthesia, which often proves challenging to manage successfully.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

The use of cytotoxic chemotherapy remains a mainstay of cancer treatment; however, these drugs are associated with unpleasant and poorly tolerated side-effects, including the development of CIPN. The incidence of CIPN varies and is influenced by a number of factors, including the chemotherapy agent used, its dosing regimen and the presence of comorbidities such as diabetes [41▪,42]. In some series, CIPN is observed in more than 50% of patients treated [43]. CIPN presents a length-dependent peripheral neuropathy, involving the 'die-back' of small unmyelinated sensory nerves from the periphery, predominantly resulting in pain and sensory symptoms such as numbness and allodynia [44].

Underlying pathophysiology of CIPN

The exact pathophysiological process underlying the development of CIPN remains poorly understood, although mitochondrial toxicity [45▪] and the disruption of microtubules [46] within neurones are proposed as potential causes. Inflammatory processes in the environs of damaged nerves are also observed in CIPN (although whether this phenomena is reactive to or causative of CIPN is not clear).

Peripheral changes

In the peripheral nervous system, a change in the cellular population of the dorsal root ganglion (not protected from chemotherapy agents by the blood–brain barrier) occurs with an increase in the number of activated macrophages present [47], accompanied by glial cell dysfunction [48,49▪]. In severe cases of toxicity, this may progress to microgliosis within the spinal cord [39]. In turn, this shift in cellular population leads to abnormal cell signalling and changes in expression of mediators and genes associated with both pain and cell death. These include reductions in the circulating levels of NGF [50], changes in interleukin-1β, interleukin-6 and interleukin-8, and TNFα production [51] and activation of pro-apoptotic genes [52], which detrimentally affect neuroregeneration following a cytotoxic insult. Distally, there is evidence that macrophages contribute to neuronal damage at the axonal level [53].

Other neuroimmune interactions

Further evidence exists for immune cell involvement in CIPN. In animal models of CIPN and other small fibre neuropathies, cutaneous Langerhans cells exist in an activated state in close proximity to sensory fibres undergoing degeneration [54–56]. This intriguing finding has also been observed in humans, in which increased Langerhans cell numbers have been demonstrated in patients with small fibre neuropathies caused by a range of conditions [57,58]. The influence of these antigen-presenting cells in the pathophysiology of CIPN remains unclear, and further work to delineate what, if any, role they play is warranted.

Future therapeutic approaches?

Current treatment for pain associated with CIPN is often suboptimal, with sparse evidence for individual agents used [59]. Recent guidelines recommend a generic approach and are largely based on evidence from other conditions, which result in neuropathic pain [60▪]. Targeting neuroinflammatory processes may offer potential future treatment approaches in CIPN. Anecdotal reports suggest that intravenous immunoglobulin may have a role in the improvement of symptoms with CIPN caused by certain agents [61], further suggesting a role for the immune system in potentiating CIPN. In other neuropathies, immunomodulatory agents have previously been used [2▪], but the efficacy of this treatment in CIPN would need to be tested in well-designed clinical trials, with robust surveillance of

participants to detect any effect on recurrence these agents may have.

NEUROPATHY CAUSED BY GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) is a common complication of allogenic haematopoietic stem cell transplantation, a technique used to treat malignancies arising from the bone marrow or blood [62]. GVHD may be acute, resolving within 100 days of engraftment or chronic, persisting for more than 100 days [63]. GVHD occurs when transplanted T cells react to unfamiliar antigen in immunocompromised patients, leading to inflammation affecting multiple systems [64]. Peripheral nerve involvement resulting in neuropathy is relatively uncommon, affecting approximately 0.6–4% of patients undergoing bone marrow transplantation [65]; however, the impact of these neuropathies and their symptoms on patients' quality of life is significant [66].

Clinical features

The neurological ramifications of GVHD represent a spectrum of disease ranging from acute Guillain–Barré syndrome-like demyelinating polyneuropathy [67] to more chronic demyelinating polyneuropathies, which may occur many months after transplantation [68]. Rarely, the central nervous system may also be affected [69]. The clinical features of the more chronic peripheral neuropathies include muscle weakness (which aids in distinguishing it from the predominant sensory features of CIPN), paraesthesia, pain and balance problems caused by impaired proprioception [70].

Management approaches

The management of GVHD revolves around the use of immunosuppressive agents, and resolution of GVHD-associated neuropathies occurs in a proportion of these patients. In patients who do not improve once their GVHD has been controlled, plasmapheresis and/or intravenous immunoglobulin therapy may be required [65]. Overall, patients who develop neurological manifestations of GVHD have poorer outcomes compared with those patients with GVHD who do not [71].

BONE METASTASES AND ASSOCIATED PAIN

Metastatic spread of cancerous cells to bone is common in a variety of malignancies, notably those arising from the breast, prostate and lung [72]. In addition, a number of primary bone tumours occur, such as myeloma, osteosarcoma and Ewing's sarcoma. These lesions are united by the fact that they often cause severe cancer-induced bone pain (CIBP), which represents a significant clinical challenge [73].

Pathophysiology of cancer-induced bone pain

CIBP is a complex entity, combining elements of inflammatory and neuropathic pain while encompassing features of tissue destruction and central neurochemical changes, distinguishing it from other pain states [74]. Our understanding of the mechanisms underlying CIBP is increasing and its multifactorial origin is becoming clear (Fig. 3). A combination of periosteal anatomical disruption, local tissue destruction, changes in sensory innervation and the release of pro-inflammatory signalling molecules from the growing tumour all contribute [75].

Influence of metastases on bone homeostasis

The bone microenvironment provides a hospitable lodging for tumour cells. Here they release a raft of signalling proteins including receptor activator of nuclear factor kappa B ligand, interleukin-1, interleukin-6 and TGF-β [76], which induce the differentiation, recruitment and activation of osteoclasts. This in turn leads to increased bone destruction, abnormal remodelling and the release of growth factors and ionized calcium, which positively feedback to promote tumour growth at the metastatic site [77]. Although traditionally bone metastases from specific tumour types were viewed as being either osteolytic or osteoblastic in nature, it is becoming apparent that the behaviour of individual metastases varies and may possess features of both phenotypes [78].

Pain generation in cancer-induced bone pain

As the tumour grows and cortical bone is destroyed, the associated periosteum becomes inflamed and disrupted [79]. The marrow, cortex and periosteum of bone is richly innervated by primary afferent nerve fibres [80], serving both a sensory and a regulatory function [81]. Pathological sprouting and reorganization of sensory fibres present at the tumour site is observed with the formation of neuroma-like structures [74]; this process is stimulated by NGF released by tumour stromal cells [82] and can be attenuated, in a mouse model of CIBP, by the

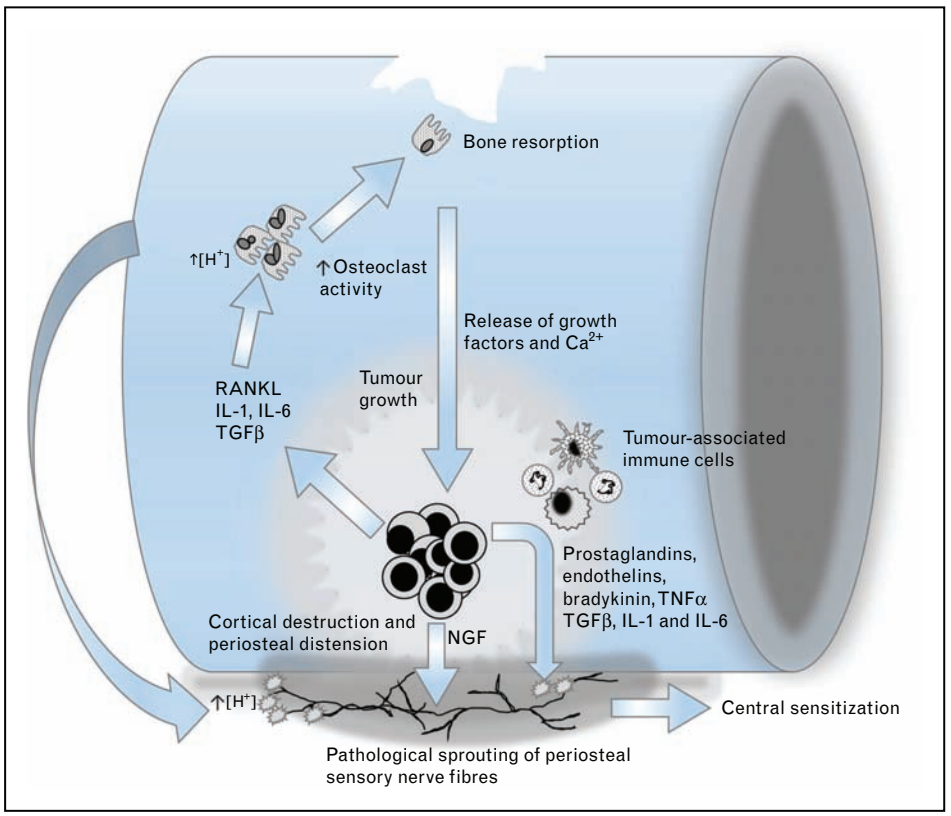

FIGURE 3. The neuroimmune factors driving pain from bone metastases. Growing tumours in the bone release mediators which stimulate bone destruction by osteoclasts and abnormal bone remodelling. Neurotrophic factors produced by the bone metastases cause pathological sprouting of periosteal sensory fibres which are stimulated by mediators, hydrogen ions and the anatomical disruption of the periosteum. In addition, central sensitization occurs (see main text for details).

administration of NGF-specific antibodies [83]. Sensory transduction by these abnormal fibres is potentiated by an array of pro-hyperalgesic mediators which sensitize the fibres leading to lower excitatory thresholds. Prostaglandins, endothelins, bradykinin, TNFα, TGFβ, interleukin-1 and interleukin-6 are present at the metastases, released by tumour cells, osteoclasts and blasts and tumour-associated immune cells such as neutrophils, macrophages and T cells [84,85]. An acidic environment engendered by both osteoclasts and the metastases itself further compounds the pain state by activating H^+ sensitive TRPV1 receptors expressed by sensory fibres [86].

Central neuronal reorganization

Changes associated with the presence of bone metastases also occur centrally with significant reorganization of both neuronal and supporting cell populations in the dorsal root ganglion (DRG) and dorsal horn of the spinal cord [87]. Immunohistochemical studies have shown levels of cyclic AMP-dependent transcription factor (ATF-3, a marker of neuronal damage) to be upregulated in the DRG and the number of c-Fos (a marker of neuronal activity) expressing neurones to increase in the spinal cord dorsal horn in animal models of CIBP [88]. Interestingly, dorsal horn changes observed in CIBP are peculiar to the condition, distinguishing it from other persistent pain states [89]. Changes in the excitatory state of neurones in the DRG are facilitated by increased expression of the Nav 1.8 sodium channel present on the surface of neurones [90]. Further work in CIBP models has demonstrated unique neuroplastic changes in the synapses of excitatory fibres in the substantia gelatinosa of the dorsal horn, resulting in spinal sensitization and alterations in sensory modulation and transmission as seen in patients with painful bone metastases [91,92].

Potential therapeutic targets related to neuroimmune interactions in cancer-induced bone pain

Despite the identification of multiple potential therapeutic targets, the management of CIBP has not advanced markedly since the introduction of

bisphosphonates with a persisting reliance on strong opioids to control pain [93▪▪]. Biopharmaceutical agents, such as denosumab, a monoclonal antibody which specifically inhibits the receptor activator of nuclear factor kappa B ligand are, however, being trialled in CIBP with initial encouraging results [94]. Similarly, tanezumab, a monoclonal antibody to NGF (which have been shown to reduce pathological nociceptor sprouting in animal models of CIBP [82,95]) is also currently being assessed in phase II clinical trials [96].

CONCLUSION

Understanding of cancer and the pain associated with it is increasing at a rapid pace. Insights into the molecular and cellular processes, which underlie the pathophysiology of these conditions, highlight the close interaction between neoplastic cells and the host immune and nervous systems. Crosstalk between the systems, facilitated by soluble mediators released into the tumour microenvironment, plays a fundamental role in potentiating the growth and spread of tumours and in the generation of cancer pain. The extent of the common pathways, signalling molecules and cell types involved in the pathological processes, resulting in both tumour development and metastasis and the generation of cancer pain, is striking.

In addition, cancer pain caused by a variety of processes (which have traditionally been viewed as being distinct entities) including CIPN, primary tumour pain and persistent postsurgical pain possess at the most fundamental level similarities in the degree of neuroimmune interactions involved in their genesis. There are also, however, distinctions to be made between the different forms of cancer pain, for example the specific and distinctive neurobiological changes observed in the spinal cord of animals with CIBP [89].

Ironically, as our greater understanding of cancer biology has led to the development and adoption of new targeted therapies, new forms of cancer pain arise. For example, the use of biopharmaceutical agents such as monoclonal antibodies, an undoubted step forward in cancer therapeutics [97], has been associated with the development of painful myalgias in a small number of patients [98]. Therefore, as more targeted therapies are introduced into clinical practice, there is a potential for these new forms of cancer-associated pain to become more prevalent. An awareness of the possibility of patients receiving these treatments to develop painful symptoms combined with active surveillance of this patient population is advisable.

Harnessing our understanding of the neuroimmune interactions which underlie cancer pain may well result in the development of novel agents, a process exemplified by the introduction of denosumab into clinical use. The potential opportunities this process offers to improve the treatment of pain related to cancer should be welcomed and encouraged.

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Conflicts of interest

The current review is an original work and has not been published elsewhere.
There are no conflicts of interest.

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