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Mini Review

# Sensory Nerves: A Driver of Bone Metastases' Vicious Cycle?

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ABSTRACT

One of the most common sites for cancer metastasis is the bone. Bone metastasis is associated with a number of problems, the most prevalent and debilitating of which is bone pain. Increased neurogenesis, reprogramming, and axonogenesis of Sensory Nerves (SNs) in tandem with sensitization and excitation of SNs in response to the tumour microenvironment formed in bone cause Cancer-Associated Bone Pain (CABP). Importantly, CABP is linked to an increased risk of death, however the exact cellular and molecular mechanism is unknown. Autonomic nerves (sympathetic and parasympathetic nerves) and Sensory Nerves (SNs) are abundantly innervated in bone. The present state of knowledge about the role of SNs innervating bone in the pathophysiology of CABP will be discussed in this review. The idea that SNs aid cancer growth in bone will then be examined in light of our recent results showing SNs are involved not only in the formation of CABP but also in the advancement of bone metastasis in a preclinical model of CABP.

**Keywords:** TRPV1, bone microenvironment, perineural invasion, cancer-related bone pain, sensory nerves, nociciceptors

## INTRODUCTION

Cancer-Associated Pain (CAP) affects the majority of people with advanced cancer and is one of the most common and feared cancer symptoms. It has significant psychological and physical effects on cancer patients, lowering quality of life and increasing morbidity and death. Cancer-Associated Bone Pain (CABP) is the most prevalent CAP encountered in patients with advanced cancer. More than 80% of individuals with metastatic cancer have CABP, whereas only 23%, 11%, and 8% of the same population of patients have pleuritic, neural, and visceral pain, respectively. It is commonly known that cancer patients who have CAP/CABP have a lower survival rate than those who do not have CAP/CABP. The mechanism by which CAP/CABP is linked to poor survival, however, is unknown [1]. CAP/CABP are primarily caused by sensitization and stimulation of peripheral primary Sensory Nerves (SNs) in conjunction with electrophysiological alterations in response to local painful stimuli produced in the tumour microenvironment. Excited SNs then produce neurotransmitters and neurotrophins, which may help to control cancer aggression. The fact that prostate cancer metastasis is reduced following spinal cord injury supports this theory, implying that nerves play an essential role in prostate cancer growth. Furthermore, the link between stress-related psychosocial factors and a higher lung cancer incidence in healthy people or a lower survival rate in cancer patients suggests that Autonomic Nerves (ANs) are involved in cancer genesis and progression.

The impact of peripheral nerves on cancer progression in bone require a thorough understanding of bone innervation. Please see current great review articles for further information on bone innervation. Bone is innervated by large networks of both ANs and SNs, according to reports. At the metaphysis, 96 percent of nerves innervating the bone marrow are AN fibres, while just 4% are SN fibres. As a result, ANs are dominant nerves that innervate the bone marrow, a location where metastatic cancer cells preferentially colonise, and have thus been linked to cancer progression in the bone marrow [2]. SN innervation in bone occurs when SNs are distributed in a density ratio of 100:2:0.1 in the periosteum, bone marrow, and cortical bone. Because the total area of the bone marrow is greater than that of the periosteum, the total number of SNs in the bone marrow is greater than that in the periosteum, which is consistent with the observation that patients with cancer that appears to colonise only within the bone marrow cavity and does not spread out on the periosteum frequently complain of CABP.

### CABP Pathophysiology

CABP is thought to be caused by three mechanisms: 1) direct injury or damage to SN fibres caused by cancer invasion; 2) activation of periosteal SNs caused by mechanical stretching of the periosteum caused by cancer expansion in the bone marrow cavity; and 3) hyper-innervation of SNs and neuroma formation caused by the presence of tumour. CABP is caused by the sensitization and stimulation of the SNs that innervate the bone. Pain is triggered by the sensitization and stimulation of primary afferent SN receptors known as "nociceptors," such as Transient Receptor Potential Vanilloid-1 (TRPV1) and Acid-Sensing Ion Channels, according to new research (ASICs). These SN nociceptors detect painful

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stimuli in the environment, become stimulated, and convert the sensations into electrochemical signals, which are then conveyed to the spinal cord (secondary afferent neuron) via the SN Dorsal Root Ganglia (DRGs, primary afferent neuron), CNS, and brain. DRG is the cell body of SN fibres and serves as a conduit for unpleasant signals from the peripheral nervous system to reach the CNS. During the advancement of bone metastases, CABP is produced by an up-regulation of nociceptor activity of SNs innervating bone. Bone provides a unique setting for CABP induction in the pathophysiology of CABP. Metastatic cancer cells in bone create a distinct tumour microenvironment and metabolic activity that is hypoxic by nature. The expression of Hypoxia-inducible Transcription Factor-1 (HIF-1) is up-regulated in a hypoxic bone microenvironment to enhance protons and lactate release via cancer cells' plasma membrane proton/lactate transporters, making the bone microenvironment acidic [3].

Furthermore, to survive and proliferate in the hostile hypoxic bone microenvironment, cancer cells promote oxygen-independent aerobic glycolysis via the Warburg effect, resulting in increased cytoplasmic protons and lactate concentrations, which are then excreted out of cancer cells, resulting in an extracellular acidic tumour microenvironment. Furthermore, osteoclasts that are activated in the presence of metastatic cancer cells secrete more protons, which are used to breakdown bone minerals. Protons released by bone-resorbing osteoclasts and cancer cells invading bone combine to form an exacerbated acidic tumour microenvironment in bone. Protons are a powerful pain inducer. As a result, it's most likely that the acidic microenvironment of bone metastases plays a role in CABP induction. TRPV1 is one of the SN nociceptors that is activated after protons are detected. TRPV1 is virtually exclusively expressed on the tiny unmyelinated c-fiber nociceptive afferent SNs and consists of 838 amino acids with a molecular size of 95 kD. TRPV1 expression has also been found in the gastrointestinal system, as well as the bladder and skin epithelium [4]. TRPV1 is expressed by both osteoblasts and osteoclasts, albeit its exact role has yet to be established. TRPV1 is a nonselective cation channel that is activated by capsaicin, acid (pH 6.0), unpleasant heat (more than 43°C), and pro-inflammatory mediators like prostaglandins, bradykinin, ATP, and 5-hydroxytryptamine, as well as Nerve Growth Factor (NGF). Under mild acidosis (pH 6–7), TRPV1 is sensitised to capsaicin, heat, and inflammatory mediators, while inflammatory mediators can sensitise TRPV1 to proton. Ca2+ influx through the TRPV1 pore also causes membrane depolarization, which is followed by the activation of voltage-gated sodium channels and the production of action potentials, which increases nociception [5].

Cancer cell invasion into surrounding nerves or into the epineurial, perineurial, and endoneurial regions of the neuronal sheath, resulting in intense nerve innervation in the tumour microenvironment, is described as PNI or NI, respectively. PNI/NI is typically seen in malignancies of the pancreas, head and neck, prostate, colorectal, biliary system, and stomach that start in densely innervated organs. Cancers that have PNI/NI diffuse along nerve fibres in the tumour, promoting axonogenesis, reprogramming, and neurogenesis of these nerves, which enhances cancer progression by allowing cancer-nerve cross-talk to form.

## REFERENCES

1. Zahalka A.H, Frenette P.S. Nerves in cancer. Nat. Rev. Cancer. 2020;20:143-157.
2. Yoneda T, Hiasa M, Okui T. Crosstalk between sensory nerves and cancer in bone. Curr Osteoporos Rep. 2018;16:648-656.
3. Mantyh PW. Mechanisms that drive bone pain across the lifespan. Br J Clin Pharmacol. 2019;85:1103-1113.
4. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain. 1997;69:1-8.
5. Riera CE, Huising MO, Follett P, Leblanc M, Halloran J, Van Andel R, et al. TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. Cell. 2014;157:1023-1036.