Oncology Treatment Discovery, 2025, Volume 3, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD
Online ISSN: 2981-8079

# Research Progress of the Occurrence Mechanism of Bone Cancer Pain

**Dan Yi [1,2], Mengnan Du[3], Wentao Li[1,2], Shuo Dong[1,2], Ying Zhang[1,2*]**

[1]First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381, China
[2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300381, China
[3]Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300250, China

***Corresponding author:** Ying Zhang, zhangyingzhongyi@sina.com



**Abstract:** As one of the common complications of patients with malignant tumors, cancer pain seriously affects their quality of life, especially the bone cancer pain, and the conventional analgesic effect of some patients with bone cancer pain is not ideal. The pathogenesis of bone cancer pain is complicated, the pathogenesis can be deeply understood and provide diagnosis and treatment thoughts for clinical relief of bone cancer pain by consulting the literature and summarizing the pathogenesis of bone cancer pain.

**Keywords:** Bone cancer pain; Mechanism; Research progress

**Online publication:** January 20, 2025

## 1. Introduction

Cancer pain, also known as malignant pain, is a symptom that mainly caused by pathological factors of tumors, anti-tumor treatment factors or other complications, social psychological factors [1]. It is one of the most common and painful symptoms for patients with malignant tumors and regarded as the fifth vital sign of cancer patients, seriously affecting their quality of life [2]. Research shows that about 70% of cancer patients experience cancer pain during the course of the disease [3]. Patients will not only feel extremely uncomfortable but also may develop or aggravate symptoms such as fatigue, insomnia, loss of appetite, anxiety, and depression if cancer pain is not well and timely controlled, seriously affecting their daily activities and self-care ability. Therefore, "Diagnosis and Treatment Guidelines for Cancer Pain (2018)" points out that controlling pain is a basic right of patients and also the duty and obligation of medical staff [4].

Bone cancer pain is a severe and common pain caused by bone metastasis or primary bone tumors. The state of pain is usually persistent, sudden, spontaneous, and accompanied by hyperalgesia [5,6]. At present, the treatment of bone cancer pain includes drug analgesia, interventional therapy, radiotherapy, surgery and so on, while some

patients with bone cancer pain still have unsatisfactory pain control. Therefore, exploring the pathogenesis of bone cancer pain can help clinicians deepen their understanding of bone cancer pain, and guide clinical analgesia treatment, provide thoughts for the relief of bone cancer pain.

The pathogenesis of bone cancer pain is the result of multiple factors, and the occurrence mechanism is mainly related to several factors, such as activation of multiple signaling pathways, sensitization of the central nervous system, ferroptosis, osteoclasts and so on. The research progress is briefly described.

## 2. Activation of multiple signaling pathways

PI3K/Akt signaling pathway: Akt, which encodes widely expressed serine/threonine protein kinase [7], is the cell homologous gene of viral oncogene v-Akt and forms the PI3K/Akt signaling pathway with its upstream protein PI3K, which plays a very important role in neuropathic pain, inflammatory mechanical pain or thermal pain, and cancerous pain [8–10]. The PI3K/Akt signaling pathway is usually up-regulated in the pathological environment, while Li *et al.* (2020) [11] found that in the process of postoperative chronic pain, the expression of inflammatory factors (IL-1β, TNF-α, etc.) increased, while the expression of PI3K/Akt decreased. By reducing the activation of PI3K/Akt, microglia promote the transformation of astrocytes into the A1 phenotype, which aggravates chronic pain after surgery. By studying the pain signal regulation pathway of bone cancer, Fu (2023) [12] observed that the expression of p-PI3K and p-Akt was up-regulated in the spinal cord tissue of bone cancer pain mice, and the expression levels of p-PI3K and p-Akt were significantly increased after pain stimulation. In addition, administration of the Akt inhibitor GSK690693 alleviated mechanical hyperalgesia associated with bone cancer. Previous studies have shown that the activation of PI3K and PKB/Akt is also involved in chronic pain, and the above study results indicate that PI3K/Akt plays different roles in the process of pain formation by activating various downstream signaling pathways [13]. Mitogen-activated protein kinase (MAPK) signaling pathway: As an important signal transduction pathway in the body, the MAPK signaling pathway is closely related to cell proliferation and apoptosis. MAPK family includes three important subfamilies: extracellular signal-regulated protein kinase (ERK), c-JUN amino-terminal kinase (JUN), and P38 [14]. Studies have found that the MAPK signaling pathway in the dorsal horn of the bone cancer pain mouse spinal cord was activated, showing that it is involved in the occurrence and development of bone cancer pain [15]. XPro1595 (a soluble tumor necrosis factor inhibitor) [16] could effectively inhibit the phosphorylation of the p38 MAPK signaling pathway, thus alleviating the pain behavior of bone cancer pain in rats, Jiao *et al.* (2021) [17] found that phenol could increase the threshold of mechanical foot retraction reflex in rats with bone cancer pain and the mechanism might be related to inhibiting activation of the MAPK signaling pathway by decreasing miR-21 expression. NF-kb signaling pathway: NF-kb is an important nuclear transcription factor in cells. As the central mediator of pro-inflammatory gene induction, NF-kb participates in important processes such as inflammatory response and immune response of the body. Its over-activation has also been confirmed to be related to many diseases, such as nerve injury [18], asthma [19], osteoporosis [20] and so on. In recent years, researchers have found that the activation of the NF-kB signaling pathway is also related to the occurrence of bone cancer pain. Zhou (2019) [21] observed the activation of the NF-kB signaling pathway itself in the rat model of tibial cancer pain, and the scorpion venom polypeptide monomer rBmK-AGAP could effectively inhibit the activation of the NF-κB signaling pathway and relieve the pain behavior of tibial cancer pain rats. Tian *et al.* (2019) [22] found that thalidomide could effectively alleviate the pain behavior of bone cancer pain rats induced by MC57G fibrosarcoma cells, and the mechanism might be

related to the down-regulation of NF-κB expression. Yi *et al.* (2024) [23] showed that by inhibiting the activation of NF-κB signaling pathway, down-regulated IL-1β, IL-6, and TNF-α inflammatory factors could alleviate bone cancer pain.

## 3. Sensitization of the central nervous system

Sensitization of the central nervous system refers to the increased response of nociceptive neurons in the central nervous system, such as the spinal cord and supraspinal cord (thalamus, brainstem, cerebral cortex), to primary afferent information at or below the normal threshold. It is a state of hyperexcitability in the nervous system [24]. Previous studies on central sensitization were mostly neuropathic pain, while researchers found that the spinal dorsal horn neurons and dorsal root ganglia of rats with bone cancer pain had unusual neurochemical changes [25], suggesting that the occurrence and maintenance of cancer pain might be related to the interaction between peripheral tumors and nerve fiber endings, and then the central sensitization caused by transmitting pain signals into the spinal cord [26]. By comparison with normal animal models, the proportion of wide dynamic range (WDR) neurons to nociceptive-specific neurons increased in bone cancer pain animal models, indicating that the receptive field of superficial neurons in the dorsal horn of the spinal cord increased, thus leading to an increased probability of central response to afferent low-threshold nociceptive information, and spinal cord slice patch clamp recordings indicated that spinal cord neurons showed an enhanced response to evoked stimuli, indicated that the overall excitability of neurons was enhanced and created central sensitization [27]. It is important to note that bone cancer pain often presents as persistent chronic pain and recent studies support the association of chronic pain with the cingulate cortex, prefrontal cortex, and ventral striatum [28]. In addition, another important factor of central sensitization, the N-methyl-D-aspartate receptor (NMDAR) of glutamate also plays an important role [29]. As a central neurotransmitter glutamate receptor, the continuous activation of NMDAR can show an excessive activation state with multiple increases under the condition that the peripheral input signal remains unchanged [30], which occurs in parallel with bone cancer pain behavior [31], providing conditions for central sensitization.

## 4. Ferroptosis

Ferroptosis is a novel form of programmed and non-apoptotic cell death triggered by iron-dependent lipid peroxidation. It is mainly the excessive accumulation of iron that transfers to mitochondria and triggers ROS, which makes various influencing factors interact, including inflammatory factors, and oxidative stress, and finally induces mitochondrial damage and cell death [32]. The current studies on ferroptosis are mostly related to osteoarthropathy, kidney disease, and nervous system disease [33–35], while Ding *et al.*'s (2023) study [36] found that the by inoculating Lewis lung cancer cells in rat femur to establish bone cancer pain model, followed by continuous intraperitoneal injection of FER-1 (selective ferroptosis inhibitor), which effectively alleviated ferroptosis related iron accumulation and lipid peroxidation, alleviated bone cancer pain behavior. Furthermore, FER-1 inhibited the pain-associated activation of ERK1/2 and COX-2 expression and prevented the loss of GABAergic interneurons, suggesting that ferroptosis could be a potential therapeutic target in patients suffering from bone cancer pain.

## 5. Activation of osteoclasts

Osteoclast (OC) is the main functional cell of bone resorption, which plays an important role in bone development, growth, repair, reconstruction and bone cancer pain. The activation of osteoclasts in bone cancer pain is affected by OPG/RANKL/RANK system. The OPG/RANKL/RANK signaling pathway is activated after stimulation, which promotes the differentiation and activation of precursor cells of osteoclasts into osteoclasts, thus producing bone resorption and inducing osteolytic pain [37]. Besides, the pain caused by osteoclasts' destruction of bone is also one of the causes of bone cancer pain. The periosteum sensory nerve distribution is abundant, and osteoclasts induce bone destruction, thus the mechanoreception of the periosteum produces pain, and osteoclasts can release H+, activate ASICs, and activate pain receptor sensitization, which aggravates pain perception.

## 6. Conclusion

To sum up, the occurrence of bone cancer pain is the result of many factors, including activation of multiple signaling pathways, sensitization of the central nervous system, ferroptosis, osteoclasts, etc. Exploring its pathogenesis can deepen the understanding of bone cancer pain so it can better find clinical analgesic methods, relieve the pain feeling of patients with bone cancer pain, providing thoughts for further treatment.

## Funding

Tuoxin Project of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (Project No.: 2020062); National Natural Science Foundation of China (Project No. 82104553)

## Disclosure statement

The authors declare no conflict of interest.

## Reference

[1] Chen JY, Yin YK, Zhang QL, et al., 2023, Data Mining for Medication Rules of External Application of Chinese Medicines Based on Syndrome Differentiation in the Treatment of Cancer Pain. World Chinese Medicine, 18(7): 1039–1043.

[2] Yi D, Du MN, Zhang X, et al., 2024, Jia Yingjie's Clinical Experiences in Treating Cancer Pain by Dismissing Turbid and Enhancing Vital Qi Theory. Liaoning Journal of Traditional Chinese Medicine, 51(11): 20–21.

[3] Mansoor MA, et al., 2021, The American Society of Pain and Neuroscience (ASPN) Best Practices and Guidelines for the Interventional Management of Cancer-Associated Pain. Journal of Pain Research, 14: 2139–2164.

[4] National Health Commission of the People's Republic of China, 2018, Diagnosis and Treatment Code of Cancer Pain 2018. Chinese Clinical Oncology, 23(10): 937–944.

[5] Zheng XQ, Wu YH, Huang JF, et al., 2022, Neurophysiological Mechanisms of Cancer-Induced Bone Pain. Journal of Advanced Research, 35: 117–127.

[6] Yang L, Liu B, Zheng S, et al., 2023, Understanding the Initiation, Delivery, and Processing of Bone Cancer Pain from the Peripheral to the Central Nervous System. Neuropharmacology, 237: 109641.

[7] Bellacosa A, Testa JR, Staal SP, et al., 1991, A Retroviral Oncogene, Akt, Encoding a Serine-Threonine Kinase

Containing an SH2-Like Region. Science, 254(5029): 274–277.

[8] Zhang W, Suo M, Yu G, et al., 2019, Antinociceptive and Anti-Inflammatory Effects of Cryptotanshinone Through PI3K/Akt Signaling Pathway in a Rat Model of Neuropathic Pain. Chemical Biology Interactions, 305(22): 127–133.

[9] Fan H, Wu Z, Zhu D, et al., 2022, Proanthocyanidins Inhibit the Transmission of Spinal Pain Information Through a Presynaptic Mechanism in a Mouse Inflammatory Pain Model. Frontiers in Neuroscience, 15(2): 804722–804738.

[10] Yuan G, Lian Z, Liu Q, et al., 2019, Phosphatidyl Inositol 3-Kinase (PI3K)-mTOR Inhibitor PKI-402 Inhibits Breast Cancer-Induced Osteolysis. Cancer Letters, 443(12): 135–144.

[11] Li T, Liu T, Chen X, et al., 2020, Microglia Induce the Transformation of A1/A2 Reactive Astrocytes via the CXCR7/PI3K/Akt Pathway in Chronic Post-Surgical Pain. Journal of Neuroinflammation, 17(1): 211–230.

[12] Fu X, 2023, Mechanism of Bone Cancer Pain in BALB/c Mice Based on PI3K/Akt Pathway WNK1, thesis, Inner Mongolia Medical University.

[13] Chen SP, Zhou YQ, Liu DQ, et al., 2017, PI3K/Akt Pathway: A Potential Therapeutic Target for Chronic Pain. Current Pharmaceutical Design, 23(12): 1860–1868.

[14] Hou GJ, 2019, Clinical Observation of Chanlong Zhentong Paste in Treating Cancer Pain and Research of Its Analgesic Mechanism in a Rat Model of Bone Cancer Pain, thesis, Hunan University of Chinese Medicine.

[15] Chen P, Pan M, Lin QS, et al., 2021, CSF-CN Contributes to Cancer-Induced Bone Pain via the MKP-1-Mediated MAPK Pathway. Biochemical and Biophysical Research Communications, 547: 36–43.

[16] Zhou KX, He XT, Hu XF, et al., 2019, XPro1595 Ameliorates Bone Cancer Pain in Rats via Inhibiting p38-Mediated Glial Cell Activation and Neuroinflammation in the Spinal Dorsal Horn. Brain Research Bulletin, 149: 137–147.

[17] Jiao M, Lei JJ, Zhang ZC, et al., 2021, Analgesic Effect of Paeonol Regulation of miR-21 on Bone Cancer Pain Rats and Its Effect on MAPK Signaling Pathway. Progress of Anatomical Sciences, 27(4): 453–457.

[18] Wu SH, 2021, Effect of JIAJI Electroacupuncture Combined with Nerve Mobilization on Expression of NF-kB and MURF1 in Gastrocnemius Atrophy with Sciatic Nerve Injury in Rabbits, thesis, Heilongjiang University of Chinese Medicine.

[19] Liu ZQ, 2021, Regulation Effect of Chaipu Decoction on HMGB1, TLR4, NF-kB in Airway Epithelial Cells of Asthmatic Mice, thesis, University of South China.

[20] Zhang XQ, Zhang XQ, Qiu XZ, et al., 2020, Effect of Raw Bone Capsule on the Expression of OPG and RANKL in Tibia of Osteoporotic Rats. Progress of Anatomical Sciences, 28(8): 21–25.

[21] Zhou TT, 2019, The Analgesic Effects of rBmK-AGAP in Rat Bone Cancer Pain Model via Inhibiting the Activation of NF-κB Pathway in Spinal Astrocytes, thesis, Dalian Medical University.

[22] Tian J, Song T, Wang H, et al., 2019, Thalidomide Alleviates Bone Cancer Pain by Down-Regulating Expressions of NF-κB and GFAP in Spinal Astrocytes in a Mouse Model. International Journal of Neuroscience, 129(9): 896–903.

[23] Yi D, Du MN, Zhang X, et al., 2024, Analgesic Effect and Mechanism of Ruanjianzhitong Ointment on Bone Cancer Pain Rats. Liaoning Journal of Traditional Chinese Medicine, 2024: 1–12.

[24] Duan YX, Zhang ZQ, Yin J, et al., 2021, Effects of Internal Heat-Type Acupuncture Needle Intervention on Chronic Soft Tissue Pain Based on Central Sensitization in the Spinal Cord. Chinese Journal of Pain Medicine, 27(12): 888–897.

[25] Huh Y, Ji RR, Chen G, 2017, Neuroinflammation, Bone Marrow Stem Cells, and Chronic Pain. Frontiers in Immunology, 8: 1014.

[26] Ji RR, Donnelly CR, Nedergaard M, 2019, Astrocytes in Chronic Pain and Itch. Nature Reviews Neuroscience, 20(11): 667–685.

[27] Zurn CA, Beauchene C, Duan W, et al., 2021, Predicting Wide-Dynamic Range Neuron Activity from Peripheral Nerve Stimulation Using Linear Parameter Varying Models. Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2021: 4428–4431.

[28] Kim YS, Chu Y, Han L, et al., 2014, Central Terminal Sensitization of TRPV1 by Descending Serotonergic Facilitation Modulates Chronic Pain. Neuron, 81(4): 873–887.

[29] Khan A, Khan S, Kim YS, 2019, Insight into Pain Modulation: Nociceptors Sensitization and Therapeutic Targets. Current Drug Targets, 20(7): 775–788.

[30] Medeiros P, Negrini-Ferrari SE, Palazzo E, et al., 2019, N-Methyl-D-Aspartate Receptors in the Prelimbic Cortex Are Critical for the Maintenance of Neuropathic Pain. Neurochemical Research, 44(9): 2068–2080.

[31] Zhang B, Wu L, Zhu Q, et al., 2021, Donepezil Attenuates the Development of Morphine Tolerance in Rats with Cancer-Induced Bone Pain: The Role of Cortical N-Methyl-D-Aspartate Receptors. Neuroscience Letters, 747: 135678.

[32] Li D, Li Y, 2020, The Interaction Between Ferroptosis and Lipid Metabolism in Cancer. Signal Transduction and Targeted Therapy, 5(1): 108.

[33] Yang HF, Liu HP, Zhang XS, et al., 2025, Research Progress in TCM Prevention and Treatment of Osteoarthritis Based on Iron Death Theory. Chinese Journal of Osteoporosis, 31(1): 118–123.

[34] Cahng YB, Ma HB, Wei JH, et al., 2025, Research Progress on Traditional Chinese and Western Medicine Treatment of Renal Fibrosis Based on the Pathogenesis of Ferroptosis. Acta Chinese Medicine and Pharmacology, 2025(2): 108–114.

[35] Zhao YH, Li Q, 2025, Targeting Ferroptosis Offers a Novel Therapeutic Approach in Epilepsy. Chinese Journal of Clinical Pharmacology and Therapeutics, 2025: 1–10.

[36] Ding Z, Liang X, Wang J, et al., 2023, Inhibition of Spinal Ferroptosis-Like Cell Death Alleviates Hyperalgesia and Spontaneous Pain in a Mouse Model of Bone Cancer Pain. Redox Biology, 62: 102700.

[37] Li K, Yu F, Yu GQ, et al., 2022, Regulatory Effect of Lnc-AK077216 on Osteoclast Differentiation and Maturation Through OPG/RANKL/RANK Pathway. China Journal of Modern Medicine, 32(11): 51–56.