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Literature Review Role Of Matrix Metalloproteinase In Cancer Pain

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Abstract. *Cancer pain occurs in more than half of cancer patients and affects their quality of life. The complexities of proinflammatory molecules in the tumor microenvironment contribute to pain. The MMPs, as proteolytic enzymes involved in cancer cell migration towards the surrounding environment, demonstrate their connection to the development of pain in cancer. As complex molecules, MMPs can be influenced by various cytokines and chemokines, mainly throughout neuroinflammation, which decreases neuron sensitivity and boosts hyperexcitability in pain-controlling mechanisms.*
Keywords: *Cancer pain, MMP, cytokine, neuroinflammation*

INTRODUCTION

Cancer has become the second leading cause of death worldwide and 70% among these occur in low and moderate income countries (WHO, 2018). Pain has been complained by over 50-90% cancer patient. This pain may relate directly with tissue damage of cancer cell proliferation, invasion and metastasis as well as body response to the damage. (Schmidt *et al.*, 2010; Russo and Sundaramurthi, 2019). Cancer related pain reduces patient's quality of life by affecting daily activities, cognitive function and family-sosial interaction (Greco *et al.*, 2014).

Neurochemistry alteration in sensory neuron and spinal cord lead to complex interaction in microtumor environment. This interaction involves neuron, lymphocyte, endothelial cells, and fibroblast that can secrete pain modulation (Honore *et al.*, 2000; Schmidt, 2014).

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Cancer pain can be differentiated into acute pain after cancer treatment such as chemotherapy, surgery, radiation therapy and chronic pain caused by cancer and pain mediator produced by cancer cell (Schmidt, 2014; Portenoy and Ahmed, 2018). The original location, metastatic location, and cell histology all influence how cancer pain manifests. (Schmidt *et al.*, 2010). Malignant effects can cause both nociceptive and neuropathic pain in cancer patients (Portenoy and Ahmed, 2018; Russo and Sundaramurthi, 2019). Neuronal damage resulting from either direct invasion of cancer cells or indirect production of mediators causes both of these symptoms. (Argroof and McCleane, 2009; Leppert *et al.*, 2016)

Matrix metalloproteinases (MMPs) are extracellular proteases that are implicated in the invasion of cancer into the stromal and nerve tissue around the tumor. (Brehmer, Biesterfeld and Jakse, 2003). MMPs role also include in angiogenesis, lymphangiogenesis, colonization and intravasation (Gonzalez-Avila *et al.*, 2019).

CANCER PAIN

Cancer patients may experience nociceptive pain, which lowers pain threshold, or neuropathic pain, which is brought on by problems with the somatosensory nerve.(Leppert *et al.*, 2016; Oosterling *et al.*, 2016; Russo and Sundaramurthi, 2019). The genes linked to pain can be classified into three groups based on the mechanism of pain: those related to ion channels, which influence neuron excitability; those related to NGF (nerve growth factor), which are linked to pain insensitivity; and those related to neurotransmitters, primarily catecholamine, which are involved in pain perception. (Jakub, 2018) .

Research on model mice showed the same Ab sensory neuron plasticity pattern in cancer-induced pain and neuropathic pain, both in dorsal root ganglion (DRG) and axon originating from the lumbar dorsal horn. This perhaps relates with chronic pain result from hypersensitivity and progressivity induction result in chronic pain (Zhu *et al.*, 2018).

Reduced nociceptor pain threshold in superficial structure (somatic pain) or internal organ of the body (visceral pain) is the source of nociceptive pain in cancer patients (Leppert *et al.*, 2016). Tumor necrosis factor and cytokines produced by cancer cells trigger damaged tissue proteolysis, induce sensitization and hyperalgesia, and influence nociceptive responses. (Russo and Sundaramurthi, 2019). Somatic discomfort can range from severe pain caused by cancer cells infiltrating bone tissues to superficial pain experienced by those with skin cancer (Leppert *et al.*, 2016). Meanwhile, there are a number of processes that can lead to visceral

pain, such as ischemia from tumor impression or blood flow compression, distention and contraction of the visceral wall, stretching of the capsule surrounding the visceral organ, ligament compression or traction, mesenterium and blood vessel, tumor infiltration that releases inflammatory mediators, nerve compression of the visceral organ, and stretching of the serous or mucosal layer. (Hanna and Zylicz, 2013).

Changes in the somatosensory nervous system may result in neuropathic pain, particularly if cancer cells directly infiltrate and destroy nerve tissues (Argroof and McCleane, 2009; Oosterling *et al.*, 2016). Neuralgia, plexopathy, and radiculopathy are caused by damaged peripheral and central nerves (Argroof and McCleane, 2009; Ji *et al.*, 2009; Russo and Sundaramurthi, 2019). Plexopathy is neuropathic pain that may attack cervicalis, brachialis and lumbosacralis plexus (Portenoy and Ahmed, 2018).

Both the nociceptive and neuropathy processes may play a role in the mechanism of pain-related malignancy. Pain hypersensitivity in bone cancer can result from spinal cord pathology, central sensitization, and disrupted regulation and signaling from dorsal root ganglion (DRG) dysfunction (Guedon *et al.*, 2016). Structural and functional neuroplasticity in the DRG can also contribute to nociceptive issues in cancer (Zhu *et al.*, 2018).

MATRIX METALLOPROTEINASE (MMP)

The zinc-dependent endopeptidase MMPs has a wide range of substrates. Connective tissues, proinflammatory and uteroplacental cells (fibroblast, osteoblast, endothelial cells, vascular smooth muscle cells, macrophages, neutrophils, lynphocytes, and sitotrophoblasts) are among the cells and tissues that can manufacture these enzymes. MMPs function on cell membranes as soluble proteinases and as proteins and proteoglycans in the extracellular matrix. Substrates of MMPs include cell adhesion receptors, growth factors, cytokines, chemokines, and growth factor receptors. MMPs function not only in physiological processes but also in pathologic conditions such as cancer and inflammation. (Parks, Wilson and López-Boado, 2004; Toriseva and Kähäri, 2009; Kessenbrock, Placks and Werb, 2015).

The MMP family has a comparable overall structure. The majority of MMPs consist of a 200 amino acid hemopexine domain, a 170 amino acid catalytic domain, a connecting peptide, and an 80 amino acid propetide. (Nagase, Visse and Murphy, 2006; Cauwe, Steen and Opdenakker, 2007; Klein and Bischoff, 2011). There are now 23 different kinds of MMPs known to exist in humans. Collagenases (MMP-1,-8, dna -13), gelatinases (MMP-2 dan -9), stromelysins (MMP-3 dan -10), stromelyisin-like (MMP-11 dan -12), MMP transmembrane (MMP-14, -15, -16, dan -24), glycosyl-phosphatidyl-inositol type MMPs (MMP-17 dan -25),

MMP-19-like MMPs (MMP-19 dan -28), dan other types of MMPs (MMP-18, -20, dan -23) are the different categories of MMPs based on their structures, substrates, and functions. (Klein and Bischoff, 2011).

MMPs Activation

To maintain the latent form of the enzyme, MMPs are secreted as N-terminal pro-doomain with cysteine residue-coordinated zinc ions in catalytic vesicles (Nagase, Visse and Murphy, 2006). The cysteine switch mechanism, which replaces the thiol group in an uncoupled cysteine with a water molecule before it can be hydroxylated later, is responsible for activated proteolytic fission (catalyzed by other MMPs or serine proteses) and thiol oxidation by other substances, such as ROS. Except for MT-MMP, MMP-11, -23, and -28, which are intracellularly activated, the majority of MMPs are extracellularly active. (Nagase, Visse and Murphy, 2006; Ra and Parks, 2007).

Pro-MMPs can be activated by active MMPs. MMP-3 has the ability to activate pro-MMP-1,-7, -8,-9, and -13. MMP-2, nevertheless, has the ability to activate pro-MMP-9. It is possible for these positive feedback loops to initiate total extracellular matrix proteolysis (Djuric and Zivkovic, 2017). MMP-2 activation on the surface of cells can build up pericellularly, resulting in localized collagenolysis activity in the extracellular space, which then causes the surrounding tissues to deteriorate (Nishida *et al.*, 2008). MMP-2 and MMP-9 can be found in neural nucleus with PARP1 and XRCC1 as substrates in inducing cell apoptosis (Lescot *et al.*, 2010; Hill *et al.*, 2012). MMP-9 may also be able to cross cell membranes through binding to translocation proteins. MMP-9-containing intracellular vesicle combines with the cytoskeleton of neurons and astrocytes, most likely moving back subcellularly (Sbai *et al.*, 2010).

MMPs Regulation

MMPs are regulated at multiple levels, including transcription, translation, zymogen activation, extracellular or subcellular localization, endocytosis internalization, and endogenous or extracellular inhibition. (Djuric and Zivkovic, 2017). Growth factors including as PDGF, TNF-κ, TNF-έ, and IL-1, as well as proinflammatory MPs, have an impact on elevated MMP levels at the transcription level. PPAR, NO, TGF-b, Il-4, IL-10, and other anti-inflammatory agents can all inhibit MMP production. TGF-β1 has the ability to reduce MMP

expression through an inhibitory region in the MMPs gene promotor. (Johnson, 2007; Rao *et al.*, 2014).

Other factors that can control MMPs include hormones, tumor promoters, intercellular interactions, and extracellular matrix-cellular interactions (Verma and Hansch, 2007). MMP-1, -2 dan -3 are regulated by modulating mRAN stability on post-transcription level (Nissinen and Kähäri, 2014). Active MMPs may regulated by general inhibitor protease like α2-macroglobulin, α1-antiprotease and TIMP (*Tissue inhibitors of metalloproteinases*) specific inhibitor. An MMP/TIMP imbalance caused by elevated MMPs or lowered TIMP levels can result in pathologic conditions such cancer, osteoarthritis, and heart failure. (Cui *et al.*, 2017).

MMP AND CANCER PAIN

MMPs, as extracellular matrix endopeptidases, have the ability to mediate the invasion of cancer cells into surrounding tissue, including the nervous system. Because of their capacity to activate different cytokines and chemokines, MMPs have a role in neuroinflammation. (Brehmer, Biesterfeld and Jakse, 2003; Ji *et al.*, 2009).

Neuroinflammation mediated by glial cells is triggered by nerve damage in malignancy. Through the activation of the ERK, p38, and JNK (c-Jun N-terminal kinase) pathways of the MAPK (mitogen activated protein kinases) pathway, glial cells (microglia and astrocytes) in the spinal cord create proinflammatory cytokines. These inflammatory processes are the cause of neuropathic pain (Milligan *et al.*, 2003; Ji *et al.*, 2006; Guo *et al.*, 2007).

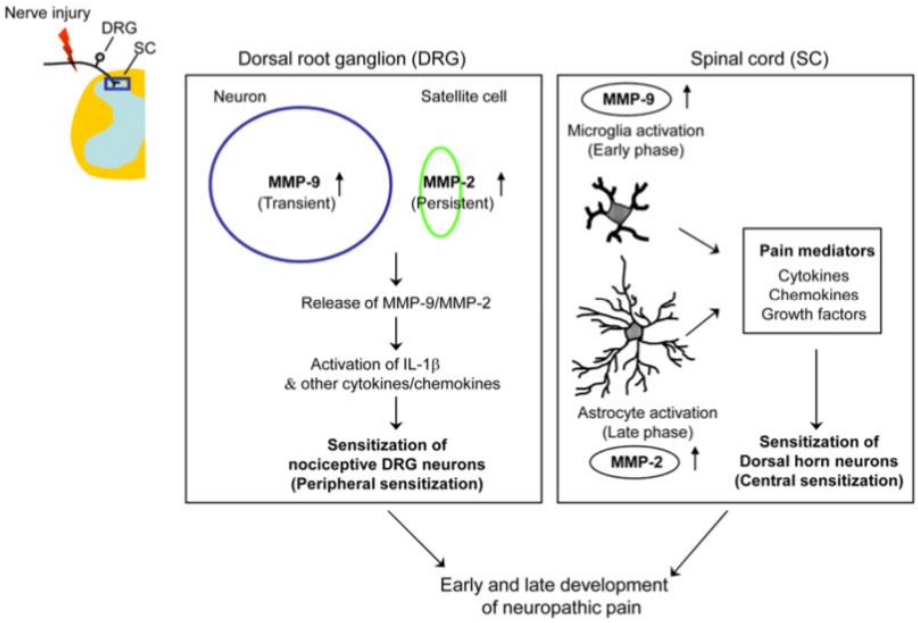
An important function of astrocytes is to preserve synaptic structure and rearrange nerve circuits. (Yao *et al.*, 2018). When a nerve is injured, microglia and astrocytes release a variety of proinflammatory cytokines, including TNF-α and IL-1β, which can alter the sensitivity to both central and peripheral pain (de Oliveira *et al.*, 2011; Hansen and Malcangio, 2013; Oliveira *et al.*, 2014; Chen *et al.*, 2018). Bradykinin receptor activation, substance P stimulation, CGRP (calcitonin gene related peptide) stimulation, enhanced NMDA receptor activity, and GABA inhibition are some of the ways that IL-1β in nerupathic pain functions. (Clark *et al.*, 2007; Oliveira *et al.*, 2014).

Dorsal root ganglion nerve damage may cause microgliosis-mediated MMP-9, which is characterized by morphological alterations, microglia migration, and proliferation (Calvo and Bennett, 2012; Von-Hehn, Baron and Woolf, 2012). MMP-9 activates p38 MAPK and IL-1β to cause neuropathic pain. Partially block MMP-9 induced by allodynia can be achieved by neutralizing IL-1β antibody (Kawasaki *et al.*, 2008; Ji *et al.*, 2009). MMP-9 first converts pro-

IL-1β into IL-1β, which in turn causes hyperexcitability around nociceptive (Kawasaki *et al.*, 2008; Rojewska *et al.*, 2014). From DRG, MMP-9 move onto central dorsal horn terminal in spinal cord to activate microglia and begin neuroinflammation (Kawasaki *et al.*, 2008). Active microglia also produce IL-6 that involve in chronic pain (Smith *et al.*, 2012). The astrocyte's receptor for the IL-18 released by microglia will bind to it, activating the NMDA receptor and the influx calcium signaling pathway, which will then cause hyperactivity (Miyoshi *et al.*, 2008; Liu *et al.*, 2018).

In the latter stage, astrocytes and satellite cells surrounding the DRG will exhibit an increase of MMP-2 due to nerve damage. By activating IL-1β, MMP-2 also contributes to the generation of persistent discomfort. (Kawasaki *et al.*, 2008; Feng *et al.*, 2016).

The significance of MMPs in the cancer pain process is also linked to the creation of NGF in cancer cells, which causes hyperalgesia and hypersensitivity to pain (Schmidt *et al.*, 2010). In the tumor microenvironment, fibroblasts, smooth muscle cells, peripheral nerve cells, and epithelial cells are among the inflammatory and structural cells that release NGF. (Arrighi *et al.*, 2010). MMP-2 increased in prostate cancer mediated by NGF (Okada *et al.*, 2003). NGF, GDNF dan MMP-9 interaction also link to perineural iunvasion and progressivity prostate cancer (Baspinar *et al.*, 2017). In D2-strial medium spinal neurons, MMPs activity in integrin-ligand binding can cause an increase in calcium-influx-stimulated NMDA receptor, which in turn activates neuromodulation, neuron hyperexcitability, and glutaminergic signaling (Bernard-Trifilo *et al.*, 2005; Y. Li *et al.*, 2016).



Picture 1 : Schematic illustration of MMP-2 and MMP-9 upregulation in DRG and spinal cord, and their role in neuropathic pain mechanism ((Ji *et al.*, 2009)

MMPs may be the focus of neuropathic cancer pain therapy due to their involvement in cancer pain. Studies demonstrate the role of MMP inhibition and suppression in lowering neuropathic pain. MMP-9 overexpression and the release of microglial nociceptive molecules are inhibited by P2X4R (Purinergic Ionotropic Receptor Microglia Type 4) (Jurga *et al.*, 2017). In addition, N-acetyl cysteine can prevent MMP-2 and MMP-9 substrates, IL-1β, from maturing. This will limit the activation of microglia, phosphorylation of NMDA receptors, activation of the MAPK pathway, and ultimately the reduction of neuropathic pain (J. Li *et al.*, 2016). Moreover, reduction of MMP-9 expression in the early stage in bone tissue and late phase in the spinal cord in model mice results in decreased behavior related to bone cancer pain (Nakao *et al.*, 2019).

CONCLUSION

Together with the development of cancer, different neurochemical complexes are involved in cancer pain. MMPs' role in stromal and neural tissue degradation is implicated in angiogenesis, cancer, and metastasis. MMP activity can both cause and be a trigger for nerve cell damage. MMPs activate proinflammatory cytokines such as TNF-κ, IL-6, and IL-1ε, which are involved in neuropathic pain and neuroinflammation. Recent research indicates that inhibition and reduction of these cascades may, in some way, lessen the process of neuroinflammation, providing a target for therapy.

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