Cytokines Regulation and Role in Modulating Cancer Related Pain: A Brief Overview

Anbreen Faisal a, Muhammad Asad Ullah b, Ayesha Bajwa a, Rizwan Nasir a, Muhammad Javed Iqbal c, Muzamil Shah b, Wali Muhammad b, *

a Department of Biochemistry and Biotechnology, Institute of Life Sciences, University of Gujrat, Pakistan.
b Department of Biotechnology, Quaid-i-Azam University 45320, Islamabad, Pakistan.
c Department of Biotechnology, University of Gujrat, Sialkot Sub Campus, Pakistan.

*Corresponding Author
walibiotech5511@gmail.com
(Tel.: +923455224994
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ABSTRACT:
Cancer linked mechanism of inflammatory and neuropathic pain came out as complex pathologic process and formidable clinical impasse. Over the decades significant headway has been made to unravel etiology of cancer pain and prime pathological maneuver tie with its microenvironment by models incited approaches. The cross talk between the cancer cell and their dynamic interaction decipher some of the cancer-induced inflammatory mediators which act in primary efferent neurons in absolute diversified way. Cytokines are the key inflammatory mediator in the microenvironment parole by cancerous cell and immune system cells that exert malicious autocrine and paracrine activity particular relevance to pain. To date very few strategies have been contemplated to modulate the release of cytokines that seems allied to cancer pain. In this scenario, the present review analyzes the main cytokines produced with peripheral and central mechanism analysis for better understanding their clinical traits. While treatment strategies are detailed with novel mechanistic insights that can have considerably cut down the pattern of neuropathic pain linked with tumorigenic estate.

Keywords: Cancer Pain, Cytokines Regulation, Pain Pathway, Cancer Pain treatment.

1 Introduction

Cancer pain is the most obstreperous phenomenon arrayed with acute inflammatory responses of malignant tumor cells that metastasize and infiltrate to vital body organ and bones. Globally more than 14 million cases of cancer reported each year and incidents are still uprising [http://www.who.int/mediacentre/factsheets/fs297/en/ (accessed Feb 2018)]. Among them almost one half of living cancer victims experience differing levels of acute pain. A number of patients surviving cancer because of early diagnosis and improved cancer therapies but they have to face the debilitating aftereffects [1]. It is prerequisite to focus on the molecular basis of cancer pain and its management. In this regard researcher deal with the underlying physiological mechanism of pain in disease state to assure the quality life of survivors. It’s been hugely investigated that cancer patients suffer distinct type of inflammatory neurochemical responses due to persistent release of neurotrophic mediators that activate pain receptors [2]. These mediators include neutrophils, T cells of immune system, prostaglandins, endothelin, TNF-α, wide variety of growth factors (TGF, EGF, PDGF), IL-1 and IL-6, not only release by malignant cells but also from lymphocytes, fibroblast and endothelial cells. All of them recruited in the microenvironment invigorate nociceptors linked with pain, fatigue and anorexic response [3]. Among them cytokines are the key inflammatory mediator in the microenvironment parole by cancerous cell that disrupt the fundamental interaction and communication within cells to exert malicious autocrine and paracrine activity in nearby and distant cells. These cytokine provide productive habitat for primary cancer cell growth, invasion and metastasis. The most potent cytokines include IL-1β, TNF-α, and IL-6 frequently describing as pro inflammatory cytokines. All these factors indicate the molecular complexity of cancer pains and make it strenuous to tease out the particular fundamental mechanisms [4].
2 Mechanisms and Management of Cancer Pain

Tumor cells produce a synergy of vicious elements in their microenvironment that are involved in inflammation, number of noxious electro-chemical stimuli for the neuropathic pains. Cancer pains can be acute with a short term central sensitization. But at the advance stage of cancer a chronic pain is observed with long term peripheral and central sensitizations [5]. Profound scientific research reported that rapidly growing tumor cells release some specific proteolytic enzymes that degrade the nerve fibers, entangle the sensory neurons and damage them account for neuropathic pain. Protease activated receptor (PAR) is one of the common receptor involved in generating neurogenic pain [6].

The cancer cells have an insistent inflammatory state due to the surrounding tissue damage that results in unobtrusive in filtering of various immune cells i.e. neutrophils macrophages T-cells and monocytes. A number of deregulated pain mediators including cytokines, prostaglandins, TNF-α, chemokine, bradykinin and nerve growth factors are produced by these immune cells [4]. These analgesic stimuli hyper-sensitize the nociceptors present in the afferent neurons at Dorsal root ganglion of brain. Consequently pain associated signals ascend to the brain which results in vasodilatation leading to severe pain and hyperalgesic effects [7].

Different histological locations of the primary neoplasm and the metastasis have diverse presentations of nociceptive events. Normally Non-steroidal anti-inflammatory drugs are used to block the prostaglandin production. Prostaglandins are pro-inflammatory elements that are involved in sensitization of nociceptors. They are synthesized by Cyclooxygenase (COX) and specific prostaglandin synthetase enzymes. Pharmaceutical application use NSAIDS for blocking COX pathway by using their inhibitors to overcome the symptoms of pain and inflammation [8] whereas the role of endothelin (ET-1) in generating cancer pain is multifaceted. It stimulates 2 different receptors (ETAR) and (ETBR) located at peripheral sensory neurons and non-myelinating cells respectively. ET-1 is an effective vasoactive peptide present at DRG where it secretes opioids [9]. The ETAR mainly facilitates vasoconstriction, bronchoconstriction, anti-apoptosis and acute pain. The antagonists of ETAR can inhibit osteoblast. The ETBR facilitates inflammatory pain and vasodilatation [10]. The other factor linked with pain stimuli are cancer cells induced acidosis. The intracellular and extracellular pH of cancer cells is very low and resultant acidic medium can stimulate the nociceptors. Whereas the High H+ ions are the hallmark of cancer cells, sensitize the transient receptor potential ion channel (TRP) that innervate to bones maintain acidic extracellular microenvironment [11] A detailed mechanism of cancer pain in term of Tumor-Nociceptor interface is illustrated in Fig.1.

Previous studies on mice model of bone cancer has shown that non painful level of mechanical stress involve in the excretion of substance P, activate neurokinin receptor and induce expression of factor c-Fos in spinal cord in response to noxious stimuli sensitize nociceptor in peripheral region [1]. There is release of substance P and calcitonin from C fibers with multiple secondary messengers activated receptors likeTRPV-1 and TRPV-4 associated with metastatic pain of bone cancer [5].

Radiotherapy or chemotherapeutic drugs of cancer treatment often modulate the cytokine productions and trigger neurotoxic effects. These contradicting effects often lead to intervention in regular treatment of the patient. Genetic variations and Polymorphism in the cytokine genes can also implement the susceptibility of pain in individuals. Subsequently, Cytokines are considered as putative targets in the management of cancer.

In addition to malignant cancer cells, tumor microenvironment predominantly consists of mast cells (macrophages) which secrete inflammatory mediators and primary efferent nociceptor. The key mediators release by these cells include bradykinin, H+, ATP, nerve growth factors (NGFs), prostaglandins (PG) and vascular endothelial growth factor (VEGF). The presence of these mediators in extracellular environment detect by receptors present on the membrane of nociceptor activate glial cells via various noxious stimuli. Result in the release of cytokines, transmit painful stimuli to the nerves in spinal cord and sensed by brain that send signals which further trigger nociceptors response and modulate the release of endothelin (ET), histamine, glutamate, substance P stimulate sensory fibers, Activate inflammatory cells and induce vasodilation. Prostaglanandin receptors (EP), Vanilloid receptor-1 (VR1), purinergic P2X3 receptor. Tyrosine kinase receptor (TrkA).
3 RANK–RANKL Pathway in Tumor-Induced Bone Pain

In advanced metastasis state, cancer-associated bone pains are highly reported. Normally, bone remodeling involves equilibrium in osteoclast-mediated bone resorption and osteoblast-induced bone formation. But in cancer cells, the balance gets disturbed and shifted to either extreme condition. The RANK–RANKL pathway is a key signal regulator in cancer-induced bone pain. Receptor activator of nuclear factor kappa-B ligand (RANKL) is a member of the tumor necrosis factor superfamily expressed in varying quantities from different organs and tissues responsible for bone growth, remodeling, and immune functioning in the body [12]. The secretions of RANKL increases and over stimulates the receptor activator of nuclear factor kappa-B (RANK) receptor expressed on osteoclast cells. Thus increased proliferation of osteoclasts is observed and results in bone degradation. The overexpression of their receptor provided to provide efficient microenvironment to the malignant cells to metastasize in bone [13]. They also reported to generate the T-cell-mediated immune response intensify the process of osteoclastogenesis and bone loss. The balance between RANK–RANKL is maintained by osteoprotegrin (OPG), produced by osteoblast and prevents RANK binding to RANK and maintain homeostasis. In this case, pain release is not associated with inhibition of nociceptors but is indirectly related to osteolytic effects of the tumor. Various OPG-based drugs and RANK-L antagonists can be used to treat the cancer-induced bone pains [14]. These are the various pathways involved in cancer-associated pains but still, there is a need to pay emphasis on further identifications of novel ion channels, receptors, and ligands that may involve in cancer-induced pain etiology.

4 Spinal Regulations of Cytokines in Cancer Pain

Peripheral inflammation associated with the release of PICs such as TNFα, IL-6, and IL-1β act as key culprits in pain hypersensitivity response in cancer and other disease conditions. These cytokines implicate in modulating excitatory and inhibitory synaptic activities demeanor pain events [15]. Although these cytokine inflammatory mediators in peripheral region predominantly release by immune cells and some non-neuronal cells induce spontaneous activity of COX-2 in dorsal root ganglion (DRG) neuron coupled with chronic pain [16].
In last decades detailed study on bidirectional regulation between immune mediators and brain controlling body homeostatic regulation on various animal model system reveals that vagus nerve predominantly control the systemic inflammation in pathological state via efferent signaling [17]. Involve in the release of neurotransmitter particularly acetylcholine activate nicotinic receptors of macrophage which inhibit the release of pro-inflammatory cytokines [18]. The anti-inflammatory effect of nicotine control activation of macrophages induce nuclear factor \( \kappa B \) (NF-\( \kappa B \)) pathway plays vital role in the release of PICs.

The patch clamp investigation of dorsal horn neuron in isolated spinal cord slice of mice model reveals that PICs responsible for altering synaptic and neuronal transmission in spine. They induce pronoceceptor gene transcription (Gox-2) and activate cyclic AMP response-element binding protein (CREB) in dorsal horn of spinal cord effect transmission of lamina II neurons thus responsible for long term neuronal plasticity [19].

5 Hypothelmic Integration in Tumor Anorexic Response

Tumorigenic estate implicate with the administration of central and peripheral release of cytokines and immune mediator’s effect differentially on hypothermic neurons interrupt homeostatic regulation and body integrity hence lead to acute phase responses. The dysregulation of hypothermic integration in cancer anorexic state coupled with rise of cortisone, plasma insulin level, tryptophan, IL-1 and IL-6 [20]. All these factors effect gastric emptying, adsorption of sugar metabolites, and meal size and meal numbers in cancer patients. The investigation of tumor bearing animal model system illustrated that upregulation of IL-1, and IL-1 beta transcription increase the level of hypothermic anorexic factors such as serotonin and dopamine while decrease neuropeptides (NYP) [21]. Indeed severely impaired neuroendocrine system that involve in regulation of metabolism in inflammatory disease state.

The another study executed by a group of scientists on anorexic cancer induce mouse model in search for therapeutic strategy, figure out that the administration of omega-3 fatty acid in mouse diet halts the production of TNF-alpha, IL-1, normalizing NYP level so as ameliorating cytokine anorexic response [22]. This finding indicates the potential use of omega-3 as safe therapeutic regimen in anorexic cancer care.

6 Treatment of Cancer Pain
6.1 Targeting Cytokines

Cytokine’s over production leads to the induction of cancer pains. Multiple drugs such as corticosteroids, NSAIDs, opioids, statins and endothelins are found to be very effective in treating cancer pains. Anti-inflammatory property of Corticosteroids prevents the expression of collagenase consequently inhibiting the activity of pro-inflammatory cytokines [23]. Glucocorticoids play a vital role in reduction of swelling and inflammation by diminishing pro-inflammatory cytokines [24]. Steroidal binding with glucocorticoid leads to the formation of a complex that interacts with DNA sequences known as glucocorticoid response elements, which antagonized with Nfk-B pathway [25]. Potential role of Nfk-B is to activate pro-inflammatory cytokines such as IL-1B, whose activity is down regulated by glucocorticoids results in pain reduction [26].

NSAIDs, unlike corticosteroids, possess inhibitory effect on the activity of COX-1 and COX-2 thus inhibiting the transformation of arachidonic acid to prostaglandins which constrain Nfk-B pathway [27]. Opioids drugs, on the other hand, include morphine and codeine. Morphine prevents the production of TNF-alpha and IL-8 mRNA along with hindering the neurons directly to stop spinal cord transmission [28]. Statins, because of cholesterol lowering capability, have a major role in cardiovascular diseases but also possess anti-inflammatory properties that are being utilized these days to terminiate inflammatory cytokines [29]. TNF-Gamma, key modulator of cannaboid receptor signaling, is released in response to immune system induce glial activation and neuropathic pain [30]. Blockage of TNF-Gamma to treat cancer pain is sensitive issue because of some potential risk involvement. IL-6 also have potential role in hyperalgesia and tumors. Attempts have been made in blocking IL-6 in reducing cancer pain. Tocilizumab, an IL-6 monoclonal antibody, has been administered for the treatment of cancer but there is no success yet [31]. Studies indicated the role of Chemokines and IL-8 in perineural invasion in pancreatic cancer, so by targeting chemokines, cancer pains can be reduced. Recent studies conducted on the use of Anti – IL-8 antibody that prevents tumor growth and metastasis of melanoma [32]. Endothelin, an amino
acid cytokines in response to tissue injury. Several cancers such as prostate cancer, ovarian cancer secretes endothelins [33-34]. Endothelin receptor antagonist has been administered to reduce cancer [35].

6.2 Electrical Stimulation in Peripheral Nerves

Since the birth of cancer, scientific community is working not only the cure of cancer but to prevent the unnecessary pain associated with cancer. Multi-dimensional approaches are required in this regard. Medicines, herbal products and nerve stimulation are most common ways to handle pain but medicinal use cause multiple side effects or minimal effect in cancer patients. The Electrical stimulations of brain, spinal cord along with peripheral nerves and skin have been utilized to treat cancer pains. One of the most promising, cheap and yet efficient technique to treat traceable pain is peripheral nerve stimulation preferably to treat chronic pain [36]. Very small electrical devices, more like an electrode is places after surgery right next to any one of the peripheral nerves. Rapid electrical impulses are delivered by implanted electrodes [37]. But there are very few cases reported with the use of peripheral nerve stimulations to treat cancer associated pains. Recorded applications of PNS are in the treatment of neuropathy.

6.3 Electrical Stimulation in Spinal Cord

Electrical Stimulation of Spinal cord is been developed and utilized since 1970s. There are very few reported cases of the use of spinal cord stimulation to treat cancer pain. Most of the reported studies focused on the treatment of angina, neuropathy, low back pain and vascular diseases along with complex regional pain syndrome. Those of the patients with cancer developed neuropathy (neuropathic cancer pain NCP) are considered to be the potential candidates for the use of spinal cord stimulation [38]. Neuropathic pain in cancer patients arises in quit similar way as in case of non-cancerous nervous system injury. The alteration of receptors, ion channels and neural pathway involvement are same in both conditions but the difference is in the timing and the nature of injury [39]. Studies showed that the efficiency of spinal cord stimulator is not up to effective level in all of the patients equally. Up to 50 percent potential candidates who experience SCS found significant relief in pain [40]. Yet spinal cord stimulation with improved frequency has been utilized these days to cure cancer pain. SCS system is not designed to eradicate the source of pain or pain related fundamental problems but to control pain signal to brain. To carry out normal standardized procedure of SCS implement involves surgery that could cause multiple complications allergic reaction to material implanted, pain at site, bleeding nut these are rather minor complication. Apart from this, hardwire related problems have been reported in previous literature including connection failure and breakage in incision area [41].

6.4 Chinese Herbs for the Treatment of Cancer Pain

The complex physio- pathological conditions of cancer-induced pain remain obscure and conventional therapeutic methodologies are inadequate to effectively relieve pain. Releasing cancer pain is crucial to improve quality of life for cancer patients as well as cancer survivors, around the globe. It is now requisite to design analgesic drugs with maximum efficacy and minimum side effects as compared to conventional chemicals. Here it is summarized a few natural herbs that can be used efficiently as medicine for cancer pain. Baicalein (BE) is extracted from a classic Chinese natural remedy Scutellaria baicalensis. It has been confirmed that it has anti-inflammatory and analgesic effects with no neurotoxicity. It is proved to be effective for all cancer pains including the most common and complex one, cancer-induced bone pain. BE has pharmacological attributes, including antioxidant, analgesic, anti-apoptotic, anti-tumor, antiviral and neuroprotective properties. Its regulatory effects on the immune system constrain inflammation and inhibit proliferation of cell by inducing apoptosis in several cancer cells. It reduces the inflammation in afferent sensory neurons in the spinal cord. BE’s attenuates the expression of the pro-inflammatory mediators i.e. cytokines including interleukins and Tissue necrosis factor –α. It indicates no gastrointestinal side effects that have been observed in conventional NSAID’s and Morphine use [9]. Xiao-Ai-Tong(XAT) is traditionally used Chinese medicine consists of mixture of herbs including Venenum Bufonis, Corydalis Tuber, wild ginger and Arisaema Tuber. Previous studies have reported it as a
traditional pain relieving medicine and its analgesic effect in cancer mediated bone pain. Besides relieving pain, it has been found effective to suppress the adverse reaction of morphine and NSAIDs, involving mechanism of the reduction of proinflammatory signals. It facilitates the action of morphine and other conventional drugs, the synergic effect of XAT and morphine is more effective in cancer pain [42]. Kushen extract is the fundamental constituent of Compound Kushen Injection (CKI) that is used to treat cancer pain. When the efficacy of CKI is compared with conventional pain relieving therapy i.e. radiotherapy and bisphosphonate, it was evident that CKI is more effective and improve the quality of life more efficiently as compared to conventional therapies. Although these evidences promote the use of CKI but extensive literature review is still required in this context [14]. All in all Chinese herbs supposed to be potent to successfully, economically, and securely manage cancer-induced pain.

References


**Conflict of Interest:**

The authors declare no conflict of interest.

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