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CCL-2 as a Potential Biomarker for Neuropathic Pain in Leprosy: A Literature Review

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ABSTRACT

Neuropathic pain is a debilitating symptom in leprosy patients that significantly impacts their quality of life. While the mechanisms underlying this pain remain unclear, recent research suggests a potential role for C-C motif chemokine ligand 2 (CCL-2), a chemokine involved in inflammatory processes. This literature review explores the association between CCL-2 levels and neuropathic pain in leprosy patients. We discuss the current understanding of CCL-2's role in nerve damage and inflammation, as well as its potential as a biomarker for predicting and monitoring neuropathic pain in leprosy. Understanding the role of CCL-2 in leprosy-associated neuropathic pain may lead to the development of novel therapeutic strategies and improve the management of this chronic condition.

Keywords: CCL-2, neuropathic pain, leprosy

INTRODUCTION

Neuropathic pain is a complex and chronic pain state that arises from injury or disease affecting the somatosensory system. It is characterized by symptoms such as allodynia (pain from stimuli that do not normally provoke pain) and hyperalgesia (an increased response to painful stimuli)[1]. This type of pain is notoriously difficult to treat, often requiring a multifaceted approach that includes pharmacological and non-pharmacological interventions[2]. Among the various mediators involved in the pathophysiology of neuropathic pain, chemokines, particularly the C-C motif chemokine ligand 2 (CCL-2), also known as monocyte chemoattractant protein-1 (MCP-1), have garnered significant attention due to their role in neuroinflammation and pain modulation[3,4].

CCL-2 is a member of the CCL family of chemokines that primarily functions to recruit monocytes and other immune cells to sites of inflammation. It is produced by various cell types, including neurons, astrocytes, and microglia, in response to inflammatory stimuli[5]. In the context of neuropathic pain, CCL-2 has been implicated in the activation of glial cells and the subsequent release of pro-inflammatory cytokines, which can exacerbate pain signaling pathways[6]. The interaction of CCL-2 with its receptor, CCR2, has been shown to contribute to the development and maintenance of neuropathic pain states, highlighting its potential as a therapeutic target[7].

Leprosy, caused by the bacterium Mycobacterium leprae, is a chronic infectious disease that primarily affects the skin and peripheral nerves. One of the most debilitating consequences of leprosy is the development of neuropathic pain, which can occur even after successful treatment with multidrug therapy (MDT)[4,8]. Neuropathic pain in leprosy is often attributed to the immune-mediated damage to peripheral

nerves, leading to sensory disturbances and chronic pain syndrome[9,10]. Studies have shown that a significant proportion of leprosy patients experience neuropathic pain, which can persist long after the infection has been treated, indicating a complex interplay between the disease, immune response, and pain mechanisms[11,12]. The pathophysiology of neuropathic pain in leprosy is complex and involves the activation of glial cells, particularly microglia in the spinal cord. These cells respond to injury and inflammation by releasing pro-inflammatory cytokines and chemokines, which can sensitize neurons and contribute to the development of pain[8]. CCL-2 is particularly important in this context, as it not only attracts monocytes to the site of injury but also promotes the activation of microglia, creating a feedback loop that perpetuates inflammation and pain[1]. The role of CCL-2 in leprosy-related neuropathic pain is particularly noteworthy. In leprosy, the presence of CCL-2 has been linked to the severity of neuropathic pain experienced by patients. Elevated levels of CCL-2 in the serum and cerebrospinal fluid have been observed in individuals with leprosy-associated neuropathy, suggesting that this chemokine may serve as a biomarker for pain severity and a potential therapeutic target[13]. Furthermore, the activation of CCL-2 signaling pathways in the dorsal root ganglia and spinal cord has been linked to the onset of neuropathic pain following nerve injury, underscoring the potential for CCL-2 to mediate pain in leprosy[14].

The modulation of CCL-2 signaling pathways has been proposed as a strategy to alleviate neuropathic pain by reducing the recruitment of inflammatory cells and the subsequent activation of pain pathways[13]. Understanding the mechanisms by which CCL-2 contributes to neuropathic pain in leprosy could pave the way for novel therapeutic strategies aimed at alleviating pain and improving the quality of life for affected individuals.

LITERATURE REVIEW

LEPROSY

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by the bacterium Mycobacterium leprae. This disease primarily affects the skin, peripheral nerves, and mucous membranes, leading to significant morbidity and disability if left untreated. Globally, leprosy remains a public health concern, particularly in developing countries, and Indonesia ranks third in the world for the highest number of leprosy cases, following India and Brazil. In 2019, Indonesia reported 17,439 new cases of leprosy, highlighting the ongoing challenge of managing this disease within its borders[15].The epidemiology of leprosy in Indonesia is characterized by a high prevalence in certain regions, particularly in East Java and Papua. The disease is often associated with socio-economic factors, including poverty, limited access to healthcare, and inadequate public health education. These factors contribute to the persistence of leprosy in endemic areas, where the stigma surrounding the disease further complicates efforts for early diagnosis and treatment[16,17]. The World Health Organization (WHO) has implemented various strategies to combat leprosy, including the introduction of multi-drug therapy (MDT), which has proven effective in curing the disease. However, the challenge remains in preventing transmission and addressing the social stigma associated with leprosy [18].

In Indonesia, the burden of leprosy is not only medical but also social, as individuals affected by the disease often face discrimination and marginalization. This stigma can lead to delayed diagnosis and treatment, exacerbating the physical and psychological impacts of the disease. Studies have shown that many leprosy patients experience significant social isolation and mental health issues due to societal perceptions of leprosy[19]. Efforts to control leprosy in Indonesia have included community-based interventions aimed at increasing awareness and understanding of

the disease. Programs such as the Leprosy Post Exposure Prophylaxis (LPEP) have been implemented to provide preventive treatment to individuals who have been in close contact with leprosy patient[20,21]

The clinical manifestations of leprosy can vary widely, with some patients presenting with atypical symptoms that complicate diagnosis. This variability underscores the importance of training healthcare professionals to recognize the diverse presentations of leprosy and to ensure timely intervention[15]. Moreover, the integration of leprosy services into general healthcare systems is essential for improving case detection and reducing the stigma associated with the disease[16].

C-C MOTIF CHEMOKINE LIGAND 2 (CCL2)

CCL-2 is primarily produced by various cell types, including monocytes, macrophages, and fibroblasts, in response to inflammatory stimuli. Its primary function is to attract monocytes to areas of tissue damage, thereby facilitating the inflammatory response necessary for tissue repair and homeostasis[22]. The significance of CCL-2 extends beyond mere chemotaxis; it is also involved in various pathological conditions, including cardiovascular diseases, neurodegenerative disorders, and cancer. The expression of CCL-2 is tightly regulated by several pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α)[23]. This regulation cannot fully explain the complexity of the inflammatory response, where CCL-2 acts as a mediator that not only facilitates the migration of immune cells but also amplifies the inflammatory cascade. CCL-2 operates primarily at the sites of inflammation, where it orchestrates the migration of immune cells to combat pathogens and facilitate tissue repair. In the context of sepsis, CCL-2 has been shown to play a critical role in the pathogenesis of acute kidney injury by modulating the inflammatory response through the regulation of microRNAs[23].

The binding of CCL-2 to its receptor, CCR2, is essential for the recruitment of monocytes and macrophages to inflamed tissues, thereby perpetuating the inflammatory process[24].In addition to its role in inflammation, CCL-2 has been implicated in various diseases, including cancer. The involvement of CCL-2 in cancer highlights its dual role as both a mediator of inflammation and a facilitator of tumorigenesis. The dysregulation of CCL-2 has been associated with neurodegenerative diseases, where it may contribute to neuroinflammation and neuronal damage[25]. Furthermore, CCL-2 levels can serve as prognostic indicators in various conditions, including traumatic brain injury, where sustained elevated levels in cerebrospinal fluid correlate with neuroinflammation and recovery outcomes[26].

The expression levels of CCL-2 are known to fluctuate significantly in response to various physiological and pathological stimuli, including infections, tissue injury, and chronic inflammatory diseases. This fluctuation is influenced by factors such as oxidative stress, cytokines, and growth factors, which can induce CCL-2 expression in various cell types, including macrophages, endothelial cells, and fibroblasts[27]. The regulation of CCL-2 expression is complex and can be influenced by various factors, including age, sex, and underlying health conditions. Studies have shown that CCL-2 levels decrease with age, which may impact the immune response in older adults[28]. Additionally, the presence of certain genetic polymorphisms can affect CCL-2 expression and its association with diseases such as latent tuberculosis infection[28]. This highlights the importance of understanding the genetic and environmental factors that contribute to the regulation of CCL-2 levels and their implications for health and disease.

PATHOMECHANISM OF NEUROPATHIC PAIN IN LEPROSY

In leprosy, neuropathic pain can manifest due to peripheral nerve damage, which is a

hallmark of the disease. The mechanisms underlying neuropathic pain in leprosy involve a combination of inflammatory processes, neurogenic inflammation, and alterations in pain signaling pathways, with chemokines such as CCL-2 playing a significant role in these processes. Leprosy primarily affects peripheral nerves, leading to a range of neurological symptoms, including sensory loss and neuropathic pain. The pathophysiology of neuropathic pain in leprosy is characterized by the degeneration of nerve fibers, which can result from direct bacterial invasion or immune-mediated damage. This damage triggers a cascade of inflammatory responses, leading to the release of various pro-inflammatory mediators, including cytokines and chemokines, which further sensitize nociceptive pathways. CCL-2 is one of the key chemokines involved in this inflammatory response. It is produced by various cell types, including macrophages, endothelial cells, and neurons, and plays a role in recruiting monocytes to sites of inflammation, thereby amplifying the inflammatory response[23,29,30].

The role of CCL-2 in neuropathic pain is particularly significant due to its ability to modulate neuronal excitability and promote central sensitization. Central sensitization refers to the increased responsiveness of nociceptive neurons in the central nervous system to their normal input, which can lead to heightened pain perception. Studies have shown that CCL-2 can enhance the excitability of dorsal horn neurons in the spinal cord, contributing to the development and maintenance of neuropathic pain[29,30]. This sensitization is mediated through the activation of CCL-2 receptors, primarily CCR-2, which are expressed on various neuronal and glial cells in the spinal cord[30,31].

In leprosy, the presence of CCL-2 in the cerebrospinal fluid and peripheral tissues has been associated with the severity of neuropathic pain. Elevated levels of CCL-2 correlate with increased monocyte infiltration and the subsequent release of additional inflammatory mediators, creating a feedback loop that perpetuates pain signaling [29,30]. The inflammatory milieu in leprosy not only affects peripheral nerves but also alters central pain processing pathways, leading to chronic pain states that can be resistant to conventional analgesics. Moreover, the interaction between CCL-2 and other inflammatory mediators further complicates the pain response in leprosy. For instance, CCL-2 can activate the p38 mitogen-activated protein kinase (MAPK) pathway in microglia, leading to the production of pro-inflammatory cytokines such as IL-1β and TNF-α can exacerbate the inflammatory response, leading to increased pain sensitivity[29,31]. CCL-2 also has been implicated in the upregulation of matrix metalloproteinases (MMPs), which are enzymes that degrade extracellular matrix components and can facilitate neuronal injury and pain sensitization [29,31].

In addition to its role in pain signaling, CCL-2 is also implicated in the repair processes following nerve injury. While this may seem contradictory, the recruitment of monocytes and macrophages to the site of injury is essential for tissue repair and regeneration. However, in the context of leprosy, the persistent activation of CCL-2 signaling can lead to chronic inflammation and neuropathic pain rather than effective healing [23,29,30]. This dual role of CCL-2 underscores the complexity of inflammatory responses in neuropathic pain conditions. CCL2 also influences neuronal excitability and synaptic plasticity, which are critical for the development of chronic pain states. Inhibiting CCL-2 or blocking its receptor CCR-2 has shown promise in preclinical models of neuropathic pain, suggesting that such strategies could be beneficial in alleviating pain in leprosy patients [30,31]. Additionally, the use of anti-inflammatory agents that can reduce the levels of CCL-2 and other inflammatory mediators may provide a dual benefit by addressing both the pain and the underlying inflammation.

RELIABILITY AND CHALLENGES OF CCL-2 AS A BIOMARKER

CCL-2 has emerged as a reliable biomarker for neuropathic pain due to its significant role in the inflammatory processes associated with nerve injury and pain modulation. The association of CCL-2 with neuropathic pain is further supported by studies demonstrating its elevated levels in various pain models. For instance, research has shown that CCL-2 levels increase significantly following peripheral nerve injury, correlating with the development of hyperalgesia and allodynia, which are hallmark features of neuropathic pain[9,33]. CCL-2 levels have been shown to correlate with pain severity and functional outcomes in spinal cord injury and diabetnic neuropathy.The reliability of CCL-2 as a biomarker for neuropathic pain is also supported by its predictive value in clinical settings. Elevated serum levels of CCL-2 have been associated with poor prognosis in patients suffering from various neuropathic pain conditions, suggesting its potential utility in monitoring disease progression and treatment response[33-35]. The understanding of CCL-2's role in neuropathic pain is further elucidated by its interactions with other signaling pathways. For instance, CCL-2 has been shown to interact with the P2X4 receptor on microglia, which is essential for the development of neuropathic pain following nerve injury[9]. This highlights the multifaceted nature of CCL-2's involvement in pain mechanisms, reinforcing its status as a reliable biomarker for neuropathic pain.

CCL-2 presents as a promising biomarker for neuropathic pain, however, there are notable challenges associated with its use. One major concern is the lack of specificity; elevated CCL-2 levels can also be observed in other inflammatory conditions, which may lead to misinterpretation of its role in neuropathic pain[32]. Additionally, the dynamic nature of CCL-2 expression in response to various stimuli complicates its utility as a reliable biomarker. For instance, fluctuations in CCL-2 levels may occur due to factors unrelated to neuropathic pain, such as concurrent infections or other inflammatory diseases[32]. Another significant limitation is the variability in individual responses to CCL-2 modulation. Genetic and environmental factors can influence the expression and activity of CCL-2, leading to heterogeneous responses among patients[32]. This variability can complicate the interpretation of CCL-2 levels as a biomarker for neuropathic pain, as different individuals may exhibit different pain profiles despite similar CCL-2 levels. Therefore, CCL-2 can be used as a reliable neuropathic pain biomarker if we can elude the pittfalls for patient selections.

THERAPEUTIC STRATEGIES TARGETING CCL-2

Recent therapeutic strategies targeting CCL-2 have shown promise in preclinical studies. For example, the use of CCL-2 antagonists or neutralizing antibodies has been demonstrated to reduce pain behaviors in animal models of neuropathic pain[36]. These approaches aim to disrupt the recruitment of inflammatory cells to the site of nerve injury, thereby mitigating the inflammatory response and its associated pain. Furthermore, the modulation of CCL-2 signaling pathways may enhance the efficacy of existing pain management strategies, such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs), by addressing the underlying inflammatory processes[37]. In addition to pharmacological interventions, non-pharmacological approaches such as physical therapy and exercise have been shown to influence CCL-2 levels and microglial activation. Exercise can reduce the expression of CCL-2 and other inflammatory markers, thereby contributing to pain relief in neuropathic pain models[38]. Despite the promising findings regarding CCL-2 in neuropathic pain, several challenges remain. The complexity of the signaling pathways involved and the potential for off-target effects of CCL-2 inhibitors necessitate further investigation. Additionally, the

translation of preclinical findings to clinical practice requires rigorous clinical trials to establish the safety and efficacy of CCL-2-targeted therapies[39].

CONCLUSION

CCL-2 serves as a reliable biomarker for neuropathic pain in Leprosy due to its significant role in the inflammatory response, and its involvement in neuroplastic changes associated with chronic pain. However, there are some challenges and major concerns to be taken into consideration to translate the use of CCL-2 in clinical settings. CCL-2 also has its potential as a target for therapeutic intervention and a valuable tool for monitoring pain progression in clinical settings.

Declaration by Authors

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