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Interleukin -18 in chronic pain: focus on pathogenic mechanisms and potential therapeutic targets.

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❖ Abstract:

It has been shown that chronic pain is an independent disease as well as an accompanying symptom of certain diseases. Interleukin-18 (IL-18), a proinflammatory cytokine with pleiotropic biological effects, is involved in immune modulation, the inflammatory response, tumor growth, and the chronic pain process. Compelling evidence suggests that IL-18 is upregulated in the development of chronic pain. Cancer-related chronic pain (CP) represents a critical clinical problem during the disease and significantly affects the quality of 0life (QoL) of patients and family environment. Neuropathic pain is defined as pain caused by an injury or disease of the somatosensory system. It can affect a single nerve, multiple nerves, or occur diffusely. The prevalence of neuropathic pain is 7 to 10% and has a significant impact on the general population. Neuropathic pain is a common complaint of patients with peripheral neuropathy (PN) and is considered one of the most disease neuropathic symptoms with adverse effects on patients quality of life.

Antagonism or inhibition of IL-18 expression can alleviate the occurrence and development of chronic pain. And IL-18 is found in microglia, while IL-18R is found mainly in astrocytes in the spinal cord. This suggests that the interaction between microglia and astrocytes mediated by the IL-18/IL-18R axis is involved in the development of chronic pain. I However, IL-18 is mainly produced by activated macrophages; It can also be expressed by Kupffer cells, T cells, B cells, keratinocytes, astrocytes and osteoblasts.

Keywords: Chronic pain, interleukin 18, cancer pain, neuropathic pain,peripheralneuropathic pain, Central neuropathic pain.

❖ Introduction:

- **Chronic pain**

A pain condition is considered chronic if it lasts more than three months or recurs frequently [1]. Chronic pain continues to be considered a major health problem with multiple impacts on quality of life and increases healthcare costs, particularly neuropathic pain (NP), inflammatory pain, and cancer pain [2].

Chronic pain is a common, complex and distressing problem that has a significant impact on society and individuals. It often occurs as a result of injury or illness; However, it is a disease in its own right and not simply a symptom that accompanies other complaints. Therefore, chronic pain has its own taxonomy and medical definition [3]. This means that it severely affects patients' daily lives. Chronic pain can be an independent disease or an accompanying symptom of certain diseases. It is dynamically influenced by a variety of physiological, psychological and social factors [1].

Chronic pain (CP) is considered a major public health problem and represents a significant economic and social burden. Furthermore, this condition not only affects the patient (as both a sensory and emotional problem) but also impacts Your family and your social environment.The biopsychosocial model, considered essential in pain, provides a framework for understanding how various diseases are related through an assessment of sensory, cognitive-affective and interpersonal factors [4].

The first-line therapy for chronic pain is opioids, which are often associated with undesirable psychoactive side effects. Therefore, new and effective treatment options for chronic pain are urgently needed and eagerly sought. Several research efforts have recently been directed toward treatment regimens for chronic pain, although effective analgesics with minimal side effects do not yet exist . Therefore, the specific mechanisms underlying the induction of chronic pain are the subject of ongoing research. Neuroinflammation is a prominent target in relieving pain . Various studies have shown that neuroinflammation plays a role in many stages of chronic pain, such as development and sensitization [2]

To date, an increasing number of studies have focused on the role of IL-18 in various types of chronic pain .Various types of chronic pain have shown that the expression of IL-18 and its receptor IL-18R is highly regulated at the spinal level and that inhibiting expression or providing neutral antibodies can prevent and reduce the development of IL-18R continuation of the pain process. These studies clearly demonstrate the critical role of IL-18 in the development and maintenance of chronic pain [1].

Pain Management. Pain is one of the main and most common reasons why people seek medical care. 6 Pain is not only an unpleasant feeling that reduces quality of life, but also an emotion that causes urgency; because pain is a sign of damage or impending damage that requires immediate attention [5].

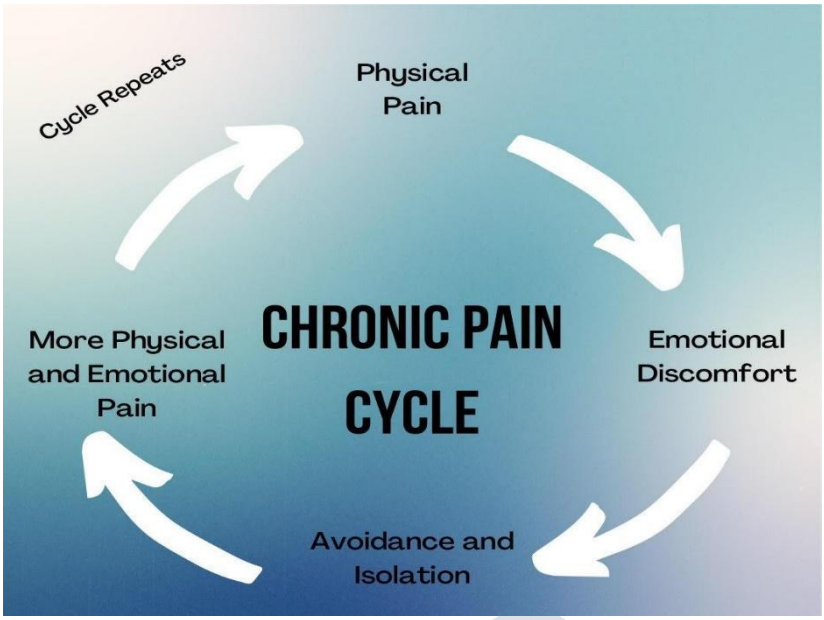

Fig 1: Chronic pain cycle

❖ Interleukin - 18:

Interleukin (IL)-18 is a pleiotropic proinflammatory cytokine involved in the regulation of innate and adaptive immune responses. IL-18, originally identified as interferon (IFN)-γ-inducing factor, was isolated from the serum of mice pretreated with Propionibacterium acnes, which stimulated Kupffer cells following stimulation with intraperitoneal lipopolysaccharide [6]. Interleukin 18 belongs to the IL-1 family of cytokines, a group consisting of 11 cytokines that promote the activity of the innate immune system [7].

- **Discovery of IL- 18:**

In 1989, Nakamura and co-worke described endotoxin-induced serum activity that induced the production of IFN-γ from mouse spleen cells. This serum activity acted not only as a direct inducer of IFN-γ but also as a costimulant along with IL-2 or mitogens. An attempt to purify activity from post-endotoxin mouse serum yielded an apparently homogeneous 50-55 kDa protein .Because other cytokines can act as costimulants for IFN-γ production, the failure of antibodies to IL-1, IL-4, IL-5, IL-6 to neutralize serum activity suggests that it was another factor.

- **Structure and production of IL – 18:**

IL-18 is a proinflammatory cytokine with 18, kDa and 157 amino acids. It is synthesized as an inactive precursor (Pro-IL-18) of 24 kDa, which is cleaved by the interleukin-1 β-converting enzyme (ICE or caspase-1), yielding the mature bioactive peptide from which the cells are easily released.

- **Molecular Structure and Gene Expression**:

The human IL-18 genes are located on chromosome 11. The human IL-18 cDNAs, which encode the precursor IL-18, consist of 193 amino acids. Genomic analysis of the promoter region showed that at least 92 base pairs of the promoter region are essential for the constitutive expression of IL-18 .

❖ Pathological role of IL – 18:

1. Liver disease:

IL-18 was shown to play a key role in the pathogenesis of acute liver injury in mice exposed to endotoxin following Propionibacterium acnes and lipopolysaccharide (LPS) priming. Concanavalin A (Con A)-induced hepatitis is an immune-mediated disease in which the interaction of CD4+ T cells and TH1 cytokines leads to Fas (6)-mediated hepatocellular death .

2. Viral infection:

Many reports suggest that IL-18 may play an important role in viral infections. A beneficial effect of IL-18 was demonstrated in mouse models of herpes simplex and vaccinia virus infections, demonstrating that IL-18 inhibits the production of human immunodeficiency virus (HIV) in peripheral blood mononuclear cells (PBMC) inhibits . However, the mechanism of this antiviral effect and its relationship to virus replication have not been clarified. IL-18 has been shown to inhibit hepatitis B virus (HBV) replication in the liver of transgenic mice.

3. Fungal infection:

IL-18, in synergy with IL-12, promotes the antifungal response to C. neoformans by inducing IFN-γ from (natural killer cells) NK cells and (nitric oxide) NO from macrophages and negatively regulating IL4 production. Therefore, administration of IL-18 during C. neoformans infection promotes the antifungal response. IL-18 appears to be effective even in the absence of IL-12. In a model of chronic fungal asthma, IL-18 promotes innate responses, thereby preventing the development of severe fungal asthma.

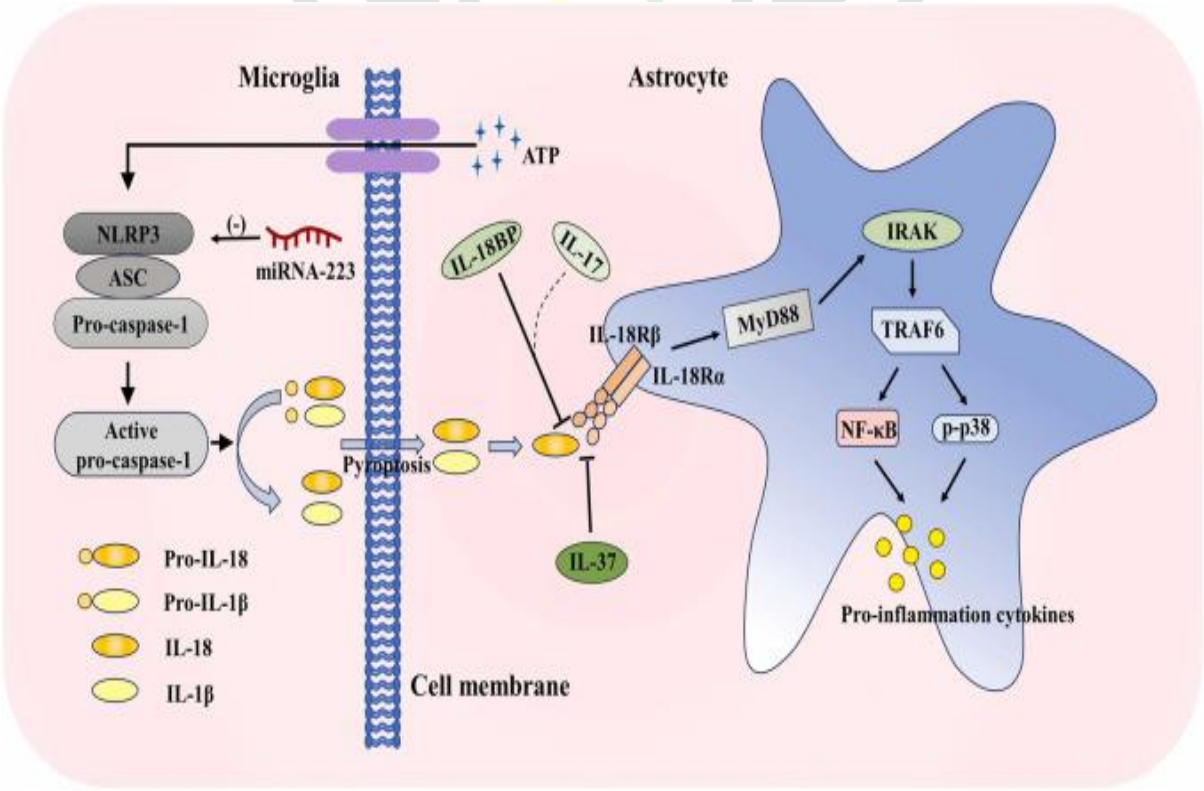

Fig 2: Schematic representation of IL-18 production and secretion in glial cells. The cysteine protease caspase-1 is activated upon recruitment of the NLRP3 inflammasome and cleaves pro-IL-18 into a biologically active form. IL-18R is a multi-chain receptor complex consisting of two parts. After IL-18 binds, it recruits common adapter proteins and activates the cascade signal transduction pathway, triggering a cascade response. IL-18BP is a specific natural inhibitor that can buffer and regulate IL-18 under physiological conditions to prevent its interaction with the cell surface receptor.IL-18: interleukin-18; IL-18R: interleukin-18 receptor; NLRP3: NOD-like receptor protein 3; pro-IL-18: processes IL-18 precursor protein; IL-18BP: IL-18 binding protein.

4. Immunotherapy:

Systemic administration of IL-18 demonstrated significant antitumor activity in animal models. Phase I clinical trials of recombinant human IL-18 have shown that it can be safely administered to patients with advanced cancer. The biological effects of IL-18 therapy include activation of monocytes, NK cells and T cells and increased production of IFN-γ. IL-18 functions Primarily as costimulatory cytokine and is therefore most suitable for cancer immunotherapy in combination with other immunostimulatory cytokines, vaccines, or monoclonal antibodies [8].

Interleukin-18 (IL-18) is classified as a member of the IL-1 family.The cysteine protease caspase-1 is activated upon inflammasome recruitment of NOD-like receptor protein 3 (NLRP3) and then cleaves and processes the IL-18 precursor protein (Pro-IL-18) with a relative molecular weight of 24 kDa into a biologically active form of the 18 kDa protein . IL-18 first binds with low affinity to its specific IL-18 receptor α (IL-18α) ligand binding chain and then recruits the IL-18Rβ auxiliary chain to form a complex. High affinity heterotrimer.. This IL-18R complex then recruits adaptive molecules that induce the expression of proinflammatory cytokines, chemokines or secondary mediators to participate in the inflammatory response . As a pleiotropic and pro-inflammatory cytokine, IL-18 can be released in large quantities after infection to participate in innate/adapted immunity, inflammation and tumor growth processes .What distinguishes it from other cytokines is that IL-18 expression is extremely stable because it contains few RNA-destabilizing elements . Therefore, the biological activity of IL-18 is thought to be regulated post-translationally, but not at the level of mRNA expression, and its rapid release occurs at the proximal end of the inflammatory cytokine cascade reaction [1].

- **IL-18 Receptor:**

The Receptor for IL-18 (IL-18R) is a heterodimer consisting of two chains: 1) a ligand binding component (one chain) responsible for the extracellular binding of IL-18 (it was identified as IL-1 receptor-related protein, IL-1Rrp). 2) A signaling component (ß chain) responsible for intracellular signal transduction (also called similar accessory protein, AcPL) because it is related to the accessory protein IL-IR, both of which belong to the IL-1R family.

- **IL-18 binding protein (IL-18BP):**

IL-18BP is the natural inhibitor of IL-18, which negatively regulates its biological effects. IL-18BP is a constitutively secreted protein with high affinity binding to IL-18 (400 pmol/L). Once IL-18 is secreted,

IL-18BP binds to it and inactivates it. IL-18BP production is increased as a negative feedback mechanism in response to increased IL-18 production to ensure protection against tissue damage due to uncontrolled proinflammatory activity. IL-18BP is highly expressed in the spleen and intestinal tract, which are immunologically active tissues. The IL-18BP promoter contains two IFN-γ response elements, and constitutive IL-18BP gene expression depends on IFN-γ, suggesting a compensatory feedback mechanism. Therefore, increased IFN-γ concentrations stimulate more IL-18BP to reduce IL-18-mediated IFN-γ production .

- **Processing of IL-18:**

The molecular mechanism for IL-18 production is mediated by TNF receptor-associated factor 6 (TRAF-6). The interleukin receptor activates myeloid differentiation factor 88 (MyD88) and IL-1 receptor-associated kinase (IRAK). This activation leads to the synthesis of pro-inflammatory genes such as inducible nitric oxide (INOS) and IFN-γ. IL-18 also increases proinflammatory activity through the induction of matrix metalloproteinases, which are responsible for the pathological chemotaxis of immune cells to target tissues (i.e. Liver tissue) . IL-18 binds to IL-18Ra and IL-18Rß, forming a high-affinity complex that, together with other members of the IL-1R family, induces signaling pathways. This involves the recruitment and activation of MyD88 and IL-1R-associated kinase (IRAK) to the receptor complex . IL-18 is converted into active forms by at least two recognized proteases. One pathway involves the same enzyme that typically activates IL-1ß, caspase-I [also known as interleukin-1 converting enzyme (ICE)]. Alternatively, IL-18 is activated by the neutrophil-derived serine protease proteinase 3 (PR3). These two activation pathways are differentially associated with cellular processes and pathologies.

❖ Function and Biological activity of IL-18:

1. IL – 18 and inflammatory process:

IL-18 is emerging as an important proinflammatory cytokine with implications for a role in inflammatory and infectious diseases. IL-18 was first described as an IGIF (interferon gamma including factor) cell. However, IL-18's ability to induce IFN-γ production occurs primarily in the context of a secondary stimulus, as it interacts with IL-12, mitogens, or microbial agents to increase IFN-γ production. IL-18 alone does not induce production of IFN-γ from T lymphocytes. However, the in vitro production of (Lipopolysaccharide) LPS and IFN-γ from murine spleen cells induced by Zymosan is greatly reduced by the use of neutralizing antibodies against murine IL-18 confirming similar results in vivo and suggesting that endogenous IL-18 is essential for IFN-γ. Production of γ by microbial agents. Because of its ability to induce the chemokines tumor necrosis factor α, IL-1β, as well as CXC and CC, and because IL-18 induces Fas ligand as well as nuclear translocation of nuclear factor kB (NFkB), IL-18 is classified alongside other inflammatory ones Pro Cytokines as a likely trigger of systemic and local inflammation .Consistent with stimulating (tumor necrosis factors) TNF production, IL-18 positively regulates Fas ligand-mediated cytotoxic activity of natural killer (NK) cells, T cells, and the myelomonocytic cell line KG-1. In addition to macrophage cells, keratinocytes produce functional IL-18 after stimulation with contact sensitizers and therefore IL-18 may play a role in the inflammatory

process after contact with allergens. During endotoxin-induced liver injury in mice, neutralizing antibodies against IL-18 reduced tissue damage.

2. **IL-18 and IFN:**

IL-18 production is induced by stressful stimuli (i.e., bacterial or neurogenic signals). In this context, it has been suggested that stress-induced release of IL-18 could lead to an escalating cycle of IFN-γ/IL-18 production. After an initial wave of IL-18 production 18-- induced IFN-γ, the newly secreted IFN-γ , can now stimulate monocytes /macrophages to increase their interleukin-1 converting enzyme (ICE) activity.As IL-18 production continues, increased (IL-18 converting enzyme) ICE activity likely leads to greater processing of IL-18, leading to increased lymphocyte IFN-γ production and thus increased ICE activity. ICE macrophages. Thus, IL-18 not only promotes the synthesis of IFN-γ but also participates in its general activities.

3. **IL-18 and apoptosis:**

IL-18 is also involved in Fas ligand (FasL)-mediated killing. FasL is a tightly regulated 40 kDa member of the TNF (tomar necrosis factors) superfamily of molecules. Binding of 81 interleukin-18 in Health and Disease FasL to its commonly expressed receptor Fas generally results in the activation of an apoptotic program in the Cell expressing Fas. The cells thought to mediate such activities are CD4+ TH1 cells and NK cells (two populations of cells that express FasL under the influence of IL-18). In this regard, IL-18 again shows a relationship with IFN-γ , which appears as a positive regulator of Fas antigen expression.IL-18 positively regulates the production of -FasL and IFN-γ in T cells, and the IFN-γ produced by can induce Fas antigen in a variety of cell types. Therefore, through the induction of IFN-γ, IL-18 could be viewed as a molecule that provides both the ability (FasL) and the ability (Fas) to trigger apoptotic cell death .

4. **IL-18 and Tumor :**

IL-18 exerts antitumor effects mediated by increasing NK cell activity, reducing tumorigenesis, inducing apoptosis, and inhibiting angiogenesis in tumor cells [8].

- **IL – 18 receptar:**

IL-18 mediates its signaling effects through its receptor, which belongs to the IL-1R family, consisting of the IL-18Rα chain (IL-18R1, IL-1Rrp) and the IL-18Rβ chain (IL-18R protein, IL-18Rβ). 18Ra chain). 1RAcPL) [2]. After IL-18 binds to IL-18Rα, IL-18Rβ binds to form a trimer. The local region contains a TIR domain that interacts with TLRs, and MyD88 binds to TIR to transmit the signal to cells. Although IL-18Rα can only bind to IL-18, its affinity is low. IL-18Rβ chain is required for binding and signaling. When IL-18Rα binds to IL-18Rβ, it causes a conformational change, resulting in an increase in the number of receptors .IL-18R expression in T cells and NK cells, induced by stimulation by IL-12 and IFN-α(human) or by signal transduction nd transcription through STAT4 (signal transducer and activator of transcription 4), is required for potent IFN. -γ production . However, IL-18R is also stably expressed on basophils, mast cells, and CD4+NKT cells; all of these secrete Th2 cytokines such as IL-4 and IL-13 in response to IL-18. IL-18R is also expressed by immune cells such as epithelial cells and stromal cells and

plays a role in cell survival and differentiation. The mechanism by which IL-18R expression is regulated in these cells is not well understood [9].

❖ Literature review :

1. **Jie ju et.al. (2024) :** It has been demonstrated that chronic pain is a separate illness rather than just a symptom of some other illnesses. Proinflammatory cytokine interleukin-18 (IL-18) has pleiotropic biological effects and plays a role in immunological regulation, inflammatory response, tumor formation, and the development of chronic pain.(1)
2. **Rania M.Saleh et.al. (2013):** Similar in structure to IL-1, interleukin-18 (IL-18) is a relatively recent immunostimulatory cytokine. Although activated macrophages are the primary source of IL-18, kupffer cells, T cells, B cells, keratinocytes, astrocytes, and osteoblasts can also express it. Through its effects on monocytes, dendritic cells, T cells, B cells, natural killer (NK) cells, and T lymphocytes, IL-18 can control both innate and adaptive immune responses.(7)
3. **Chiara filipponi et.al. (2022) :** Chronic pain (CP) associated with cancer is a serious clinical problem that negatively affects patients' quality of life (QoL) and the environment in which they live with their families. The current review used a narrative approach, adopting a multidimensional and triple vision: patients, caregivers, and patient-caregiver perspective, to summarize the key findings about the influence of cancer-related CP on QoL.(11)
4. **Koichi Obata et.al. (2008) :** An essential modulator of both innate and acquired immune responses is interleukin (IL)-18. Here, we demonstrate that tactile allodynia following nerve injury is dependent on both IL-18 and IL-18 receptor (IL-18R), both of which are produced in the spinal dorsal horn. The dorsal horn showed a substantial rise in the expression of IL-18 and IL-18R during nerve damage, and hyperactive microglia and astrocytes also showed an upregulation of IL-18 and IL-18R.(13)
5. **Silvin Alboni et.al. (2010) :** The cytokine interleukin (IL)-18 was identified as a significant immune response modulator and later demonstrated to be pleiotropic. Within the central nervous system (CNS), IL-18 and its receptors are expressed and have a role in neuroinflammatory and neurodegenerative processes as well as influencing behavior and homeostasis.(17)

❖ IL- 18 in pathologogic condition :

Many autoimmune diseases are believed to be associated with increased production of IFNγ and IL-18. Diseases such as systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, Crohn's disease, psoriasis, and graft-versus-host disease are thought to be related18 and have been previously reviewed.4,5,6,7 In this overview we consider IL-18 It will discuss the role of in the pathogenesis of inflammatory bowel disease, metabolic syndrome and cardiovascular disease, lung disease , sepsis, hemophagocytic syndromes. and systemic juvenile idiopathic arthritis.

1. **IL-18 in inflammatory bowel disease** :

Innate immunity and inflammatory activation, particularly NLRP3, are involved in the early stages of Crohn's disease. In addition to IL-18 (based on 400 pg/ml) and IL-18BP. IL-18 colocalized with lamina propria cells in the serum of adult patients with severe Crohn's disease but not in ulcerative colitis.

2. **Chronic Obstructive Pulmonary Disease :**

Chronic Obstructive Pulmonary Disease (COPD) includes emphysema and chronic bronchitis, both of which are characterized by chronic inflammation, alveolar destruction, airway remodeling and fibrosis (secondhand), and bad air. Cigarette smoke contains more than 4,500 products, oxidants, and free radicals that activate the immune system and cause lung damage. 142 IL-18 has been found to be highly expressed in alveolar macrophages, CD8 T lymphocytes, and bronchiolar and alveolar epithelial cells in the lungs of patients . Circulating T cells expressing 18Ra are higher in COPD patients, 143 , 144 , 145 Serum IL-18 is increased in COPD and smokers compared to healthy non-smoker controls; This is related to the severity and seriousness of the disease. Mandatory expiration date tests.

3. **IL-18 in hemophagocytic syndrome:**

Hemophagocytic syndromes or hemophagocytic lymphohistyocytosis (HLH), liver, hepatomegali, splenomegali, cytopenia, hypertriglyceridemia, hypertrighylyceridemia It is characterized by a combination of HR and biological symptoms. The presence of hemophagocytosis in the bone marrow is not required for diagnosis, but the presence of this clinical picture strongly suggests the disease. Interestingly, showed that hemophagocytosis was more common in the bone marrow of sepsis patients [10].

❖ IL-18 and chronic cancer related pain:

Chronic cancer-related pain is defined as pain caused by the cancer itself (primary tumor or metastatic tumor) or by treatment (surgery, chemotherapy, radiotherapy, etc.) [50] and is a common accompanying symptom. Between 75% and 90% of patients with metastatic or advanced cancer experience chronic cancer-related pain which significantly impacts diagnosis and patient survival. Bone pain caused by tumors is the most common pain in patients with advanced cancer and spontaneous, unpredictable pain often occurs over time intensive. which significantly affects the quality of life of patients. The most commonly used analgesics for bone cancer pain are nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, but their use is limited due to their apparent side effects . Therefore, there is an urgent need for more effective drugs to treat cancer pain in clinical practice, which requires continuous exploration of new molecular mechanisms to achieve new therapeutic targets [1].

Persistent cancer pain (CP) represents a significant clinical problem throughout the disease process (from diagnosis to long-term survival), affecting approximately 40-70% of patients with cancer. In particular, Bennett et al.reported that this pain is between 33% reported. and 40% of long-term cancer survivors have CP, whereas 66% of advanced cancer patients have pain [11] .Cancer is a common disease in which pain management is often a concern for a group of long-term care patients. The global incidence of cancer is 6-7 million patients per year, and half or more of these occur in developing countries. Approximately 4.5 million patients die from cancer every year and 3.5 million patients are diagnosed with cancer every day, very few of whom receive adequate pain treatment[12].

❖ IL-18 and chronic neuropathic pain:

Neuropathic pain is caused by nerve damage that damages peripheral nerves or diseases such as diabetes, immunodeficiency syndrome, or cancer. The most common symptom of neuropathic pain is tactile allodynia, which is characterized by painful responses that are usually harmless. Current treatments for this type of chronic pain appear futile and the molecular mechanism of action is unknown [13]. Various drug classes have been compared with placebo in clinical trials in patients with different types of neuropathic pain, including antidepressants, anticonvulsants, local anesthetics [14].

Neuropathic pain refers to pain caused by injury or disease of the somatosensory system (such as nerve injury, spinal cord injury, stroke and diabetes) and is characterized by mechanical and thermal hyperalgesia.Epidemiology shows that the prevalence of neuropathic pain in the general population can reach 7–8%, corresponding to 20–25% of patients with chronic pain. The mechanism of neuropathic pain is extremely complex, involving pathological and physiological phenomena in the central and peripheral nervous system [1].

- **Muscle pain:**

Musculoskeletal disorders are an important cause of chronic health problems, disability, and poor quality of life.Among these health problems, musculoskeletal pain is a common phenomenon associated with various pathologies. Musculoskeletal pain can present as neck and shoulder pain, nonspecific back pain, and myofascial pain syndrome (MPS).Neck and shoulder pain affects approximately 30% of the working population and is long-term. It is a risk factor for work. illness. long-term absence from work. Low back pain has a lifetime prevalence of up to 84% and causes disability in 11-12% of the general population. MPS is common in the general population and therefore its prevalence may vary. It is as high as 54% in women and 45% in men [15].

❖ IL- 18 and chronic peripheral neuropathic pain:

Peripheral nerve damage can cause neuropathic pain in many ways . Although the insults are local, they are not the effects of chronic pain. Peripheral pain processing by unruffled C fibers and smooth Aδ fibers can accelerate the development of neuropathic pain after exposure to metabolic insult, toxins , drugs, cytokines, and other inflammatory mediators resulting in changes in fiber density and neuronal hyperexcitability [16].

a. Chronic neuropathic pain after peripheral nerve injury:

Typical symptoms of a peripheral nerve injury include motor and sensory disturbances in the area innervated by the injured nerve. Some of these can be repaired, but persistent nerve injuries can cause unbearable pain that is inconvenient for patients' lives. IL-18 and IL-18R were found to be upregulated in the spinal cord in animal models of peripheral nerve injury, such as: B. the ligation model of the fifth lumbar spinal nerve (SNL) and the constriction injury model (CCI). And tetanic stimulation of the sciatic nerve model (SST) . And inhibition of the IL-18/IL-18R axis can inhibit or attenuate the tactile allodynia and hyperalgesia caused by these nerve lesions. These indicate that IL-18 plays an

important role in neuropathic pain caused by peripheral nerve injury and that further research is required. Microglia can express Toll-like receptors (TLRs) .The TLR family member, TLR4, was upregulated in the spinal cord in the SNL model. Further investigation revealed that in microglia, high TLR4 activation could induce p38 MAPK phosphorylation and subsequently IL-18 expression. And disrupting TLR4 expression or using the p38 inhibitor SB203580 could reduce IL-18 levels and relieve abnormal pain after injury. In addition, this study revealed that high expression of IL-18 could increase IL-18R levels in astrocytes and induce phosphorylation of NF-κB. Intrathecal injection of an NF-κB inhibitor can alleviate IL-18-induced hyperalgesia in a dose-dependent manner . These indicate that peripheral nerve injury can increase the expression of IL-18 in activated microglia via the TLR4/p38 MAPK pathway and then activate the IL-18R/NF-κB pathway in astrocytes, leading to the appearance of neuropathic tumors Pain leads.

b. Polyneuropathy:

Chronic neuropathic pain often occurs in polyneuropathy caused by autoimmunity, infectious diseases, exposure to environmental toxins, or treatment with neurotoxic drugs. Chemotherapy-induced peripheral neuropathy is a form of painful polyneuropathy .Oxaliplatin is a common chemotherapeutic agent in the clinical treatment of cancer and the most serious side effect is a dose-limiting neurotoxicity known as oxaliplatin-induced peripheral neuropathy (OIPN).During chemotherapy, patients may experience symptoms such as limb paresthesia, ataxia, and neuropathic pain associated with OIPN [1].

- **IL-18 in the CNS :**

IL-18 transcripts were detected by RT-PCR in various brain regions, including the hippocampus, hypothalamus, and cerebral cortex. In vivo studies have shown that IL-18 protein is present in the pituitary gland, ependymal cells, central med habenula neurons (where its synthesis increases with stress), Purkinje cells, and astrocytes in the cerebellum . It has also been shown that microglia and astrocytes in vitro can produce IL-18 and that its level can be controlled after LPS stimulation or treatment with INF-γ [17].

❖ Chronic central neuropathic pain:

Chronic central NP associated with spinal cord injury In summary, chronic central NP is associated with spinal cord injury caused by injury or disease of the somatosensory pathway in the spinal cord . This may also come from the category of 'chronic pain after spinal cord injury', which refers to patients experiencing neuropathic attacks [18].

a. Chronic central neuropathic pain after spinal cord injury:

A spinal cord injury (SCI) is an extremely devastating injury. It can cause severe sensorimotor dysfunction of the limbs below the injured segment or even paralysis, which can pose a great economic burden to society and families. Neuroinflammation and oxidative stress in the dorsal horn of the spine are the main causes of neuropathic pain after SCI leading to neuronal damage or even death and persistent neuropathic pain . The converging evidence suggests that the expression of IL-18 is significantly up egulated in the spinal cord of the rat SCI model .In microglia, the inflammatory response

induced by SCI can increase IL-18 levels via the MAPKs-NF-κB pathway, pyroptosis, NLRP3 mechanisms could reverse the expression.However, the role of IL-18 itself in SCI requires further investigation.

b. Chronic central poststroke pain:

Central post-stroke pain (CPSP), which is related to damage to the central nervous system, often occurs after a hemorrhagic or ischemic stroke. CPSP is one of the most common serious sequelae after a stroke, with an incidence of 1–14% in stroke patients. And hemorrhagic CPSP caused by stroke is more common than ischemic stroke.A large proportion of patients with CPSP suffer from persistent or indirect pain, hyperalgesia and paresthesias. Medications remain the main treatment in clinical practice , but they cannot completely relieve patients' pain symptoms. Therefore, it is particularly important to search for new pathogenic mechanisms of CPSP to develop therapeutic drugs.

In CPSP (Central post stroke pain) model mice, time-dependent thalamic hemorrhagic pain resulted in a significant decrease in the expression level of miR-223, but markedly increased the expression level of NLRP3 and its downstream factors caspase-1, IL-18 and IL-1β.Injection of exogenous miRNA-223 significantly reduced thalamic pain and reversed the expression levels of NLRP3, IL-18 and IL-1β. Furthermore, administration of NLRP3 inhibitor significantly reduced IL-18 and IL-1β levels and alleviated CPSP militated by inhibiting miR-223 in naïve mice. These results suggest NLRP3 and IL-18. Provides evidence for the existence of the miR-223/NLRP3/IL-18 signaling pathway in the mechanism of CPSP caused by cerebral hemorrhagic brain injury [1].

- **Bone cancer pain :**

Bone cancer pain is one of the most common symptoms in patients with primary and metastatic bone cancer.The pain pattern of bone cancer is complex and may include a combination of acute and neuropathic pain, with unique characteristics. Fortunately, despite the passage of decades, the specific cellular and molecular mechanisms underlying bone cancer pain are still unclear, and treating bone cancer pain remains a major challenge in medicine. Recently, evidence has been found that spinal cord cells play a role in the development and/or maintenance of chronic painss [19].

❖ IL-18 and opioid analgesic tolerance and opioid induced hyperalgesia :

Opioids such as morphine are the preferred option for treating intractable pain due to their strong and effective analgesic effects. However, they usually have some side effects such as addiction, constipation, nausea, vomiting, respiratory depression, etc.Patients may become insensitive to morphine after long-term treatment, i.e. H. tolerance to morphine with analgesic effect gradually decreases at the same dose and opioid-induced hyperalgesia may even occur.Significantly, the important role of IL-18 in morphine tolerance was confirmed,

Previous studies have shown that activation of microglia contributes to the development of morphine tolerance .Chen et al. found that chronic morphine treatment can upregulate the expression of P2X7R and IL-18 in microglia and IL-18R in astrocytes .Antagonism against IL-18, P2X7R and protein kinase C gamma (PKCγ), respectively, impedes the progression of morphine tolerance, suggesting that they all play an

important role. In subsequent studies, both P2X7R antagonist and targeting siRNA can inhibit the upregulation of IL-18 and PKCγ, indicating that IL-18 and PKCγ are downstream molecules of P2X7R. IL-18BP can inhibit astrocyte activation, which is similar to the effect of P2X7R antagonist and targeted siRNA. In vitro studies have shown that the increased excitability of nociceptive-sensitive spinal cord neurons caused by chronic morphine administration can be completely blocked by the P2X7R antagonist. Chronic morphine administration leads to a significant increase in D-serine in the dorsal horn of the spinal cord and its degrading enzyme may attenuate the onset of tolerance to morphine analgesia. In fact, D-serine synthesized and released by astrocytes is known to be an endogenous ligand for the NMDAR glycine site .Therefore, morphine tolerance stimulates the intimate connection between glial cells and spinal cord neurons via the P2X7R-IL-18-D-serine-NMDAR-PKCγ signaling pathway. It is an important discovery in the mechanism of morphine tolerance [1].

- **Malignant bone pain :**

Skeletal involvement is a common and disturbing problem in many patients with neoplastic disease. It is the third most common location after the lungs and liver (Tubiana-Hulin, 1991). The appearance and distribution of bone spurs are difficult to determine. Autopsy series, bone series, and hospital databases show significant variation. Metastatic cancer affects bone at a rate of 60-84%. Myeloma is a hematological malignancy frequently associated with bone disease. Bone involvement is common in lung and prostate cancer in men and in breast cancer in women: bone involvement is seen at autopsy in up to 85% of patients who die from breast, prostate or lung cancer (Nielsen et al., 1991). In patients with bone disease, patient survival can vary greatly [20].

❖ Targeted IL-18 therapy for pain treatment:

Overall, existing research has shown that IL-18 is a therapeutic target worth exploring. As previously mentioned, the application of IL-18BP can significantly alleviate the occurrence of pain in chronic pain models of rodents supporting its further development for the treatment of pain. In fact, basic research paves the way to new clinical therapies. The increase in total IL-18 levels in some inflammatory diseases has a high specificity, which is further improved by routine detection of free IL-18 and IL-18BP.It is noteworthy in this context that there are already data from clinical studies and cases that demonstrate the therapeutic potential of IL-18BP .

Recent studies have shown that melatonin may be a valuable therapeutic target for IL-18. The benefits of melatonin in the treatment of many diseases associated with chronic pain, including fibromyalgia, cancer and neuropathic diseases, are increasingly recognized. Pain.Melatonin inhibits the induction of the NF-κB/NLRP3 inflammasome signaling pathway and subsequent cytokine levels (IL-18 and IL-1β) to relieve pain .The use of photo biomodulation therapy (PBM) to relieve fibromyalgia provides evidence for the importance of circadian rhythms in chronic pain conditions . Recent work suggests that nocturnal pineal melatonin (along with gut microbiome-derived butyrate inhibits nuclear translocation of the glucocorticoid receptor, with significant consequences for preparing the CNS and systemic processes for the next day..It will be important for future research to examine the role of pineal melatonin and gut microbiome-derived

butyrate in regulating the consequences resulting from elevated cortisol levels during the night, culminating in the cortisol response upon awakening in the morning. Investigating the role of circadian rhythms in regulating the NLRP3 inflammasome and IL-18/IL-18R should better clarify the complexity of the physiological processes underlying chronic pain in various diseases [1]

❖ Conclusion:

The significant global burden of disease caused by chronic pain needs to be addressed by targeting the causes and effects of chronic pain at both individual and population levels.

Based on the existing evidence, this review concluded that IL-18 plays an important role and mechanism in various types of chronic pain. Chronic pain is a complex process. Medications cannot completely relieve patients pain symptoms due to different mechanisms in different types of chronic pain. This review summarized not only the role of the IL-18/IL-18R axis but also the individual mechanism of IL-18 in different types of chronic pain. In addition to IL-18BP, a specific natural inhibitor, this review concludes that there is an effective treatment targeting IL-18 in various chronic pain conditions. These provide strong evidence that IL-18 may play an important role in the development of chronic pain and suggest a potential new therapeutic target for pain control.

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