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REVIEW

Inflammatory Cytokines as a Shared Pathophysiological Pathway in Depression and Chronic Insomnia: A Narrative Review of Mechanisms and Clinical Implications

Ning Ren[1], XiaoNa Zhang[1], Zhe Yu[1,2], Yangfei Che[1,2], YaJie Zhang[1,2], Mingfen Song[1], Hongjing Mao[1]

[1]Affiliated Mental Health Center, Zhejiang University School of Medicine (Hangzhou Seventh People's Hospital), Hangzhou, Zhejiang, People's Republic of China; [2]The Fourth Clinical Medical College of Zhejiang Chinese Medical University, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Mingfen Song; Hongjing Mao, Affiliated Mental Health Center, Zhejiang University School of Medicine(Hangzhou Seventh People's Hospital), Hangzhou, Zhejiang, People's Republic of China, Email songmingfen2005@163.com; 13777861972@163.com

Abstract: The comorbidity of depression and chronic insomnia is very common in clinical practice, and there is a complex and close relationship between these two diseases, yet its underlying mechanisms remain incompletely understood. In recent years, inflammatory cytokines have been widely studied as important etiological factors for depression comorbid with chronic insomnia. However, whether inflammation is a cause or consequence of this comorbidity remains debated.This review synthesizes emerging evidence to position inflammatory cytokines not merely as correlates, but as central drivers in the pathophysiological nexus of depression and chronic insomnia. It systematically expounds the inflammatory characteristics and clinical significance of patients with depression comorbid with chronic insomnia, with the aim of reviewing the evidence of the association between inflammatory cytokines and depression comorbid with chronic insomnia, and discussing the potential pathophysiological mechanisms that may explain this association, thereby providing a robust scientific foundation for the development of novel ant-inflammatory therapeutic strategies and precision medicine approaches for this challenging comorbidity.

Keywords: inflammatory cytokines, depression, chronic insomnia, comorbidity, pathological mechanisms

Introduction

Depression is a common mental disorder, clinically characterized by prominent and persistent low mood, depressive pessimism, diminished interest, and anhedonia. According to statistics from the World Health Organization (WHO), there are more than 350 million people with depression worldwide. It is projected that by 2030, depression will become the leading cause of global disease burden.[1] Majority of people with depression have sleep disorders, which can intensify the patient's additional clinical symptoms, such as fatigue and drowsiness. Regular sleep is of vital importance for living beings in the natural world to maintain immune homeostasis. However, both humans and animals are faced with varying degrees of sleep deprivation. Insomnia is the most common type among all sleep disorders, characterized by a chronic course. The prevalence rate in the Chinese population is approximately 12%, and nearly half of patients with severe insomnia can experience symptoms for more than 10 years.[2] Insomnia is primarily characterized by difficulty falling asleep, difficulty maintaining sleep, and early-morning awakening. Patients are dissatisfied with their sleep duration and quality, and insomnia can affect their daytime social functioning.[3] Studies have shown that insomnia has an adverse impact on mood. Early sleep problems are highly predictive of potential emotional and behavioral issues in the future, particularly those problems closely related to depression.[4]

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This strong association naturally raises the question of why these two conditions so frequently coexist. Previous views held that there was a unidirectional causal relationship between depression and insomnia, that is, depression leads to insomnia. However, current research tends to believe that there is a close and complex bidirectional relationship between depression and insomnia: depression can lead to insomnia, and insomnia can also induce and exacerbate depression.[5,6] Clinical and epidemiological evidence indicates that at least 80% of patients with depression report comorbid insomnia symptoms.[7] Depression is present in 31% of individuals suffering from chronic insomnia.[8] A study has shown that the risk of new-onset depression in patients with chronic insomnia is 3 to 4 times higher than that in non-insomnia individuals.[9] Insomnia is recognized as an independent risk factor for the onset of depression, which exacerbates the severity of depressive symptoms and elevates the risk of recurrence.[10] However, despite this established clinical link, the precise neurobiological mechanisms underlying the depression-insomnia comorbidity are not yet fully understood.

In recent years, research on the potential impact of inflammatory cytokines on the development of mental disorders has attracted much attention.[11,12] Clinical studies have shown a significant correlation between inflammatory responses and depressive behaviors.[13] Inflammatory responses activate astrocytes and microglia through pro-inflammatory cytokines released by peripheral immune cells such as lymphocytes, monocytes, and neutrophils, thereby driving neuroinflammation and regulating brain regions that govern emotions.[14] Therefore, some studies suggest that inflammatory responses can regulate neuronal activity and affect the normal function of the hypothalamic-pituitary-adrenal (HPA) axis, thereby triggering depressive symptoms.[15] However, inflammatory cytokines are not only associated with depression but also related to sleep disorders. There is a positive correlation between the increase in inflammatory cytokine levels and sleep disorders. When sleep is insufficient, the expression of inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor(TNF), and interleukin-6 (IL-6) in the body increases.[16] Additionally, abnormal expression of inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 not only affects normal sleep patterns but may also induce or exacerbate depressive symptoms by influencing the normal function of the hypothalamic-pituitary-adrenal (HPA) axis.[13,17] This also indicates that inflammatory cytokines play a pivotal role in the pathological mechanisms underlying the comorbidity of depression and insomnia.

Despite these associations, the specific role of inflammatory responses and cytokines in the comorbidity of depression and chronic insomnia disorders remains incompletely understood. Clarifying this connection is critical, as current treatments have significant limitations. The primary treatment for depression currently primarily relies on the monoamine hypothesis, with commonly used medications including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). While existing medications are effective for some patients, clinical data indicates that a significant portion of patients experience treatment-resistant depression.[18] For chronic insomnia, standard treatments include cognitive-behavioral therapy and pharmacological interventions. The use of hypnotics can temporarily improve sleep but often fails to address the underlying depressive or anxiety-related pathology that causes insomnia.[19] Once the medication is discontinued, sleep problems often recur. These limitations provide an even more compelling reason to explore novel biological targets such as cytokines.

Therefore, this review aims to systematically synthesize and evaluate the current body of evidence regarding the role of inflammatory cytokines in the comorbidity of depression and chronic insomnia. Specifically, this review seeks to: (1) Characterize the differential expression profiles of pro- and anti-inflammatory cytokines in patients with this comorbidity compared to healthy controls or those with a single condition; (2) Elucidate the shared and distinct pathophysiological mechanisms (eg, HPA axis dysfunction, neurotransmitter metabolism, microglial activation) mediated by these cytokines; and (3) Identify current research gaps and propose future directions for biomarker development and targeted therapeutic interventions. For this review, we conducted a broad survey of the literature using the PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) databases. The search focused on studies published between January 2000 and December 2025. Key search terms included combinations of "depression", "major depressive disorder", "insomnia", "sleep disorder", "inflammatory cytokines", "IL-1β", "IL-6", "TNF-α", and "CRP". Priority was given to peer-reviewed original articles, meta-analyses, and high-impact reviews that explored the mechanistic links between inflammation, mood disorders, and sleep. The reference lists of retrieved articles were also manually screened to ensure comprehensive coverage of this interdisciplinary field.

Inflammatory Responses and Inflammatory Cytokines

The inflammatory response is a complex defense mechanism adopted by the human immune system to combat injury or infection and promote tissue repair. When the body is confronted with harmful stimuli or pathogen invasion, the immune system is often activated. It achieves the goal of eliminating pathogens and repairing tissues by releasing inflammatory cytokines and initiating a series of inflammatory cascade reactions, ultimately maintaining the body's homeostatic balance.[20] The inflammatory response is characterized by five typical manifestations: redness, swelling, heat, pain, and dysfunction. Its core process can be summarized into three stages: the initiation stage, the inflammatory cascade amplification stage, and the resolution stage.[21] In the initiation stage, pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) activate pattern recognition receptors (such as Toll like receptors and Nucleotide-binding Oligomerization Domain-like Receptors) to trigger the inflammatory response. During the inflammatory cascade amplification stage, inflammatory mediators (cytokines and chemokines) are released to recruit immune cells to the injury site. In the resolution stage, anti-inflammatory mediators (such as interleukin-10 and lipoxins) initiate the inflammatory resolution program to promote tissue repair.[22] It can be seen that inflammatory mediators and anti-inflammatory mediators play a huge role in the entire inflammatory response process, and the dynamic balance between these two substances is an indispensable part of the physiological inflammatory response. However, inflammation is a double-edged sword: moderate inflammation protects the body, while uncontrolled inflammation leads to diseases. Throughout history, most immunological research in psychiatry has been based on empirical findings and early epidemiological studies. Although the results of epidemiological studies to date have varied significantly, some evidence suggests that immune-inflammatory responses play a role in the pathogenesis of depression and sleep disorders.[23,24] The inflammation hypothesis has been proposed as a potential mechanism linking depression and sleep disorders.

Key inflammatory mediators involved in the inflammatory response include: cytokines (such as TNF-α, IL-1β, IL-6), chemokines (such as interleukin-8, Monocyte chemoattractant protein-1, regulated upon activation normal T cell expressed and secreted), lipid mediators (such as prostaglandin E2, leukotrienes), reactive oxygen species (such as superoxide anions, hydrogen peroxide), and the complement system (such as Complement C3a Protein, Complement C5a Protein, membrane attack complex MAC), etc. Detailed information is provided in Table 1. Among them, cytokines are particularly important. Cytokines are small proteins or polypeptides produced by immune cells (such as lymphocytes, macrophages, etc.) or non-immune cells (such as endothelial cells, fibroblasts, etc)., which can affect cell functions and interactions between cells. Cytokines play a crucial role in intercellular signal transduction. By binding to receptors on the surface of target cells, they regulate various physiological and pathological processes, including immune inflammatory responses, cell proliferation and differentiation. According to different sources, cytokines can be roughly divided into 6 types, namely interleukins (ILs), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferons (IFN), tumor necrosis factors (TNF), growth factors, and chemokines. In addition, cytokines also have two functional subtypes: pro-inflammatory cytokines (IL-1, IL-1β, IL-2, IL-6, IFN-γ, TNF-α, TNF-β, etc.) and anti-inflammatory cytokines (IL-1RA, IL-4, IL-5, IL-10, IL-13, etc)., whose roles lie in promoting and inhibiting immune activation, respectively.[25] Prolonged activity of pro-inflammatory cytokines impairs the synthesis, reuptake, and release of neurotransmitters,[26,27] consequently, the aberrant transmission of emotion-related neurotransmitters mediated by these processes exerts detrimental effects on affective regulation.[28] Numerous studies have shown that the impact of immune-inflammatory responses on depression and sleep is mainly achieved through the release of inflammatory cytokines. Moreover, in many individuals with depression and insomnia, the levels of inflammatory cytokines have been observed to exhibit varying degrees of changes compared to those in normal people.[29]

The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Depressive Disorders

The development of depression involves multiple bodily systems, including the nervous, immune, and endocrine systems. A large body of evidence now links imbalanced inflammatory responses to the occurrence, progression, and treatment of depression.[30,31] Both preclinical and clinical studies indicate that depression is associated with immunoin flammatory abnormalities.[32] These include alterations in peripheral immune cell subsets and function, cytokine and inflammatory mediator levels, intracellular inflammatory signaling pathways, and neuroinflammation.[33,34] Moreover,

Table 1 A Detailed Breakdown of Major Inflammatory Mediators and Their Roles

Category	Representative Mediators	Source	Key Function in Inflammation
Cytokines	ILs	Lymphocytes; Monocytes; Macrophages; Bone marrow	IL-1β:Promotes inflammatory responses, induces fever, and activates endothelial cells. IL-6: Stimulates the production of acute-phase proteins, promotes B cell differentiation, and regulatesTh17 cell polarization. IL-10: Inhibits the secretion of pro-inflammatory cytokines and plays an anti-inflammatory role.
	GM-CSF	T lymphocytes; Fibroblasts; Endothelial cells; Keratinocytes	Promotes the differentiation and maturation of granulocytes and macrophages, enhances thephagocytic function of macrophages, and participates in the regulation of inflammatory responses.
	IFN	Virus-infected cells; T lymphocytes; natural killer cells.	Inhibit viral replication, activate immune cells (such as NK cells and macrophages), and regulate the immune response.
	TNF	Macrophages; T lymphocytes	Induce cell apoptosis, promote inflammatory responses, enhance vascular permeability, and recruit immune cells to the site of inflammation.
	Growth Factors	α-granules of platelets; Activated macrophages; Endothelium and smooth muscles; Certain tumour cells	Promote cell proliferation, differentiation, and tissue repair. For example, TGF-β has both pro-inflammatory and anti-inflammatory effects, and can regulate the balance of the immune system.
	Chemokines	T lymphocytes; Macrophages; B lymphocytes; Endothelial Cells	Mediate the recruitment of immune cells to the site of injury or infection, andpromote the occurrence and development of inflammatory responses.
Lipid mediators	Prostaglandin PGE2; Leukotrienes	Macrophages; Neutrophil granulocyte; Endothelial Cells; epithelial cells	Initiate inflammation, regulate the inflammatory response, promote inflammation resolution, and regulate chronic inflammation.
Reactive Oxygen Species (ROS)	Superoxide anions; H2O2	Mitochondrion; NADPH oxidase; Xanthine oxidase	Destroy invading microorganisms, promote and amplify the inflammatory response, and regulate the inflammatory response.
Complement System	C3a; C5a; MAC	Cleavage of C3; Cleavage of C5; Assembly of C5b, C6, C7, C8, C9	Pathogen clearance and immune defense, activate immune cells, and promote the release of inflammatory mediators.

Abbreviations: ILs, Interleukins; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IFN, Interferons; TNF, Tumor Necrosis Factors.

these factors are linked by complex regulatory processes. Many studies have found that the levels of pro-inflammatory cytokines in patients with depression are significantly elevated, including but not limited to the following pro-inflammatory cytokines: IL-1β, IL-5, IL-6, IL-7, IL-8, granulocyte colony-stimulating factor (G-CSF), IFN-γ, and TNF-α.[35–37] Levels of pro-inflammatory cytokines vary across different populations and conditions. A recent meta-analysis revealed that elderly individuals with more severe depression exhibit significantly greater increases in plasma IL-6, TNF-α, and CRP levels.[38] Studies have also found that plasma levels of TNF-α and IL-6 are higher in patients with treatment-resistant depression, exceeding those in healthy controls and in patients who were previously resistant to SSRIs but are currently in a normal mood state.[39] Additionally, a study evaluating inflammatory markers in depression subtypes has found that compared with non-depressed control groups, patients with atypical depression exhibit higher levels of CRP, IL-6, and TNF-α.[39] This suggests that unique inflammatory profiles exist among subtypes of depression. More compelling evidence is that traditional antidepressants have anti-inflammatory effects and can inhibit the secretion of pro-inflammatory cytokines such as IL-1β, TNFα, IL-6, and IFNγ.[40,41] Antidepressant treatment in patients with depression increases serum IL-10 levels, inhibits the IFNγ/IL-10 ratio, and reduces elevated baseline TNFα levels to those seen in healthy controls.[42] Additionally, studies have shown that treatment with SSRIs for depression significantly reduces IL-6 levels, but does not affect TNFα and IFNγ levels.[43] In summary, pro-inflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ have been shown to trigger clinically significant depressive symptoms, and these cytokines respond to antidepressant therapies. After receiving antidepressant treatment, patients exhibit reduced levels of IL-2, IL-4, IL-10, and IL-6 in their bodies, while IL-22 levels increase following treatment.[44,45] Inflammation and inflammatory cytokines

also participate in the pathophysiological process of depression, and the involved potential mechanisms include: direct effects of pro-inflammatory cytokines on monamine levels, activation of the hypothalamic-pituitary-adrenal (HPA) axis, pathological microglial activation, impaired neuroplasticity, alterations in the composition and diversity of the gut microbiota, and structural and functional brain changes.[43,46]

Pro-inflammatory cytokines can directly act on the brain, influencing the synthesis, transport, and release of monoamine neurotransmitters.[47] Research indicates that pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), which catabolizes tryptophan, thereby reducing the generation of serotonin precursor 5-hydroxytryptophan (5-HTP) and ultimately leading to diminished serotonin levels—a pivotal pathophysiological basis of depression.[48,49] Moreover, pro-inflammatory cytokines inhibit tyrosine hydroxylase (TH) activity, thereby reducing the synthesis of dopamine and norepinephrine.[50] Moreover, pro-inflammatory cytokines inhibit tyrosine hydroxylase (TH) activity, thereby reducing the synthesis of dopamine and norepinephrine.[51] Tetrahydrobiopterin (BH4), an essential cofactor for synthesizing serotonin, dopamine, and norepinephrine, has been shown to be depleted by inflammatory cytokines through oxidative stress pathways.[50,52] Figure 1 shows a more specific process.

Abnormal function of the HPA axis is one of the important pathophysiological mechanisms of depression. Patients with depression typically exhibit hyperactivity of the HPA axis, elevated levels of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), and enhanced glucocorticoid (GC) resistance.[53] Numerous studies have shown that pro-inflammatory cytokines can activate the HPA axis through multiple mechanisms. IL-1β and IL-6 are potent activators of the HPA axis, capable of stimulating the paraventricular nucleus of the hypothalamus to secrete CRH, thereby promoting the secretion of ACTH and GC.[54] TNF-α activates CRH neurons in the paraventricular nucleus of the

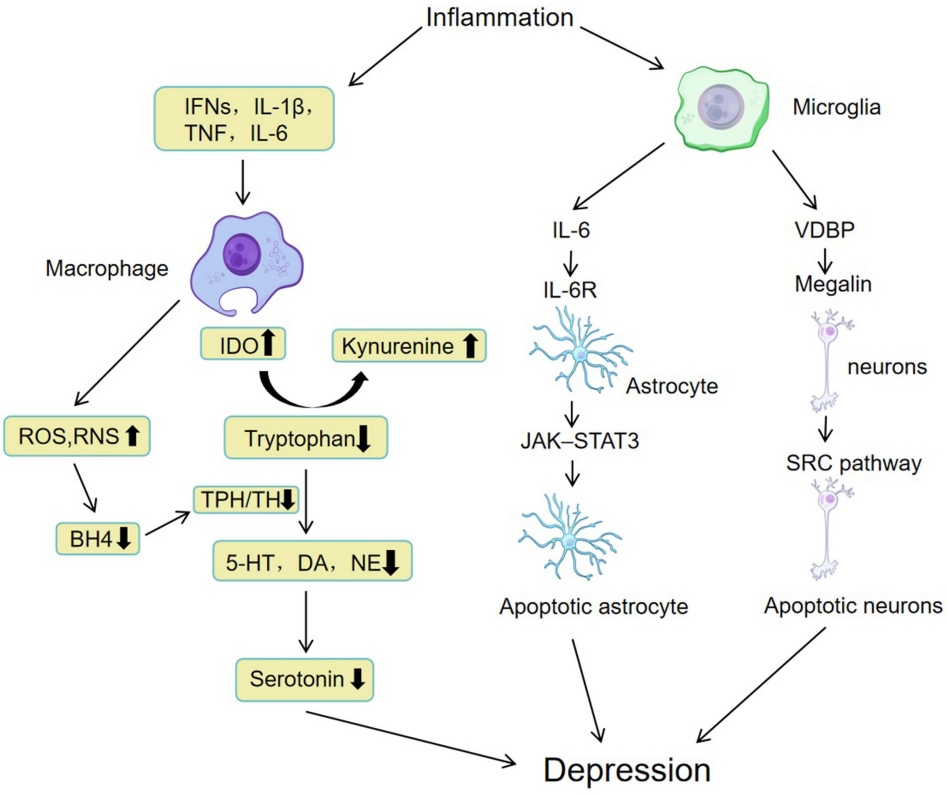

Figure 1 The Relationship Between Pro-inflammatory Cytokines and Depression. The inflammatory response produces inflammatory cytokines that activate macrophages, leading to the upregulation of IDO (indoleamine 2,3-dioxygenase), which increases the metabolism of tryptophan to kynurenine, along with an increase in ROS (reactive oxygen species) and RNS (reactive nitrogen species). Tryptophan levels decrease, resulting in reduced activity of TPH (tryptophan hydroxylase) and TH (tyrosine hydroxylase), ultimately leading to a decline in the neurotransmitters 5-HT (serotonin), DA (dopamine), and NE (norepinephrine), and a drop in serotonin levels.IL-6 released by microglia induces astrocyte apoptosis through the IL-6/IL-6R signaling pathway, resulting in hippocampal neurogenesis disorders and the occurrence of depression. Microglia-derived vitamin D-binding protein (VDBP) binds to the neuronal receptor Megalin, activates the SRC pathway, causes synaptic damage and neuronal apoptosis, and exacerbates depressive symptoms. The upward arrow indicates activation or increased expression, while the downward arrow indicates suppression or decreased expression.

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hypothalamus, leading to increased levels of ACTH and GC, while inhibiting the negative feedback regulation function of the HPA axis.[55] Long-term exposure to inflammatory factors impairs the negative feedback regulation mechanism of the HPA axis, damages the function of glucocorticoid receptors (GR), and leads to persistent hyperactivity of the HPA axis.[56] In addition, studies have shown that excessive glucocorticoid secretion can lead to neuronal atrophy, apoptosis, and reduced neurogenesis in the hippocampus, further inhibiting the negative feedback regulation of the HPA axis.[57] In summary, inflammatory cytokines significantly influence the occurrence and development of depression by activating the HPA axis and interfering with neurotransmitter metabolism. Abnormal HPA axis function further exacerbates neuroplasticity damage and emotional regulation disorders.

A growing body of evidence suggests that pathologically activated microglia may serve as a trigger for depression.[58] Microglia play a crucial role in maintaining internal homeostasis and immune defense.[59] They engage in phagocytosis and, when activated by cytokines and other stimuli, exhibit a spectrum of activation states. These are classically categorized into M1 ("classically activated") and M2 ("alternatively activated") types,[60,61] which are generally regarded as pro-inflammatory and anti-inflammatory phenotypes, respectively. Figure 2 shows us this very well. M1 microglia secrete pro-inflammatory cytokines, including reactive oxygen species (ROS), reactive nitrogen species (RNS), TNF-α, IL-1β, IL-6, and IL-12. These inflammatory mediators have been shown to induce neuronal damage and depressive-like behaviors through associated inflammatory signaling pathways.[62,63] Studies have shown that IL-6 released by microglia induces astrocyte apoptosis through the IL-6/IL-6R signaling pathway, leading to hippocampal neurogenesis disorders and depressive-like behaviors.[64] Additionally, vitamin D-binding protein (VDBP) derived from microglia binds to the neuronal receptor Megalin, activating the SRC pathway, causing synaptic damage and neuronal apoptosis, and exacerbating depressive phenotypes.[65] This is also shown in. In contrast, M2-type microglia secrete anti-inflammatory cytokines such as transforming growth factor-β (TGF-β), brain-derived neurotrophic factor (BDNF), and interleukin-10 (IL-10).[66] When microglia are activated by low-dose lipopolysaccharide (LPS), the released adenosine triphosphate (ATP) triggers the synthesis of brain-derived neurotrophic factor (BDNF) through the P2Y1 receptor (P2Y1R) of astrocytes, promoting hippocampal neurogenesis and rapidly relieving depressive symptoms. This mechanism suggests that microglial activation under specific conditions may have antidepressant effects.[58,67]

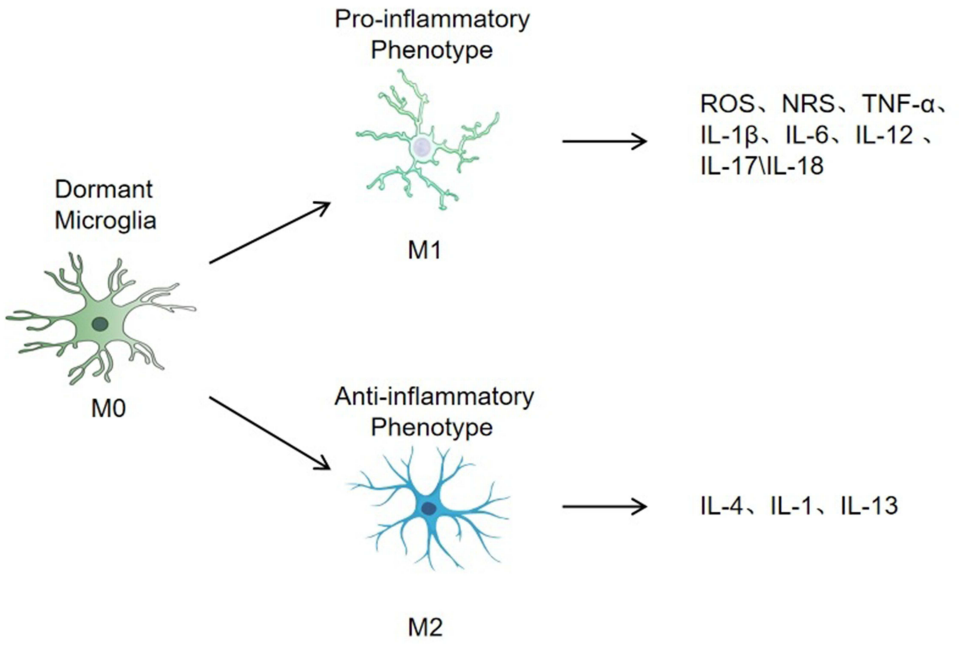

Figure 2 Microglia's two primary activation states. Upon inflammatory stimulation, microglia differentiate into either the M1 ("classically activated") or M2 ("alternatively activated") phenotype. M1 microglia secrete pro-inflammatory mediators, including reactive oxygen species (ROS), nitrogen-reactive species (NRS), TNF-α, IL-1β, IL-6, and IL-12, whereas M2 microglia release anti-inflammatory factors such as TGF-β, brain-derived neurotrophic factor (BDNF), and IL-10.

The gut-brain axis is a two-way neural and humoral signaling that plays a crucial role in connecting mental disorders and intestinal health, and mediates their interrelationship.[68] The intestinal microbiota is an important component of the human immune system. Disorders of the intestinal flora can lead to increased expression of intestinal mucosal inflammatory factors such as TLR-4, NF-κB, and NOD-like receptor thermal protein domain associated protein 3 (NLRP3). The upregulation of these inflammatory factors further damages the intestinal mucosal barrier, increasing intestinal mucosal permeability.[69,70] At this point, bacteria and their metabolites that were originally blocked by the intestinal barrier enter the circulatory system, thereby activating the systemic immune response. Pro-inflammatory cytokines in the blood enter the brain and damage the blood-brain barrier, leading to an increase in the content of pro-inflammatory cytokines such as IL-6 and IL-1β in the brain, and activating NLRP3. This immune process may be the cause of depression.[71] A recent review has indicated that patients with major depressive disorder (MDD) exhibit a distinct gut microbiota profile compared to healthy individuals, characterized by an increase in pro-inflammatory bacteria (eg Eggerthella) and a decrease in anti-inflammatory bacteria (eg Coprococcus and Paracoccus).[72] Additionally, short-chain fatty acids (SCFAs) metabolized by gut microbiota, such as acetic acid, propionic acid, and butyric acid, exert significant regulatory effects on the immune system.[73] Multiple meta-analyses and systematic reviews have reported a relative decrease in the abundance of specific microbial taxa, such as Faecalibacterium and Coprococcus, among individuals with depression, and have linked these findings to differences in the microbiome and inflammatory markers within the depressed population.[74] A review on sleep disturbances also reported a negative correlation between Faecalibacterium and the severity of sleep disturbances.[75]

The genetic polymorphism of pro-inflammatory cytokines is also associated with the occurrence of depression. Studies have found that depressive-like behaviors are reduced in IL-6 gene-knockout mice, accompanied by increased expression of serotonin transporter. This suggests that high expression of IL-6 may promote depression by inhibiting neurotransmitter function.[68] The single nucleotide polymorphism (SNP) in the promoter region of the TNF-α gene can affect its transcriptional activity. Individuals carrying the TNF-α high-expression genotype are more prone to depressive symptoms under chronic inflammatory conditions, which may be related to TNF-α inhibiting neuroplasticity through the NF-κB pathway.[76] The genetic polymorphism of CRP may indirectly increase the risk of depression by affecting the systemic inflammatory state. For example, carriers of the rs1205 G>A polymorphism may be more susceptible to external stress due to lower CRP levels, thereby exhibiting a higher risk of depression.[77] The polymorphism of NLRP1 gene can enhance the secretion of IL-1β, activate the neuroinflammatory pathway, and disrupt hippocampal neurogenesis, thereby increasing the risk of depression.[78] These findings collectively reveal the association between pro-inflammatory cytokines and the pathogenesis of depression, providing a new biological perspective for the diagnosis and treatment of depression.

The Role of Pro-Inflammatory Cytokines in Insomnia Disorder

It is well known that naturally occurring sleep is a physiological process mediated by the central nervous system, which regulates the immune system by altering physiological systems that affect immune cell distribution and inflammatory cytokine production. Sleep helps the human body recover from infections or other disease states, and increased sleep during infections has a protective effect. One function of sleep is to support host defense. Therefore, when sleep is disturbed, the effector systems that regulate the immune system change, leading to abnormal increases in inflammatory responses.[79] Pro-inflammatory cytokines produced by inflammatory responses play a significant role in insomnia disorder. Elevated expressions of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α have been observed in insomnia patients, which may be associated with the pathophysiological mechanisms of insomnia disorder. The increase in these pro-inflammatory cytokines may exacerbate insomnia symptoms, while insomnia itself further aggravates the expression of pro-inflammatory cytokines by activating the inflammatory response, thus forming a vicious cycle.[80] The role of pro-inflammatory cytokines in insomnia disorder is multifaceted, encompassing both direct effects on sleep architecture/quality and regulation of inflammatory responses. Studies indicate that pro-inflammatory cytokines exhibit bidirectional effects in insomnia: low doses of cytokines like IL-1β and TNF-α promote sleep, while high doses suppress it.[81] This bidirectional effect may be related to the dosage of pro-inflammatory factors and their mechanisms of action. Additionally, animal studies have found that three consecutive days of sleep disturbance can induce depression-like

behaviors in rats, disrupt the integrity of the blood-brain barrier (BBB), promote microglial activation, and increase the levels of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α.[82] Studies have also demonstrated that insomnia treatment can effectively reduce levels of pro-inflammatory cytokines IL-6 and TNF-α, thereby improving sleep quality.[80] In summary, the involvement of pro-inflammatory cytokines in the pathophysiology of insomnia is multifaceted, encompassing alterations in sleep architecture, activation of the NF-κB pathway, hyperactivation of the HPA axis, and upregulated expression of the NLRP3 inflammasome, among others. Research indicates that elevated expression of pro-inflammatory cytokines is closely associated with alterations in sleep architecture. Specifically, nocturnal monocyte-derived IL-6 production correlates with reduced sleep-wake transitions and prolonged REM sleep duration. Higher IL-6 production levels correspond to shorter slow-wave sleep (SWS) and extended rapid eye movement (REM) sleep periods.[83] However, pro-inflammatory cytokines not only affect sleep architecture but are also closely associated with insomnia. Studies have found that the serum IL-8 levels in patients with chronic insomnia (insomnia group) are significantly higher than those in patients without insomnia (control group). Additionally, the sleep latency, arousal index, and time awake after sleep in the insomnia group are notably higher than those in the control group, while the total sleep time, sleep efficiency, and the proportion of stage 3 non-rapid eye movement sleep (N-3) are significantly lower than those in the control group.[84] This indicates that pro-inflammatory cytokines may play a significant role in the pathogenesis of chronic insomnia.

Insomnia activates the NF-κB pathway through multiple pathophysiological mechanisms, triggering inflammatory responses. NF-κB, a key transcription factor, induces various pro-inflammatory genes, like those coding for cytokines and chemokines, and regulates inflammasomes. During insomnia disorders, signals causing NF-κB activation involve heightened adenosine levels, oxidative stress, metabolic changes, abnormal clock protein expression, and increased sympathetic nerve activity.[85] Neural fibers from the sympathetic nervous system release the neurotransmitter norepinephrine into primary and secondary lymphoid organs. Adrenaline is then stimulated to release stored adrenaline into the systemic circulation. Subsequently, the activation of NF-κB occurs through the stimulation of white blood cell adrenergic receptors. This process leads to the induction of various pro-inflammatory genes and an increase in the production of pro-inflammatory cytokines.[16] These cytokines interact with the brain through humoral, neural, and cellular pathways, forming a brain - cytokine network. The bidirectional communication between the brain and periphery allows the brain to modulate inflammatory activities. In turn, these activities affect neural processes in the brain and alter sleep.[86] Thus, insomnia disorders can exacerbate inflammatory responses by activating the NF-κB pathway, and the increased pro-inflammatory cytokines can, in turn, worsen insomnia symptoms.

Sleep affects two major effector systems: the hypothalamic - pituitary - adrenal (HPA) axis and the sympathetic nervous system (SNS), both of which help regulate immune responses. During sleep, blood levels of cortisol, epinephrine, and norepinephrine decline, while levels of growth - promoting substances (such as growth hormone, prolactin, and the pineal hormone melatonin) rise.[87] Chronic insomnia can significantly activate the HPA axis. This overactivation promotes the release of pro-inflammatory cytokines like IL-6 and TNF-α. These cytokines not only disrupt normal sleep rhythms but may also further activate the HPA axis via a positive feedback loop, leading to increased cortisol levels.[88] Cortisol secretion follows a clear circadian rhythm. Abnormalities in this secretion can disrupt circadian rhythms, potentially leading to or worsening insomnia.[89] Also, heightened cortisol can suppress neurotrophic factor expression and reduce hippocampal neurogenesis, worsening sleep disorders. Overall, a vicious cycle exists between insomnia and HPA axis overactivation. Insomnia causes sustained HPA axis activation, and this overactivation, in turn, exacerbates insomnia symptoms. Details can be found in Figure 3.

Innate immune NLRP3 inflammasome, a multi - protein complex of NLRP3, caspase-1 and apoptosis - associated speck - like protein containing a CARD, is important in insomnia. In an animal experiment, NLRP3 inflammasome-knockout mice had less NREM sleep, while after LPS treatment, mice showed a significant increase in NREM sleep. This shows NLRP3 inflammasome is key in sleep regulation.[90] Some studies indicate that the NLRP3 inflammasome can significantly promote microglia activation. This leads to increased NLRP3 inflammasome expression and higher levels of pro-inflammatory cytokines like IL-1β and IL-18, thereby triggering neuroinflammatory responses.[91] This inflammatory response may exacerbate insomnia symptoms by impairing neuronal function and synaptic plasticity. Some studies have shown that, in individuals with insomnia, the upregulation of NLRP3 inflammasome-related proteins is positively correlated with short sleep duration,

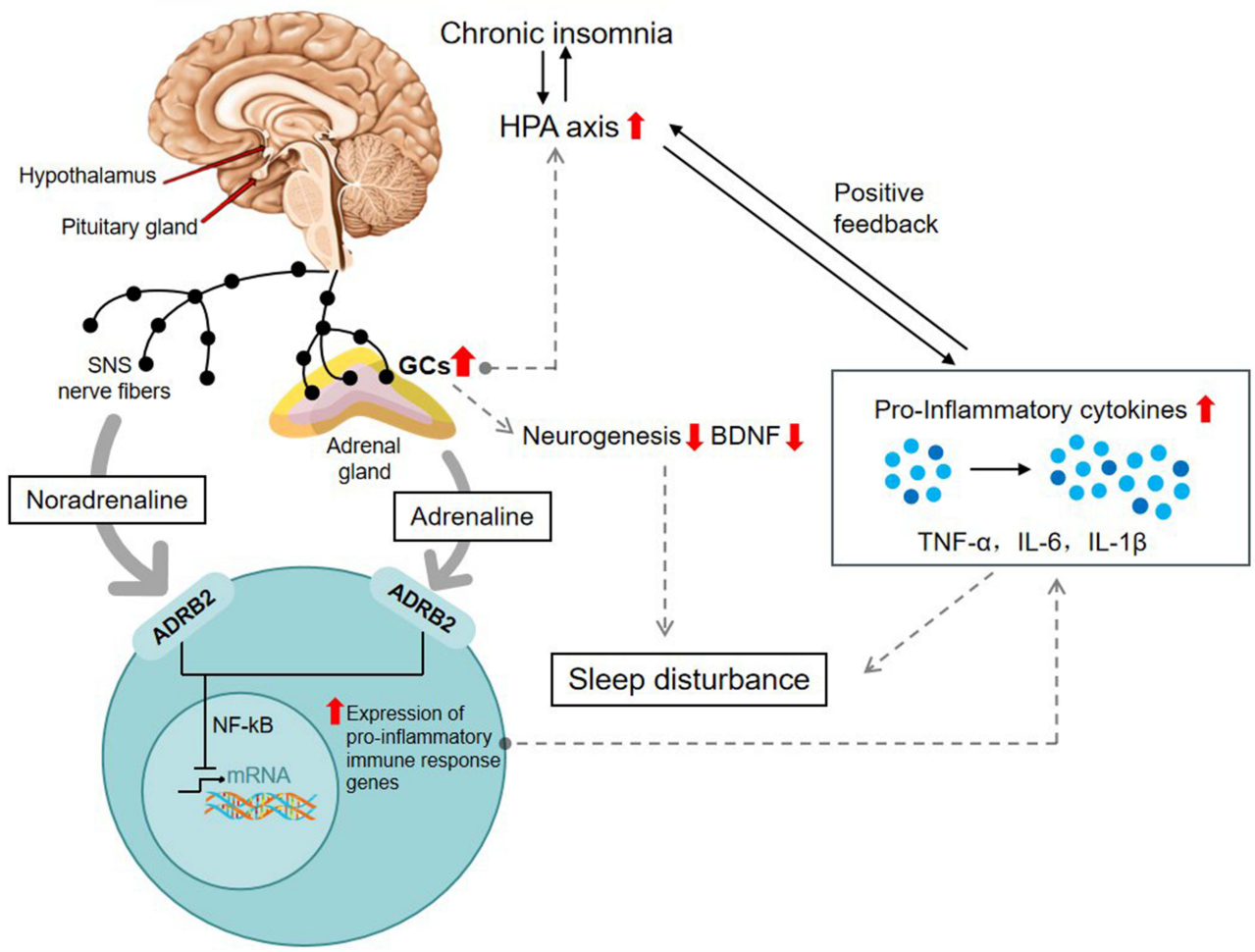

Figure 3 The role of the HPA axis and SNS in regulating inflammatory cytokines, as well as their impact on sleep. Chronic insomnia can lead to significant activation of the HPA axis, and the overactivation of the HPA axis promotes the release of pro-inflammatory cytokines such as IL-6 and TNF-α. These cytokines can further activate the HPA axis through a positive feedback mechanism, resulting in elevated cortisol levels. Elevated cortisol levels can not only inhibit the expression of nerve growth factors but also reduce neurogenesis in the hippocampus, further exacerbating sleep disorders. The upward arrow indicates activation or increased expression, while the downward arrow indicates suppression or decreased expression.

reduced slow - wave sleep, and sleep fragmentation.[92] Furthermore, NLRP3 inflammasome activation is also linked to depression, anxiety, and cognitive dysfunction. One study revealed that chronic stress and sleep deprivation can activate the NLRP3 inflammasome, leading to increased IL - 1β levels and triggering depressive-like behaviors.[93]

Pro-Inflammatory Cytokines and the Comorbidity of Depression and Insomnia

Recent clinical studies have highlighted the significance of pro-inflammatory cytokines in the pathophysiology of depression and insomnia. Elevated serum levels of cytokines like IL-1β, TNF-α, and IL-6 can disrupt normal sleep patterns, leading to insomnia. Moreover, these cytokines can interfere with the HPA axis, potentially inducing or exacerbating depressive symptoms.[17] In summary, the body's inflammatory status is crucial for maintaining normal sleep. Immune - cell - derived signals induce sleep and activate cytokines, which may impact depression. Thus, insomnia - induced inflammatory marker increases could serve as early diagnostic warning signals. They indicate a potential risk of depression recurrence, progression, and heightened suicide probability.[79] Additional animal research has measured pro-inflammatory cytokines in rats' brain tissue and peripheral blood under chronic stress. The significant increase in these cytokines aligns with markedly poorer sleep quality and higher depression - related behavioral scores. This indicates that pro-inflammatory cytokines might be key mediators in depression comorbid with insomnia.[94,95] Some studies have used anti-inflammatory treatments to reduce inflammation with drugs that have anti-inflammatory effects. The results have shown significant relief of depressive symptoms

and sleep disorders.[96] This shows that inflammatory cytokines are key mediators in pathophysiological processes and offers new therapeutic targets for treating depression and insomnia. However, some studies have failed to reveal significant increases in cytokines. Potential reasons for this may include differences in patient populations (eg, age, severity, comorbidities), variations in medication use, or differences in cytokine measurement methodologies (eg, plasma vs serum, single-time point vs multiple-time points). Using high - throughput proteomics and multi-omics analysis to explore the roles and mechanisms of inflammatory cytokines in sleep disorders and depression can clarify their specific functions in this complex pathology.[97,98] Such research can offer scientific evidence and theoretical guidance for developing more precise biomarkers and new therapeutic strategies for insomnia and depression.

IL-1β and Depression Comorbidity Chronic Insomnia

IL-1β is a key pro-inflammatory cytokine linked to depression and chronic insomnia. It strongly stimulates the HPA axis, increasing glucocorticoid levels and inducing depressive - like behaviors.[99] IL-1β suppresses BDNF expression and signaling, reducing hippocampal neurogenesis, decreasing neuron numbers and plasticity, and triggering depressive-like behaviors.[100] We can see in the Figure 4. IL-1β can regulate the levels of neurotransmitters like serotonin, norepinephrine, and dopamine, thereby influencing mood and cognitive function.[101] Some research shows that there's a significant link between IL-1β gene polymorphisms and depression risk and treatment response, indicating that genetic factors play an important role in the relationship between IL-1β and depression.[102] Chronic insomnia is a common comorbidity of

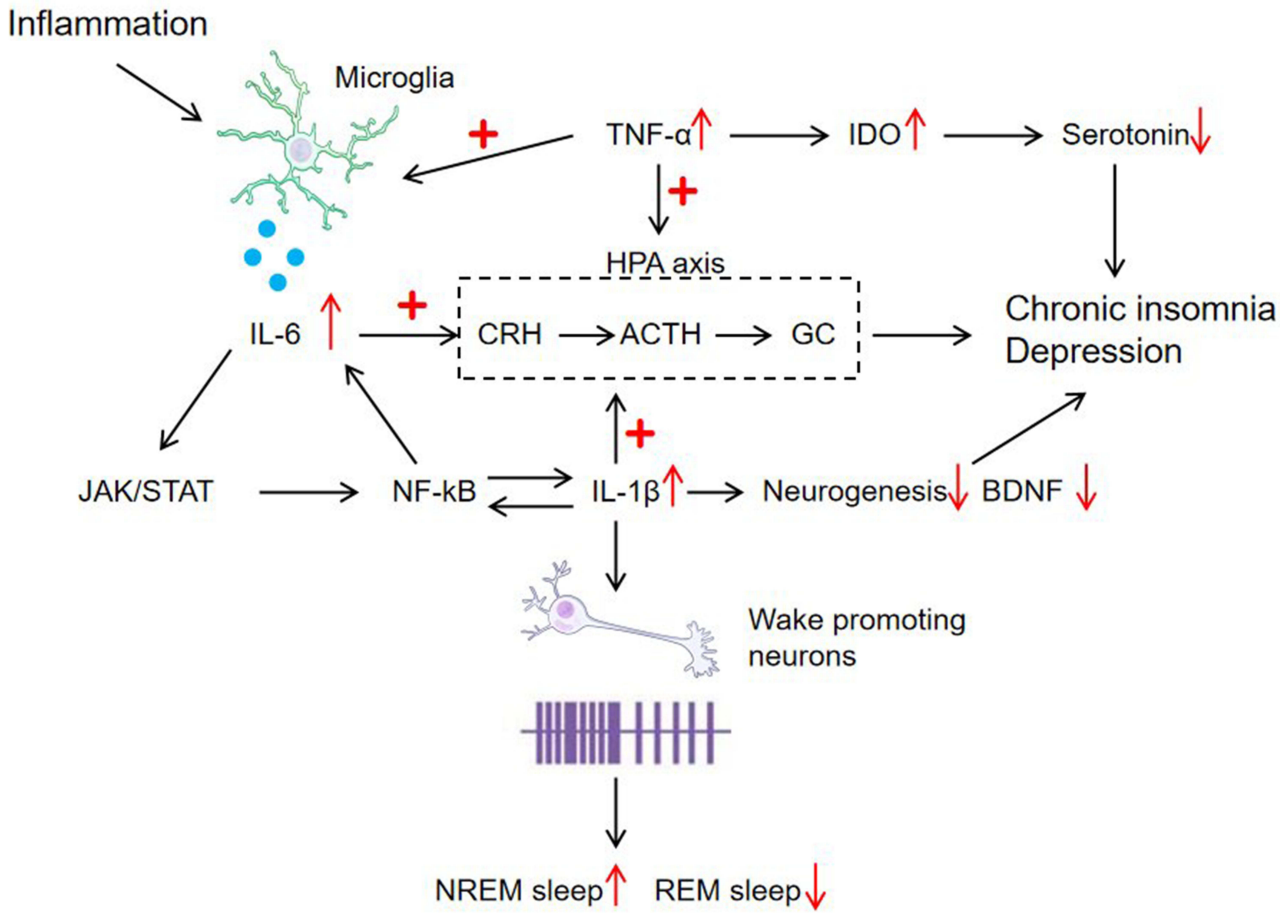

Figure 4 The relationship between IL-6, IL-1β, TNF-α and depression comorbid with chronic insomnia. IL-6 can activate the NF-κB signaling pathway to amplify the inflammatory response, thereby altering neurotransmitter expression and disrupting hypothalamic–pituitary–adrenal (HPA) axis function. IL-6, IL-1β, and TNF-α all stimulate the HPA axis, leading to abnormal cortisol levels that contribute to chronic insomnia and depression. IL-1β suppresses brain-derived neurotrophic factor (BDNF) expression and signaling, reducing hippocampal neurogenesis and precipitating depressive-like behaviors. In addition, IL-1β increases NREM sleep while decreasing REM sleep duration. TNF-α induces indoleamine-2,3-dioxygenase (IDO) expression, resulting in reduced serotonin availability and subsequent disturbances in mood and sleep. The upward arrow indicates activation or increased expression, while the downward arrow indicates suppression or decreased expression.

depression. Many studies have explored the role of IL-1β in this comorbidity. They indicate that elevated IL-1β levels are positively correlated with chronic insomnia severity. In perimenopausal non - organic insomnia (PNSD) patients, the observation group has higher IL-1β levels than the control group. IL-1β levels are positively correlated with PSQI and liver qi stagnation scores. So, higher IL-1β expression is linked to more severe liver qi stagnation and worse insomnia.[103] Elevated IL-1β levels are associated with altered sleep architecture. Specifically, IL-1β increases NREM sleep while decreasing REM sleep time. This effect may stem from IL-1β's inhibition of serotonergic neurons in the dorsal raphe nucleus (DRN) of the hypothalamus.[104] Moreover, IL-1β can disrupt the normal sleep - wake cycle and exacerbate insomnia by activating the NF-κB transcription factor, which in turn affects the expression of circadian rhythm - related genes.[105] A clinical study on elderly patients with insomnia and anxiety - depression found that joint treatment with Bailemian capsules and trazodone significantly reduced serum IL-1β and IL-17 levels and improved sleep quality and depressive symptoms.[106] IL-1β plays a crucial role in the development of depression and chronic insomnia. It induces depressive behaviors by activating the HPA axis and suppressing neurogenesis. It also worsens insomnia by altering sleep architecture and impairing cognitive function. Importantly, elevated IL-1β levels are closely tied to the severity of depression and chronic insomnia. Antidepressant treatments and interventions can reduce IL-1β levels and improve symptoms.

Tumor Necrosis Factor (TNF)-α and the Comorbidity of Depression and Insomnia

There are complex interactions between TNF-α and depression comorbid with chronic insomnia. As a pro-inflammatory cytokine, TNF-α has been widely studied in the CNS. Its levels are significantly increased in patients with depression comorbid with chronic insomnia, and are closely related to the severity of depressive symptoms and the duration of insomnia. Animal and clinical studies have shown that TNF-α can induce depressive-like behaviors, such as reduced social behavior, decreased motor ability, loss of appetite, and sleep disorders.[76] Studies have shown that in patients with depression, plasma TNF-α levels are significantly elevated. Moreover, TNF-α levels can be reduced to near-normal levels in healthy controls following antidepressant treatment.[42] This indicates TNF-α plays a key role in depression and its level changes may relate to antidepressant treatment responses. Research by Wu Zixing et al found that in severe insomnia groups, serum TNF-α levels are higher than in mild and moderate groups, and are positively correlated with sleep quality scores like the PSQI.[107] This shows that as insomnia worsens, TNF-α levels rise and correlate with its duration and severity. In patients with depression and insomnia, elevated TNF-α levels may lead to comorbidity through various mechanisms. First, TNF-α can activate the HPA axis, increasing cortisol levels and affecting emotion regulation and sleep.[76] Second, TNF-α can induce IDO expression, reducing serotonin and affecting mood and sleep.[108] We drew these in the. Additionally, under neuroinflammatory conditions, high expression of TNF-α can lead to the activation of microglia and astrocytes, induce the production of reactive oxygen species (ROS), and consequently damage neurons and synapses, resulting in cognitive dysfunction and sleep disturbances.[109] Given TNF-α's significant role in depression and insomnia, TNF-α antagonists are promising therapeutic targets for this comorbidity. Animal experiments and clinical studies show that these antagonists can alleviate depressive symptoms and improve sleep quality. A 2024 review indicates that TNF-α antagonists such as infliximab, adalimumab, and golimumab have demonstrated varying degrees of effectiveness in improving depressive symptoms in clinical trials, particularly in patients with elevated inflammatory markers.[110] A clinical trial on 36 patients with treatment-resistant depression showed that TNF-α antagonists reduced nighttime spontaneous awakenings, improved sleep continuity, and increased deep sleep stage time.[111]

IL-6 and the Comorbidity of Depression and Chronic Insomnia

IL-6 is a pro-inflammatory cytokine that plays a significant role in depression comorbid with chronic insomnia. Elevated IL-6 levels can exacerbate depressive symptoms, such as low mood and reduced interest, and also disrupt sleep structure, leading to sleep disorders like difficulty falling asleep, early awakening, and sleep interruptions. A study found that serum IL-6 levels in patients with depression and insomnia were significantly higher than in healthy controls, and were positively correlated with the severity of depression and chronic insomnia.[112] Even in the absence of comorbid

depression, patients with chronic insomnia exhibit elevated IL-6 levels. Research by REN et al indicates that the plasma IL-6 levels in chronic insomnia patients are elevated compared to the normal population.[113] Additionally, elevated IL-6 levels may be associated with circadian rhythm disturbances in individuals with chronic insomnia. When IL-6 levels are elevated during the daytime, this may contribute to feelings of daytime fatigue and tiredness.[114] The pro-inflammatory effects of IL-6 may contribute to the pathophysiology of depression and chronic insomnia through multiple mechanisms. Studies show that IL-6 can activate the NF-κB signaling pathway, exacerbate inflammation, and affect neurotransmitter expression and HPA axis function.[115] These can be manifested in the. Moreover, IL-6 may influence the HPA axis, leading to abnormal cortisol levels, which can disrupt sleep and affect mood.[116] These shared pathological mechanisms may explain why patients with depression and chronic insomnia are more prone to sleep disorders and depressive symptoms. In animal experiments, increased peripheral IL-6 has been shown to induce depressive-like behaviors, whereas inhibiting IL-6 can reduce such behaviors.[117] Another study found that IL-6 levels are positively correlated with scores of depression symptoms, and this effect remains statistically significant even after adjusting for multiple covariates.[118] In addition, elevated IL-6 levels may be associated with treatment response. Patients with high IL-6 levels may have a poor response to SSRI antidepressants.[112] Reducing serum IL-6 may alleviate depression and chronic insomnia, serving a preventive and early therapeutic role. IL-6 could be a valuable biomarker and treatment target for depression and chronic insomnia, offering promise for personalized medicine.

IL-8 and the Comorbidity of Depression and Chronic Insomnia

IL-8, a pro-inflammatory cytokine produced mainly by neutrophils and microglia, is involved in immune responses and inflammation, with its expression increasing rapidly during inflammation. Given the bidirectional relationship between depression and chronic insomnia, IL-8 may act as a mediator. Studies indicate that IL-8 levels are significantly elevated in patients with Major Depressive Disorder (MDD), and there might be gender differences in its role.[119,120] In a study of 108 patients with treatment-resistant depression, it was found that in females, IL-8 levels were significantly negatively correlated with the total Hamilton Depression Scale (HAM-D) scores (standardized $\beta = -0.41$, $p = 0.004$), while no such relationship was observed in males (standardized $\beta = 0.02$, $p = 0.91$).[120] Additionally, changes in IL-8 levels have been associated with the response to antidepressant treatment. Patients with higher baseline plasma IL-8 levels or those who experienced an increase in IL-8 during treatment were more likely to show improvement in their depressive symptoms.[121] Treatment responses may also be gender - specific. In females, baseline plasma IL-8 levels and IL-8 changes related to electroconvulsive therapy are associated with depression improvement, while no such relationship exists in males.[121] Chronic insomnia, as a chronic stress process, can lead to immune dysfunction and trigger neuroinflammation. A study found that patients with chronic insomnia often have elevated levels of pro-inflammatory cytokines like IL-8. Moreover, nocturnal awakenings in these patients are linked to heightened sympathetic nervous system activation, which may initiate inflammation via NF-κB signaling.[122] IL-8 may play a significant role in the development of depression and chronic insomnia, especially in the context of inflammation and immune dysfunction. Given its involvement, IL-8 could serve as a potential therapeutic target and biomarker for these conditions. Research has linked elevated IL-8 levels to the severity of depressive symptoms and treatment responses, suggesting that modulating IL-8 levels might help improve symptoms of depression and chronic insomnia.[123]

CRP and the Comorbidity of Depression and Chronic Insomnia

CRP is a classic marker of inflammation, often elevated during infections or inflammatory responses. Recent studies indicate that CRP is also associated with several non-infectious conditions, including chronic insomnia, anxiety, and depression.[122] The relationship between CRP and depression has been widely studied. Many studies have found that CRP levels are significantly elevated in patients with depression and that this increase is correlated with the severity of depressive symptoms.[124] A cross-sectional study of 6,126 Czech residents showed that subjects with depressive symptoms had CRP levels 0.43 mg/L higher than those without, and this link remained even in subjects free of other chronic diseases.[125] There is a significant comorbidity between chronic insomnia and depression, and CRP may play a mediating or moderating role. A study found that in chronic insomnia patients with anxiety and depression, CRP levels were significantly higher than in the normal group. Also, CRP levels are related to depressive symptoms (like fatigue,

appetite changes, and sleep problems) and anxiety symptoms (such as irritability and worry about control).[126] CRP may be involved in the pathological process of depression and chronic insomnia through multiple mechanisms. First, elevated CRP levels may be linked to increased activation of the sympathetic nervous system, affecting sleep quality. Second, CRP may influence central neurotransmitter systems, such as dopamine, serotonin, and norepinephrine, whose imbalance is a core feature of depression. Additionally, CRP may worsen insomnia symptoms by affecting circadian rhythms and sleep architecture.[126] In summary, there are complex relationships among CRP, depression, and chronic insomnia. CRP is related to both conditions and may influence their pathological processes through inflammatory mechanisms. Although some studies have explored these relationships, the exact nature and mechanisms are still unclear. However, due to its high sensitivity to inflammatory responses, CRP has been suggested as an early biomarker for depression.[127] Therefore, in clinical practice, the detection of CRP should be emphasized, and combined with other assessment tools, individualized treatment plans should be formulated. Future studies should further explore the mechanism of action of CRP in depression comorbid with chronic insomnia and verify its potential as a biomarker.

Anti-Inflammatory Cytokines and Depression Comorbid Insomnia

In patients with depression comorbid with chronic insomnia disorder, serum levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are significantly elevated, while levels of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 are relatively decreased. IL-10 is a classic anti-inflammatory cytokine that can inhibit the expression of pro-inflammatory factors such as IL-1, IL-6, and TNF-α, thereby exerting anti-inflammatory effects. Patients with depression often exhibit abnormalities in IL-10 levels. A study has found that serum IL-10 levels in patients with major depressive disorder (MDD) are significantly lower than those in healthy controls.[128] Antidepressant medications can reverse immune system imbalances, inhibit immune activation, and exert their effects by increasing IL-10 levels. Studies have found that antidepressants such as clomipramine, sertraline, and trazodone can significantly inhibit the secretion of IFN-γ and stimulate the secretion of IL-10, thereby producing a negative regulatory effect on the immune system.[129] This further supports the potential role of IL-10 in antidepressant therapy. Anti-inflammatory cytokines may inhibit the production and action of pro-inflammatory cytokines through multiple mechanisms. In patients with depression, reduced IL-10 levels may lead to an imbalance in the inflammatory response, thereby exacerbating depressive symptoms. Long-term chronic insomnia may cause dysfunction of the immune system, affecting IL-10 secretion and further worsening depressive symptoms. Meanwhile, decreased IL-10 levels may further aggravate insomnia symptoms, forming a vicious cycle. IL-13 is also an anti-inflammatory cytokine. As a pleiotropic TH2 cytokine produced by T lymphocytes, monocytes, or macrophages, it exhibits anti-inflammatory effects by inhibiting lipopolysaccharide (LPS)- and TNF-induced production of multiple inflammatory mediators (such as IL-1, IL-6, TNF-α, ICAM-1, IL-2, etc.) in monocytes and macrophages. It also downregulates the expression of pro-inflammatory factors, including IL-1, IL-8, and TNF-α.[130] Studies have shown that levels of IL-4, IL-5, IL-10, IL-13, and TGF-β1 are lower in patients with depression comorbid with chronic insomnia.[131] Although IL-13 itself is not a direct regulator of sleep, it may indirectly affect sleep quality by influencing the immune system and inflammatory responses. Some studies have also found that the expression of IL-13 may differ by gender: IL-4 is elevated in female patients with depression, while IL-13 is elevated in male patients with depression.[132] This suggests that the role of IL-13 may vary between genders, and future studies are needed to further explore this gender difference. Current research has found that Dupilumab, a monoclonal antibody targeting the IL-4/IL-13 signaling pathway, can significantly improve sleep quality in patients with CRSwNP (chronic rhinosinusitis with nasal polyps).[133] This indicates that the IL-13 signaling pathway may emerge as a novel therapeutic target for insomnia. IL-37, a newly discovered member of the IL-1 family, may improve depressive symptoms by inhibiting inflammatory responses and excessive immune activation as an anti-inflammatory factor. It can also ameliorate sleep and emotional states by regulating the function of the hypothalamic-pituitary-adrenal (HPA) axis to reduce excessive cortisol secretion. Specifically, IL-37 inhibits the activation of NLRP3 inflammasomes, thereby reducing the secretion of IL-1β and alleviating inflammatory responses and tissue damage. This mechanism has been validated in an experimental colitis model, where IL-37 transgenic mice exhibited milder inflammatory responses and less tissue damage.[134]

Prospects and Conclusions

The comorbidity of depression and chronic insomnia is highly prevalent in clinical practice. The underlying cause lies in the highly overlapping molecular and biological pathways between the two, which may trigger comorbidity through similar pathological changes. Currently, inflammatory cytokines are being widely studied as important etiological factors for depression comorbid with chronic insomnia. Most studies have shown that inflammatory cytokines play a key role in the pathogenesis of depression comorbid with insomnia, with their abnormal expression observed in both serum and cerebrospinal fluid of depressed patients. Further analysis indicates that these inflammatory factors not only change under pathological conditions but also closely correlate with patients' sleep patterns, suggesting that inflammatory cytokines can serve as biological markers linking sleep disorders and depression. However, there are challenges and variations in methodology within this field, such as different methods for detecting cytokines, confounding variables like BMI or medications, and certain studies with relatively small sample sizes. This paper reviews the research progress of inflammatory cytokines in depression, insomnia disorder, and depression comorbid with insomnia disorder, systematically expounds the inflammatory characteristics and clinical significance of patients with depression comorbid with chronic insomnia. It aims to revisit the evidence of the association between inflammatory cytokines and depression comorbid with chronic insomnia, discuss the potential pathophysiological mechanisms explaining this association, and provide new methods and ideas for the treatment of depression comorbid with chronic insomnia. However, as a narrative review, we do not provide quantitative synthesis or formal evidence tables, this is a weakness in our research. We encourage readers to consult the cited meta-analyses for pooled estimates of cytokine levels.

It is now known that elevated levels of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6) are closely associated with depressive and insomnia symptoms, and may lead to memory disorders and emotional disturbances by affecting neuroplasticity, neurotransmitter systems, and cognitive functions. The reduction of anti-inflammatory cytokines may further exacerbate these symptoms. Additionally, there is a bidirectional relationship between depression and insomnia, forming a vicious cycle, and the elevation of pro-inflammatory cytokines may exacerbate this cycle by influencing the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Therefore, pro-inflammatory cytokines may become important targets for the treatment of depression comorbid with insomnia. Follow-up studies should not only focus on the interaction between inflammation and sleep disorders but also on how to apply such biomarkers for early prediction and treatment.

While the evidence summarized in this review supports a role for inflammatory cytokines in the comorbidity of depression and chronic insomnia, several methodological limitations must be considered when interpreting these findings. First, heterogeneity in cytokine measurement—including differences in sample type (plasma, serum, cerebrospinal fluid), timing of collection (diurnal variation), and assay sensitivity—complicates cross-study comparisons and may contribute to inconsistent findings. Second, many studies fail to adequately control for potential confounders such as body mass index, smoking, alcohol use, physical activity, and medication status (particularly antidepressant and hypnotic use), all of which can influence circulating cytokine levels. Third, the predominance of cross-sectional designs precludes causal inference; it remains unclear whether inflammation precedes the onset of depression and insomnia or is a consequence of these conditions. Fourth, sample sizes in many studies are modest, increasing the risk of type II error and limiting the generalizability of findings. Fifth, publication bias may lead to overrepresentation of positive findings in the literature. Finally, while animal studies provide valuable mechanistic insights, translational limitations must be acknowledged, including species differences in immune function and the difficulty of modeling complex human psychiatric symptoms in animals. Future research should prioritize large-scale, longitudinal cohort studies with standardized protocols and rigorous control for confounders to establish causality and identify robust biomarkers.

In terms of clinical treatment, depression comorbid with insomnia increases treatment difficulty and suicide risk, and is more likely to transform into treatment-resistant depression. Insomnia can serve as a predictor for depression relapse and disease progression. Therefore, understanding the potential interactive mechanisms between depression and chronic insomnia is crucial for clinical diagnosis and treatment. However, there are still significant gaps, challenges, and unresolved questions in related research. For example, the mechanisms of action of inflammatory cytokines may vary among different populations, and most studies rely on cross-sectional designs, making it difficult to establish causal relationships.[135] Therefore, A critical priority is the execution of large-scale, longitudinal cohort studies to determine whether peripheral cytokine elevations precede

the onset of comorbid insomnia and depression, thereby establishing temporal causality. Furthermore, randomized controlled trials are urgent needed to test the efficacy of targeted anti-inflammatory interventions, such as IL-6 or TNF-a inhibitors, in patients with this specific comorbidity, stratified by baseline inflammatory biomarker profiles.

Discussions about the future direction of treatment have recently highlighted advanced approaches to managing mood disorders. While these methods often focus on bipolar disorder (BD), they are highly relevant to depression-insomnia comorbidity due to shared mechanisms such as circadian rhythm dysregulation and inflammatory pathways. Studies have shown that targeted psychotherapies like interpersonal and social rhythm therapy can stabilize patients' circadian rhythms, thereby indirectly modulating HPA axis function and downstream inflammatory pathways, and breaking the pathological cycle at the behavioral level.[136] Additionally, there has been an introduction of precision medicine frameworks to stratify individuals with high inflammatory profiles based on their immunogenetic characteristics, guiding the personalized application of adjunct therapies such as anti-inflammatory medications.[137] Furthermore, cutting-edge technologies have been integrated, utilizing artificial intelligence to real-time monitor sleep quality, activity levels, and emotional data, enabling dynamic prediction and early warning of fluctuations in the condition.[138] This presents an ideal opportunity to incorporate artificial intelligence as a novel monitoring and intervention tool. These three cutting-edge future treatment directions have opened up new avenues of thought, potentially overcoming current treatment limitations and driving mental health services toward a more precise and forward-looking direction.

Abbreviations

WHO, World Health Organization; HPA, hypothalamic-pituitary-adrenal; CRP, C-reactive protein; TNF, tumor necrosis factor; TNF-α, tumor necrosis factor-α; TNF-β, tumor necrosis factor-β; IFN, interferons; IFN-γ, interferons-γ; ILs, interleukins; IL-1, interleukin-1; IL-1RA, interleukin-1 receptor antagonist; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-7, interleukin-7; IL-8, interleukin-8; IL-10, interleukin-10; IL-13, interleukin-13; IL-22, interleukin-22; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLRs, Toll like receptors; NLRs, Nucleotide-binding Oligomerization Domain-like Receptors; PGE_2, prostaglandin E2; C3a, Complement C3a Protein; C5a, Complement C5a Protein; MAC, membrane attack complex; ROS, Reactive Oxygen Species; RNS, reactive nitrogen species; SSRIs, Selective Serotonin Reuptake Inhibitors; IDO, indoleamine 2,3-dioxygenase; HTP, 5-hydroxytryptophan; TH, tyrosine hydroxylase; BH4, Tetrahydrobiopterin; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GC, glucocorticoid; GR, glucocorticoid receptors; VDBP, vitamin D-binding protein; BDNF, brain-derived neurotrophic factor; LPS, low-dose lipopolysaccharide; ATP, adenosine triphosphate; P2Y1R, P2Y1 receptor; NLRP3, NOD-like receptor thermal protein domain associated protein 3; MDD, major depressive disorder; SCFAs, short-chain fatty acids; SNP, single nucleotide polymorphism; SNS, sympathetic nervous system; BBB, blood-brain barrier; SWS, shorter slow-wave sleep; REM, rapid eye movement; PNSD, perimenopausal non - organic insomnia; PSQI, Pittsburgh sleep quality index; DRN, dorsal raphe nucleus; HAM-D, Hamilton Depression Scale; CRSwNP, chronic rhinosinusitis with nasal polyps.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no competing interests in this work.

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