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Role of high mobility group box protein 1 in depression: A mechanistic and therapeutic perspective

Wang S *et al.* HMGB1 in depression

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Abstract

As a common and serious psychiatric disorder, depression significantly affects psychosocial functioning and quality of life. However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods. Recent studies demonstrated that neuroinflammation activation plays an important role in the pathophysiology of depression. In this respect, High mobility group box 1 (HMGB1) may be a possible signaling inducer of neuroinflammation and can be a potential mechanistic and therapeutic target for depression. Herein, we review recent studies on the mechanistic and therapeutic targets of HMGB1 in depression and propose potential perspectives on this topic.

Key Words: Neuroinflammation; Depression; High mobility group box 1; Mechanism; Review; Perspective

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Core Tip: Limited reviews in the literature contributed to the high mobility group box 1 (HMGB1) in depression. This review provides a comprehensive mechanistic and therapeutic perspective on this topic and proposed that the future perspectives of HMGB1 in depression should be understanding the full signaling pathway of HMGB1 in depression, deeply investigating potential HMGB1 related therapeutic targets, and exploring the role of HMGB1 in depression and combined disease.

INTRODUCTION

Depression is one of the most common, serious, and costly psychiatric disorders that affect psychosocial functioning and quality of life^[1]. The aggregate point, one-year, and lifetime prevalence of depression in the community is about 12.9%, 7.2%, and 10.8%, respectively^[2]. Crucially, the number of people suffering from depression worldwide has increased from 172 million in 1990 to 258 million in 2017, with an increase of 49.86%^[3,4]. The stress of the outbreak of coronavirus disease 2019 and interpersonal isolation makes it even more people suffer depression recently^[5-7]. However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods^[8,9]. Recent studies demonstrated that the activation of neuroinflammation might play an important role in the pathophysiology of depression^[10]. High mobility group box 1 (HMGB1), a chromosomal protein, has been found to perform an essential job in the neuroinflammation of several central nervous system diseases, which might also be a potential therapeutic target^[11-15]. Rana *et al*^[11] proposed that HMGB1-mediated neuroinflammation in depression could have insights into the pathogenesis understanding and therapeutic promise. Herein, with recent studies concerning this topic, we review the role of HMGB1 in depression and propose several potential key mechanistic and future therapeutic perspectives.

RESEARCH PROGRESS OF HMGB1 IN DEPRESSION

HMGB1: a potential mechanistic direction in depression

HMGB1 is the most researched protein in the HMGB family for inflammation as innate immune responses^[16]. Expressed in nearly all eukaryotic cells, HMGB1 is a kind of chromatin-binding molecule to function in chromatin remodeling in the nucleus under normal physiological situations^[13]. Whereas in stressful situations or pathological situations, caused by immune and other cells or cell injury and death, HMGB1 secretes or translates from nuclei to the cytoplasm and eventually excretes or releases to the extracellular milieu, acting as a mediator of inflammation extracellularly^[17]. Placing on extracellular milieu, HMGB1 is acknowledged by plenty of binding receptors, mainly including ⁹ Toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE), resulting in the expression of proinflammatory response elements and eventually in the inflammatory cascade^[18]. The TLRs and RAGE are transmembrane proteins, which are located ¹⁴ in the membrane of several cells such as monocytes, macrophages, dendritic cells, and neural cells^[12]. For the HMGB1-TLRs pathway (mainly including TLR2 and TLR4), MyD88 dependent and independent pathways were activated, resulting in the simulation of NF- κ B and induction of pro-inflammatory response^[19]. For MyD88-dependent pathway, MyD88 serves as a domain-containing adaptor for the cytoplasmic Toll/IL-1 receptor^[20]. Stimulated by ² ligands, MyD88 recruits IL-1 receptor-associated kinase-4 (IRAK-4) to TLRs; and IRAK-1 is phosphorylated and then ² associates with TRAF6, thereby activating the IKK complex and leading to activation of MAP kinases (JNK, p38 MAPK) and NF- κ B^[21,22]. The MyD88-independent pathway also mediates the immune response ² via TRIF and TRAF3, leading to recruitment of IKK ϵ /TBK1, phosphorylation of IRF3, and expression of interferon- β ^[23,24]. A recent study also indicated that the HMGB1-TLR4 pathway could activate Nod-like receptor protein 3 (NLRP3) inflammasome and then enhanced the production of interleukin-1 β (IL-1 β)^[25]. For the HMGB1-RAGE pathway, the downstream signaling is propagated by the ¹² activation of phosphatidylinositol 3 kinase-protein kinase B (Akt), mitogen-activated protein kinase (MAPK), ERK, JAK-STAT1, and Rac pathways, ultimately promoting the activation of NF- κ B and expression of the ¹ proinflammatory cytokines and chemokines, which contributes in the immune cells'

maturation and migration and surface receptors' expression^[26,27]. Fully reduced HMGB1 (fr-HMGB1), which is a kind of three redox states (fr-HMGB1, disulfide HMGB1, and sulfonyl HMGB1), can act as a chemoattractant through connections with RAGE^[28]. Furthermore, binding with chemokine receptor type 4 (CXCR4), promotes chemotactic activity (stimulates leukocyte recruitment)^[29]. It should be noted that such inflammation activation can lead to inflammatory responses and cell injury and death, which promotes the further release of HMGB1 and upgrade of its receptors^[30]. This may contribute to the aggravation and drug-resistance of HMGB1 related disease^[15].

More recently, neuroinflammation has been proposed to play a significant role in several diseases including depression, epilepsy, stroke, traumatic brain injury, Parkinson's disease, and Alzheimer's disease^[11-15]. HMGB1 is considered as an essential neuroinflammatory facilitator, which is released by glial cells and neurons upon inflammasome activation and acts as a pro-inflammatory cytokine^[15]. Neurons are considered as a primary and necessary driver of neuroinflammation through release of HMGB1, with the subsequent amplification *via* recruitment of immunocompetent cells, including microglia and astrocytes^[31]. HMGB1 has been proved that it releases from neurons in many central nervous system (CNS) diseases and then triggeres neuroinflammation as an upstream inflammatory mediator^[15,32]. Activated by HMGB1, microglia functions as key contributor of the inflammatory processes sequentially influences neural cells, following by the activation of microglial NF- κ B pathway and production of pro-inflammatory cytokines^[33]. The study of Gao *et al*^[34] using a Parkinson's disease model revealed that HMGB1 released from inflamed microglia and/or degenerating neurons, bound to microglial Mac1 and activated NF- κ B pathway and nicotinamide adenine dinucleotide phosphate oxidase to stimulate production of multiple inflammatory and neurotoxic factors. Astrocytes are also a population of CNS cells with distinctive morphology and functions. Xiao *et al*^[35] suggested that HMGB1 promoted the release of sonic hedgehog from astrocytes through signal pathway JNK, p38 and stat3 mediated by receptor RAGE in an animal model of multiple sclerosis, suggesting the important role of HMGB1-astrocytes mediated neuroinflammation.

Also, some types of reactive astrocytes can also be induced by activated neuroinflammatory microglia and take parts in various human neurodegenerative diseases, formulating a complex immune network^[36].

Depression is also found to closely link with neuroinflammation, which is mainly characterized by the increased mediators of inflammation and neurodegeneration^[37]. Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules, including IL-1 β , IL-6, TNF- α and CRP^[38,39]. Preclinical study based on animals also exhibited the activation of microglia together with enhanced inflammatory mediators. In a chronic mild stress (CMS) mouse model of depression, NLRP3-inflammasome/caspase-1/IL-1 β axis microglia-mediated neuroinflammation was found being activated^[40]. Another study suggested rats exposed to CMS exhibited a significant increase in inflammatory mediators, including TNF- α and IL-1 β , activation of NF- κ B signaling pathway in the hippocampus. Icaritin, a flavonoid inhibiting neuroinflammation, could negatively regulated the activation of the NLRP3 inflammasome/caspase-1/IL-1 β ^[41]. Chronic treatment with corticosterone and intraperitoneally administration of lipopolysaccharide depressed models also showed a higher expression level of pro-inflammatory phenotype characterized by IL-1 β , IL-6, TNF- α and I κ B- α ^[42,43]. These findings provide a powerful connection of neuroinflammation and depression.

Concerning HMGB1 mediates depression, recent studies suggested that HMGB1 might be a probable inducer of stress-mediated neuroinflammation in depression^[11]. It has been proven that HMGB1 could activate neuroinflammatory reactions by inducing TNF- α to exhibit anhedonia-like behavior^[44]. Based on the inescapable tail shock rats' model, Weber *et al*^[45] indicated that HMGB1 in the brain is a probable inducer of stress-mediated microglial priming by acting on the NLRP3 inflammasome and pro-inflammatory cytokines. Based on recent studies, stress-mediated depression-like behaviors were found to be induced by HMGB1 and glycogen synthase kinase-3 (GSK-3) dependent TLR4 signaling, resulting in the activation of NF- κ B and NLRP3 inflammasome; and the HMGB1 was additionally promoted in mice^[46]. This stress-

induced neuroinflammation can further make it more susceptible to depression^[47]. Based on rats' chronic unpredictable stress (CUS)-induced behavioral deficits, Franklin *et al*^[48] discovered that CUS caused consistent upregulation of HMGB1 mRNA and RAGE mRNA in hippocampal microglia. They also found that HMGB1 infusion into the hippocampus caused anhedonic behavior and suggested that HMGB1-RAGE increased vulnerability to depressive-like behaviors long^[10,48]. In addition, HMGB1 could also induce depressive behaviors by limiting the kynurenine pathway *via* suppression of activated enzymes^[37]. Furthermore, based on preclinical studies, neuroinflammation induced by HMGB1 can mediate depressive behaviors such as reduction of locomotor activity and sucrose preference, which are analogs to the motivational deficits in depression^[49,50].

HMGB1: a potential therapeutic target in depression

Current studies proposed that interventions in the HMGB1 and related molecular in its neuroinflammation pathways have the potential to be a therapeutic target in several diseases like depression, epilepsy, cancers, stroke, and other local and systemic neuroinflammatory diseases^[4,13,15]. The main potential therapeutic targets include anti-HMGB1 monoclonal antibody (mAb), HMGB1 inhibitors, and HMGB1 receptors and its related molecular in neuroinflammation pathway^[15].

For depression, although several studies provided evidence on mediating HMGB1, this topic is still needing more effort. Traditionally commonly used anti-depression drugs based on the theory of serotonin-like ⁵selective serotonin reuptake inhibitors (SSRIs) as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) may be complicated to treat motivational deficits symptoms, suggesting additional neurotransmitters like dopamine dysfunction might be involved^[51,52]. Also, recent studies suggested the anti-inflammatory and anti-oxidative effects may be one of the potential mechanisms of these anti-depression drugs^[53]. Only limited studies are based on animal models concerning the therapeutic target of HMGB1 in anti-depression. Liu *et al*^[50] and Fu *et al*^[54] indicated that the anti-depressive-like behavior compound

Hesperidin and Baicalin reduced the CUS-induced model by inhibition of neuroinflammatory actions *via* HMGB1-TLR4-NF- κ B pathway or HMGB1-RAGE-NF- κ B pathway. The anti-HMGB1 mAb is highly specific for HMGB1, which shows the value of target validation but also has potential for the treatment of neuroinflammation diseases, including depression^[14]. Hisaoka-Nakashima *et al*^[55] used the model of partial sciatic nerve ligation to introduce neuropathic pain and anxiodepressive-like behaviors in mice. They observed increased HMGB1 and microglia activation in the frontal cortex. Anti-HMGB1 mAb and glycyrrhizic acid (HMGB1 inhibitor) can reduce microglia activation and anxiodepressive-like behavior^[55]. HMGB1 inhibitors can be another possible anti-HMGB1 strategy. Based on the CUS-induced model both *in vivo* and *in vitro*, glycyrrhizic acid, the inhibitor of HMGB1, may restrain HMGB1 thus improving depressive-like behaviors through regulating the kynurenine pathway^[47,56]. Encouragingly, a recent clinical trial found that depressive symptoms are relieved more in SSRI+ glycyrrhizic acid than SSRI+ placebo, proving anti-inflammatory agents is effective in clinical use^[57]. The HMGB1 receptors and their related molecular in neuroinflammation pathway can also be a therapeutic target. Cheng *et al*^[46] based on an inescapable tail shock model suggested that TLR4 knockout mice were resistant to learned helplessness and GSK3 (a TLR4 signaling dependent kinase) inhibitor TDZD-8 reduced the stress-induced increases of hippocampal cytokines and chemokines.

HMGB1: summarize of HMGB1 in depression

Based on current studies, HMGB1 may be a possible signaling inducer of stress-mediated depression behaviors *via* HMGB1-TLRs signaling and HMGB1-RAGE signaling, followed by the activation of NF- κ B and expression of the proinflammatory cytokines and chemokines, resulting in the neuroinflammation procedure^[10]. This pathway suggests a possible mechanistic direction for depression. HMGB1 can also be a potential therapeutic target in depression by playing an important role in neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors^[11]. However, there are still many challenges in further exploring

HMGB1 as a potential mechanistic and therapeutic direction. The mechanistic illustration of HMGB1 in depression is provided as Figure 1.

PERSPECTIVES OF HMGB1 IN DEPRESSION

Focus on the complete signal pathway mechanism

As a multifunctional protein, HMGB1 has been extensively researched. Encouragingly, cell stresses and plenty of disease processes are found related to this important inflammation facilitator^[58]. HMGB1 needs to translate from nuclei to the cytoplasm and eventually release to the extracellular milieu for its inflammatory function^[16]. Thus, location and translocation are the keys to function^[59]. The potential mechanism of HMGB1 translocation, however, is still not clear and requires further exploration in depression. Furthermore, most current studies only focus on the release of HMGB1 in neuroglial cells (especially neuroimmune cells), which requires more studies on the role of other neuronal cells^[11]. Another potential perspective is about HMGB1 receptors. The different functions, distribution, and potential relationship among various HMGB1 receptors emerge as a research focus in inflammation^[60,61]. For depression, the mechanism of neurotransmitters and neuroinflammation may make this question more interesting and meaningful^[53,62]. It has to be admitted that only limited studies explored some parts of the HMGB1 as a mechanism in depression. There still is a long way to understand 10 the full signaling pathway of HMGB1 and the complete mechanism of depression introduced by the neuroinflammation.

A potential therapeutic target needs more evidence

Although several studies indicated potential therapeutic targets as neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors, current researches are far from enough to provide evidence for potential therapy or clinical application^[11]. The potential anti-inflammatory mechanisms and collaboration of neurotransmitter-related anti-depression drugs might be a clinically translational direction^[53]. Furthermore, some anti-inflammatory and antiapoptotic

compounds [such as (-)-Epigallocatechin-3-gallate and different microRNAs] can inhibit the HMGB1-NF- κ B signaling pathway, which showed great potential in therapy of other HMGB1 related diseases^[15]. These may also show effects in depression, which deserves further researches. The future need of the research is to deeply investigate potential HMGB1 related therapeutic targets using different animal models^[63]. The ultimate goal is for contribution to human clinical applications, while the clinical study on glycyrrhizic acid (HMGB1 inhibitor) as an adjunctive treatment for depression is a meaningful attempt^[57].

Combined disease: a future perspective

It is commonly observed in clinical practice that depression may combine with other diseases, such as epilepsy, stroke, and heart disease^[64-66]. HMGB1 is found widely participating in different inflammation-related diseases on the nervous system, circulatory system, and others^[13]. Thus, HMGB1 may be at the crossroads of depression and other combined diseases. These diseases may have consistent or similar pathogenesis as HMGB1 and response to the same therapeutic target on HMGB1. The researches and discussion of HMGB1 as a potential common mechanistic and therapeutic direction in depression and combined inflammation-related disease may be meaningful and beneficial. Figure 1 shows an illustration of mechanistic and therapeutic perspective of HMGB1 in depression.

CONCLUSION

Neuroinflammation activation plays an important role in the pathophysiology of depression. Playing an important role in neuroinflammation activation, HMGB1 may be a possible signaling inducer of depression. HMGB1 can also be a potential therapeutic target in depression by playing an important role in neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors. However, there are still many challenges in further exploring HMGB1 as a potential mechanistic and therapeutic direction. The future perspectives of HMGB1 in depression

are understanding the full signaling pathway of HMGB1 in depression, deeply investigating potential HMGB1 related therapeutic targets, and exploring the role of HMGB1 in depression and combined disease.

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