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HMGB1 in depression: An overview of microglial HMBG1 in the pathogenesis of depression

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ABSTRACT

Depression is a prevalent psychiatric disorder with elusive pathogenesis. Studies have proposed that enhancement and persistence of aseptic inflammation in the central nervous system (CNS) may be closely associated with the development of depressive disorder. High mobility group box 1 (HMGB1) has obtained significant attention as an evoking and regulating factor in various inflammation-related diseases. It is a non-histone DNA-binding protein that can be released as a pro-inflammatory cytokine by glial cells and neurons in the CNS. Microglia, as the immune cell of the brain, interacts with HMGB1 and induces neuroinflammation and neurodegeneration in the CNS. Therefore, in the current review, we aim to investigate the role of microglial HMGB1 in the pathogenetic process of depression.

Depression is a common mood disorder characterized by a persistent low mood and anhedonia, often accompanied by cognitive impairment and social deficits in daily life (Benasi et al., 2021; Dubovsky et al., 2021; McNamara et al., 2021). In severe cases, suicidal behaviors may emerge, with suicide rates increasing by roughly 35% in the USA since 1999 (Hedegaard et al., 2020; McCarron et al., 2021). Worldwide, over 300 million people of different ages suffer from depression, contributing to the disability and years of potential productive life lost (Bloom et al., 2018; Monroe and Harkness, 2022; Theo Vos et al., 2016; Touloumis, 2021). Furthermore, it is expected that the global economic cost associated with depression will nearly double by 2030 (Hajat and Stein, 2018; McCarron et al., 2021). Though lots of antidepressant therapies have been developed and/or discovered and proved to be quite useful through decades of study (Greenberg et al., 2012; Jones and Nemeroff, 2021; Kverno and Mangano, 2021), most researchers have concentrated on the monoaminergic neurotransmission and neurotrophic system in the antidepressant field (Ceskova and Silhan, 2018; Duman and Monteggia, 2006; Nestler et al., 2002). The unsatisfactory treatment effect warns us that the exact mechanisms underlying the development of depression remain abstruse (Kverno and Mangano, 2021; Souery et al., 2006). Recently, an aseptic inflammatory response in the central nervous system has been projected, and the role of immune system activation in the pathogenesis of depression has been confirmed by several significant studies (Dantzer, 2012; Miller and Raison, 2016; Troubat et al., 2021).

There is a wealth of evidence supporting the role of inflammation in depression, including findings from patients and animals (Cao et al., 2020; Kohler et al., 2016; Yirmiya et al., 2015; Zhang et al., 2019b). Microglial cells, the most common innate immune cells in the brain (Nayak et al., 2014), originate from myeloid progenitors and are closely related to peripheral macrophages (Ginhoux et al., 2010). Typically, microglia are involved in maintaining neuronal integrity and network functioning in the brain by releasing neurotrophic factors (Prinz et al., 2019). However, under conditions of disrupted brain homeostasis, some microglia not only become activated but also secrete proinflammatory cytokines and chemokines (Wolf et al., 2017).

The occurrence of a central inflammatory response is closely related to damage- or danger-associated molecular patterns (DAMPs) that can

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initiate and perpetuate a noninfectious inflammatory response (Chen and Nuñez, 2010; Zindel and Kubes, 2020), which often drive autonomously and become more active in response to cellular stress and tissue damage (Fleshner et al., 2017; Gong et al., 2020). High mobility group box 1 (HMGB1), a chromatin-associated protein and a member of the DAMP family, plays a significant role in this context (Xue et al., 2021). In this review, we described the activation states of HMGB1 in animal models and clinically depressed patients, aiming to elucidate the underlying mechanisms of depression and explore the therapeutic potential of targeting HMGB1and microglia.

1. Structure and features of HMGB1

Structurally, HMGB1 is located on human chromosome 13q12 and consists of a 215 amino acid polypeptide with two DNA-binding domains named Box-A and Box-B, as well as a C-terminal acidic domain (Lotze and Tracey, 2005; Stros, 2010). Recent work has demonstrated that HMGB1 contains three conserved cysteines at positions 23 and 45 in Box-A and at position 106 in Box-B, and its biological activity depends on the redox states (Kang et al., 2014; Yang et al., 2013). Different redox forms of HMGB1 interact with different receptors at different stages of pathophysiology (Chen et al., 2022a; Singh et al., 2016; Wang et al., 2019). Depending on the redox state, there are three forms of HMGB1, namely, disulfide HMGB1 (ds-HMGB1), fully reduced HMGB1 (fr-HMGB1) and fully oxidized HMGB1 (ox-HMGB1) (Frank et al., 2015; Kang et al., 2014). Ds-HMGB1 promotes inflammation and ultimately results in systemic inflammation (Frank et al., 2016; Kvivik et al., 2021; Xiong et al., 2022) via binding to Toll like receptors (TLRs, e.g., TLR2 and TLR4) when cysteines at positions 23 and 45 become oxidized, while cysteine at position C106 remains in a reduced thiol state (Yamasoba et al., 2016). Several studies indicate that ds-HMGB1 exacerbates neuroinflammation, resulting in anxiety, aversion and fatigue in mice or patients (Du et al., 2022; Kvivik et al., 2021). Xiong et al. demonstrated that ds-HMGB1 bound to myeloid differentiation protein-2 to activate NLRP3, thereby releasing inflammatory factors (e.g., TNF-α, IL-1β, and IL-10) and impairing cognitive behaviors in mice with sepsis-associated encephalopathy (Xiong et al., 2022).

In contrast, when cysteines at positions C23, C45, and C106 are all reduced and remain in thiol states, it is called fr-HMGB1 which functions as a chemotactic factor via interacting with the receptor for advanced glycation end-product (RAGE), potentiates chemotactic activity by interacting with C-X-C chemokine receptor type 4 (CXCR4), and forms a heterocomplex with CXC chemokine ligand (CXCL12) (Allette et al., 2014; Di Maggio et al., 2017; Fassi et al., 2019). Chen and colleagues indicated that fr-HMGB1 and non-oxidizable chemokine-HMGB1 (non-oxid-HMGB1), but not ds-HMGB1, promoted axon elongation and neurite outgrowth, eventually, ameliorating traumatic brain injury-mediated cognitive impairment (Chen et al., 2022a). Liesz et al. suggested that cerebral ischemia induced the release of fr-HMGB1 from necrotic brain lesions (Liesz et al., 2015). Di Maggio and colleagues demonstrated that fr-HMGB1 could ameliorate cardiac performance by enhancing neoangiogenesis and reducing the infarcted area and fibrosis after myocardial infarction (Di Maggio et al., 2017). A biological function of ox-HMGB1 cannot be identified in vivo (Kang et al., 2014; Yang et al., 2013).

The redox state of HMGB1 cysteines dictates its extracellular activities, from inflammation and neurodegeneration to tissue repair (Chi et al., 2015; Gaikwad et al., 2021; Vénéreau et al., 2015). Our previous studies have identified and established the significant role of actively released HMGB1 during pathogenetic process of depression (Wu et al., 2015). Furthermore, we investigated the redox states and receptor mechanism of HMGB1's association with the development of depressive-like behavior (Lian et al., 2017; Wang et al., 2019):1)both ds-HMGB1 and fr-HMGB1, instead of ox-HMGB1, induced depressive-like behaviors through different mechanisms; 2) ds-HMGB1 induced depressive-like behaviors via TLR4, mediating tumor necrosis factor (TNF)-α increase and myelin basic protein (MBP) reduction; 3) fr-HMGB1 was presumably converted into ds-HMGB1 partially in vivo. Subsequently, TLR4 and proinflammatory cytokines (e.g., TNF-α) were activated by ds-HMGB1 oxidized from fr-HMGB1. Proinflammatory cytokines contribute to the generation or enhancement of ROS (Roca et al., 2022), S100s (Li et al., 2020) and CXCL12/CXCR4 (Li et al., 2016), which bind to RAGE or CXCR4 receptors. As the receptors of fr-HMGB1, RAGE and CXCR4 may also exert proinflammatory effects, leading to depressive-like behaviors. It is reported that the half-life of fr-HMGB1 in serum is very short (17 min) compared with that of ds-HMGB1 (8 h), suggesting that HMGB1 exhibits more pro-inflammatory properties after being released from the extracellular space (Zandarashvili et al., 2013). Therefore, the relationship between the redox state and functional characteristics of HMGB1 deserves further exploration.

2. Functions and regulation of HMGB1

HMGB1 has entirely different biological activities depending on its location (Tang et al., 2016). In the nucleus, HMGB1 acts as a DNA chaperone and is involved in physiological functions including replication, transcription, and repair (Kang et al., 2014; Mandke and Vasquez, 2019; Thomas and Stott, 2012). Under certain stress conditions, HMGB1 can be transported to the cytoplasm to take part in immune responses and mediate autophagy (Andersson et al., 2018). When released to the extracellular environment, HMGB1 exerts distinct functions depending on the receptors and complexes with which it interacts (Haque et al., 2020; Pilzweger and Holdenrieder, 2015; Zhang et al., 2022). There are two mechanisms by which HMGB1 is released: it can be released passively by almost all cells undergoing various types of death and be actively secreted by innate immune cells in the absence of cell death (Chen et al., 2022b). When necrosis occurs, HMGB1 is separated from chromatin and released from broken cells in to the extracellular space, triggering an inflammatory response (Rana et al., 2021; Yang et al., 2015a). However, when cells undergo apoptosis, HMGB1 is still bound to chromatin and will be recognized by immune cells without causing inflammatory response (Kono and Rock, 2008; Scaffidi et al., 2002). The above passive release mechanism is widely researched in various types of cells in the body (Chen et al., 2022b).

Besides, it is actively secreted by innate immune cells in the absence of cell death, such as, but not limited to, macrophages, monocytes, neutrophils, and hepatocytes, epithelial or endothelial cells (Cai et al., 2019; Chen et al., 2022b; Tsung et al., 2005). Recent research has demonstrated that central nervous system cells produce HMGB1 in response to various acute stressors (e.g., lipopolysaccharideor inescapable tail shock) (Weber et al., 2015; Wu et al., 2015). It was reported by Qiu et al. that HMGB1 translocation and release occurred in neurons of brain ischemia (Qiu et al., 2008), and Weber et al. found that acute stress induced microglia to actively release HMGB1 (Weber et al., 2015). In our experiments, hippocampal microglia and neurons of mice were both found to secrete HMGB1 after chronic unpredictable mild stress (CUMS) exposure (Wang et al., 2020). The active secretion process of HMGB1 mainly exists in innate immune cells, and it generally includes two steps (Rana et al., 2021; Volchuk et al., 2020). After the lysine residues of domains A and B hyperacetylating by tyrosine kinase/transcriptional activator protein 1 (JAK/STAT1) (Lu et al., 2014a), HMGB1 is translocated from the nucleus to the cytoplasm, and then innate immune cells such as nuclear cells and macrophages are actively secreted to the outside of the cell (Bonaldi et al., 2003; Lee et al., 2018; Lu et al., 2014b), eventually leading to an inflammatory response.

3. The relationship between microglia and HMGB1–*The role of microglia in CNS*

At the beginning, glial cells, including microglia, astrocytes and oligodendrocytes, were considered to act as "glue" in the CNS. It was not until the 20th century that Spanish neuroscientists Pio del Rio-Hortega

described microglia as a separate cell type (Lee et al., 2018). Thanks to advancements in microglia biology, we have gained a better understanding of microglia over the past few decades, including their development, fate, and function in the CNS(Borst et al., 2021; Tay et al., 2019; Wolf et al., 2017).

There are an estimated 3.5 million microglia in the adult mouse brain, with various densities in different regions (Keller et al., 2018). For instance, the substantia nigra (SN), basal ganglia, olfactory telencephalon, and HIP all contain more microglia, while the bulk of the brainstem, cerebellum, and fiber tracts all show fewer microglia (Keller et al., 2018; Lawson et al., 1990). During neonatal development, early yolk-sac-derived microglial progenitors resemble macrophages (Schulz et al., 2012)and lack heavily ramified processes (Nayak et al., 2014). However, they eventually undergo a maturation program that involves proliferation and the subsequent acquisition of ramified processes, giving rise to the microglial architecture frequently seen in the adult CNS (Nayak et al., 2014). It is now believed that microglia resemble peripheral macrophages in terms of their appearance and functions and belong to the immune system (Kanazawa et al., 2017; Mildner et al., 2007; Wright-Jin and Gutmann, 2019).

Normally, microglia influence the surrounding cellular environment by secreting trophic substances which can protect and nourish neurons (Jurga et al., 2020; Rock et al., 2004). They can also stimulate astrocytes, and the phagocytic activity of microglia is important in synaptic homeostasis (Paolicelli et al., 2011; Wake et al., 2009). Under pathological conditions, such as injury, neurodegeneration or infections caused by parasites or bacteria, microglia are quickly activated, change their expression profiles, and undergo morphological alterations (Calcia et al., 2016; Davalos et al., 2005; Jia et al., 2021; Shemer et al., 2015). More specifically, microglial processes migrate quickly and precisely toward the site of infection or injury to help tissue repair (Carbonell et al., 2005; Dibaj et al., 2010). The fully activated microglia take on a distinctive amoeboid morphology, which shows complete retraction of all processes (Kettenmann et al., 2011; Wang et al., 2022). The function of activated microglia alters from supporting neurons to causing neuronal dysfunction (Garaschuk and Verkhratsky, 2019). In some circumstances, this adaptive process neutralizes pathogenic challenges; however, under certain circumstances, such as neurodegenerative diseases, activated microglia can lead to the death of neurons and glial cells (Heneka et al., 2014; Heppner et al., 2015).

Given the important role of microglia in normal brain development and homeostasis, it is not unexpected that microglial dysfunction may contribute to the pathogenesis of depressive disorders (Deng et al., 2020). There is a strong relationship between microglia activation and depression in both patients and animal models. Clinical data reveal that patients with major depressive disorder (MDD) exhibit high blood cytokine levels, and the depressive episodes are correlated with enhanced PET detection of translocator protein (TSPO), which is considered as a sign of activated microglia and neuroinflammation (Woodburn et al., 2021).

Furthermore, microglia activation is engaged in both inflammatory and non-inflammatory animal models of depression. For example, the administration of endotoxin such as lipopolysaccharide (LPS) can induce depressive symptomatology, and the intensity of these symptoms is associated with blood levels of inflammatory cytokines (Hoogland et al., 2015). Depression-related stress could also lead to microglial activation along with an increase in pro-inflammatory cytokines (Han and Ham, 2021). Another line of evidence demonstrating the role of microglial activation in depression comes from the treatment of microglial inhibitory drug minocycline, which can suppress microglial activation and neuroinflammation. Minocycline has been shown to prevent depressive-like behavior in a rat model of chronic unpredictable mild stress, which is consistent with our findings that the treatment of minocycline exhibits significant anti-depressive effects in a mice model of CUMS (Wang et al., 2020; Zhang et al., 2019a).

Even though the mechanisms of how microglia contribute to depression are still obscure, there is evidence suggesting that several factors may be involved. First, microglia-derived cytokines such as TNF-α and IL-1β can stimulate the proliferation of inflammatory cells, release proteolytic enzymes, synthesize prostaglandins, and promote the secretion of more cytokines, resulting in cytotoxicity, which in turn promotes the inflammatory response (Valentinova et al., 2019; Zhang et al., 2017a). Second, overactivated microglia can suppress neurogenesis in the hippocampus (Kreisel et al., 2014). Third, the activation of microglia can induce depression by activating kynurenine pathway (KP), which is important for tryptophan metabolism, and increasing neurotoxic products (Garrison et al., 2018; Verdonk et al., 2019). In addition to the involvement of microglia activation in depression, studies also show that microglial decline may be associated with depression (Tong et al., 2017).

4. The possible mechanism underlying HMGB1-induced depression

Numerous experimental studies have shown that HMGB1 may induce depressive-like behavior through membrane receptors, such as TLR4 and RAGE (Liu et al., 2019; Xie et al., 2021; Xu et al., 2020a; Yan et al., 2021). Upon binding to the RAGE receptor on the cell surface, HMGB1 initiates two common downstream pathways in the cell. One pathway involves the activation of guanosine triphosphatase (Hudson et al., 2008; Yang et al., 2007); the other pathway activates mitogen activated protein kinases (MAPKs) (Chen et al., 2016; Qiu et al., 2016), phosphatidylinositol3 kinase (PI3K), serine/threonine protein kinase (AKT) (Wang et al., 2021), and extracellular signal-regulated kinase (ERK) pathways (Huang et al., 2018) (Fig. 1). The latter pathway eventually results in the translocation of nuclear factor kappa light chain enhancer of activated B cells (NF-κB) (Fig. 1), induction of chemokines and proinflammatory cytokines expression, which contribute to cell maturation and migration, neuroinflammation, surface receptor expression, and tumor proliferation (Akirav et al., 2012; Hudson and Lippman, 2018; Yang and Tracey, 2005). Furthermore, these pathways are activated by the binding of RAGE's adaptor protein, termed diaphanous-1/mDia1 (Fig. 1), which is currently the only protein that binds directly to RAGE's cytoplasmic domain (Hudson and Lippman, 2018; Zhou et al., 2018).

Binding of HMGB1 to TLR2/TLR4 receptors activates multiple pathways (Fig. 1), including myeloid differentiation factor 88 (MyD88) dependent and independent pathways (Kang et al., 2014),MAPKs (Chaochao et al., 2017), nod-like receptor protein 3 (NLRP3) (Kim et al., 2018), ultimately leading to the inflammatory genes' expression and microglial activation (Yang et al., 2015b).

Following the activation of the aforementioned pathways, the synthesis and release of interleukin 1β (IL-1β), interleukin 6 (IL-6) and TNF-α occur in target cells (Cheng et al., 2016; Şahin et al., 2015; Zhang et al., 2017b). Levels of other inflammatory factors increase, and the above factors are involved in the pathological process of depression and play a crucial role in it (Troubat et al., 2021). Studies have shown that intraperitoneal or lateral ventricle injection of IL-Iβ receptor antagonists can significantly prevent CUS-induced depression-like behavior in mice. Anti-IL-1β receptor antibody overexpression or IL-1β receptor gene knockout in mice also have the above characteristics (Iwata et al., 2016; Kreisel et al., 2014). Certainly, the similar effect can be observed inIL-6 and TNF-α(Şahin et al., 2015; Zhang et al., 2017b). Moreover, microdialysis technology has confirmed that IL-1β is released earlier than TNF-α during the acute stress response. (Iwata et al., 2016).

In addition to the activation of NF-κB, HMGB1 can also activate other intracellular pathways (Felger and Treadway, 2017; Shah et al., 2016; Verdonk et al., 2019). They are speculated to be linked to the changes in neurotransmitters metabolism (e.g., 5-hydroxytryptamine). Our group (Wang et al., 2018b) previously found that HMGB1 acted on microglia in the hippocampus, leading to the activation of some important enzymes in the KP, which may be responsible for the pathogenesis of

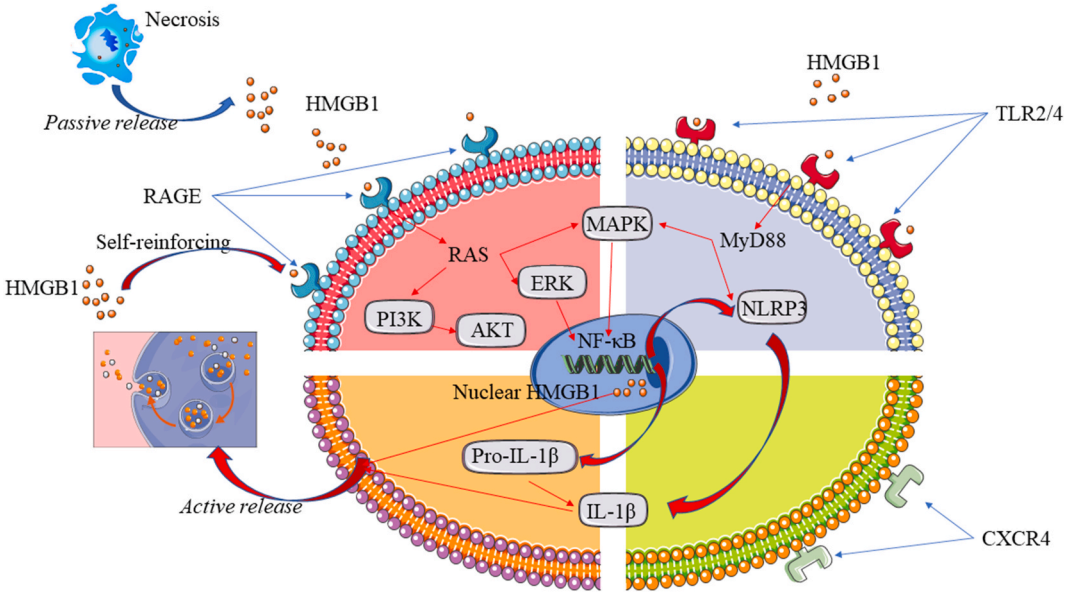

Fig. 1. Schematic diagram presentation of the self-reinforcing release and the mainly signaling pathways of HMGB1. Abbreviations: mDia1, mammalian diaphanous-1; PI3K, phosphatidyl inositol 3-kinase; AKT, serine/threonine protein kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation factor 88; NLRP3, nod-like receptor protein 3; NF-κB, nuclear factor kappa light chain enhancer of activated B cells.

CUMS-induced depression-like behavior in rodents (Fig. 2).

Accumulating evidence has shown that CUMS can regulate microglial activation by increasing extracellular HMGB1 levels in the hippocampus and induce depression-like behaviors in mice (Franklin et al., 2018; Hisaoka-Nakashima et al., 2019; Takizawa et al., 2017; Wang et al., 2020). CUMS-induced microglial activation is primarily manifested in the same number of cells but with obvious changes in cell shape: an increase in cell body size, number of protrusions, length and volume of protrusions, as well as an enhanced ability to synthesize and secrete inflammatory factors (Fig. 2) (Franklin et al., 2018; Wang et al., 2020). Conversely, several researchers have found a decline in microglial cells after rodent CUS exposure (Kreisel et al., 2014; Tong et al., 2017). Therefore, further work needs to be conducted to determine the association between the kinds of microglial morphology and function and the development of depression. In addition, microglial activation and impairments in neural plasticity and neurogenesis of the CNS are associated with depression (Beumer et al., 2012; Gao et al., 2011; Jia et al., 2021). Exposure of mice to CUMS elicited microglial activation and decreased hippocampal neurogenesis (Zhang et al., 2017a), whereas a polarization of microglia (M2) can enhance neurogenesis (Yuan et al., 2017; Zhang et al., 2017a). Thus, neuroinflammation and neurogenesis are both associated with depression (Jia et al., 2021; Rana et al., 2021). Some preclinical studies have also exhibited the activation of microglia together with increased inflammatory mediators, except in depressive patients (Kinuthia et al., 2020).

Initially, an inflammatory response does not occur when HMGB1 interacts with microglia, but it sensitizes them toa highly activated state. Upon exposed to a stressor again, activated microglia function as key contributors to the inflammatory processes that sequentially affect neural cells (Fonken et al., 2016). This may explain the delayed healing

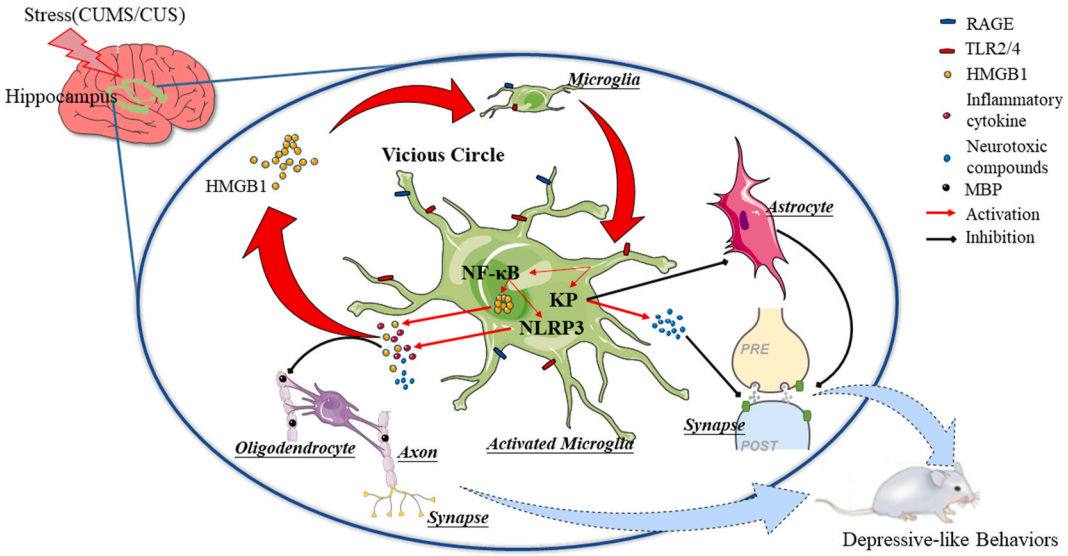

Fig. 2. The scheme of possible mechanisms underlying HMGB1 contribution to depressive-like behaviors and the vicious loop between the HMGB1 and microglia occurred after chronic stress. Abbreviations: KP, kynurenine pathway; NLRP3, nod-like receptor protein 3; MBP, myelin basic protein; PRE and POST, pre- and post-synapse.

and easy recurrence of depression in patients. Interestingly, Franklin found that persistent microglial HMGB1-RAGE expression increased the vulnerability to depressive-like behaviors after chronic unpredictable stress (CUS) exposure (Franklin et al., 2018).

Microglia are not only the main target cells of HMGB1, but also important source cells for the active secretion of HMGB1 (Wang et al., 2020). We speculate that there is a positive feedback phenomenon in the interaction between HMGB1 and microglia (Fig. 2). Specifically, extracellular HMGB1 levels elevate after injury or stress to the animal's CNS. Then, the high level of HMGB1 acts on microglia to activate them, and the latter can not only bring about an inflammatory response but also an increase in the active release of HMGB1, resulting in the expansion of the inflammatory response and the occurrence of diseases (Fig. 2). Fortunately, this self-reinforcing vicious loop between HMGB1 and microglia has been partly confirmed by the writer's new group (Tan et al., 2021).

HMGB1-induced neuroinflammation mediates depression-like behaviors in rodents, including decreased sucrose preference and reduced locomotor activity, which are analogues to the motivational deficits in patients with MDD (Fu et al., 2019; Lian et al., 2017; Wang et al., 2018a). However, such symptoms associated with motivational deficits complicate clinical treatment (Schulz, 2020; Treadway, 2016), suggesting the involvement of additional neurotransmitters. Randall et al. found that the lesions of dopaminergic neurons could induce anhedonia-like behaviors in the mesolimbic system in rats (Randall et al., 2014). Our previous research (Lian et al., 2017)demonstrated that injection of HMGB1 into the lateral ventricle caused a decrease in the content of MBP in the hippocampus of mice, suggesting a link between HMGB1-induced depression-like behavior and axonal myelin damage (Fig. 2). Thus, further exploration is needed to understand the regulation of psychomotor retardation in depression.

5. Current progress of MDD's treatment with HMGB1

Although various strategies have been proposed to inhibit HMGB1 expression, release and activity, such as HMGB1-neutralizing antibody, DNA-binding A box (Box-A) protein, gene editing technologies like RNAi, endogenous hormones, anti-coagulant agents and chemicals, limited studies have focused on HMGB1 as a therapeutic target for depression, especially in clinic. In animal models, the traditional Chinese herbal medicine arctiion and its aglycone arctigenin have been reported to reduce microglia activation and inflammation via the HMGB1/TLR4 and TNF-α/TNFR1 signaling pathways (Xu et al., 2020b). Anti-HMGB1 monoclonal antibody (mAb), which is highly specific for HMGB1, also shows the potential for the treatment of depression (Nishibori et al., 2019).

Another possible anti-HMGB1 strategy is HMGB1 inhibitors. We have performed a clinical trial to prove the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs) plus GZA, a natural inhibitor of HMGB1 cytokine, which has shown to reduce symptoms of depression (Cao et al., 2020). Furthermore, HMGB1 receptors and their associated molecular pathways can also be therapeutic targets. In an inescapable foot shock stress model, administration of the glycogen synthase kinase-3 (GSK3) inhibitor TDZD-8 attenuated NF-κB activation downstream of HMGB1 and reduced the stress-induced increases of most hippocampal cytokines and chemokines (Nishibori et al., 2019).

6. Conclusion

Yet our understanding of the pathogenesis of depression is still rudimentary. Fortunately, a growing body of research has shown that when the body encounters some stressful events or injuries, HMGB1 can be actively released from microglia, triggering inflammatory responses and activating some depression-related pathways, such as the kynurenine pathway. This mechanism may be involved in the development of depression.

Nevertheless, there are still many unresolved questions and obstacles regarding HMGB1-induced depression. First, the initial mechanism behind the increased level of extracellular HMGB1 remains unknown. Second, it is unclear which signaling pathways HMGB1 activates and what roles do these pathways play in depression. Therefore, researches on HMGB1 not only contribute to a better understanding of the pathological mechanism underlying depression, but also exert a profound impact on the treatment of clinical depression patients. Further investigation in this field is highly warranted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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