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Review

Epochal neuroinflammatory role of high mobility group box 1 in central nervous system diseases

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Abstract: The central nervous system (CNS) is enriched with a developed reaction reserve dubbed "neuroinflammation", which facilitates it to cope with pathogens, toxins, traumata and degeneration. Inflammation is a significant biological activity in reaction to injury, infection, and trauma agonized by cells or tissues. A positive inflammatory reaction mechanism removes attacking pathogens, initiating wound healing and angiogenesis. The High Mobility Group Box 1 (HMGB1) protein is abundant and ubiquitous nuclear proteins that bind to DNA, nucleosome and other multi-protein complexes in a dynamic and reversible fashion to regulate DNA processing in the context of chromatin. Complex genetic and physiological variations as well as environmental factors that drive emergence of chromosomal instability, development of unscheduled cell death, skewed differentiation, and altered metabolism are central to the pathogenesis of human diseases and disorders. HMGB1 protein, senses and coordinates the cellular stress response and plays a critical role not only inside of the cell as a DNA chaperone, chromosome guardian, autophagy sustainer, and protector from apoptotic cell death, but also outside the cell as the prototypic damage associated molecular pattern molecule (DAMP). This DAMP, in conjunction with other factors such as cytokine, chemokine, and growth factor activity, orchestrating the inflammatory and immune response. All of these characteristics make HMGB1 a critical molecular target in multiple human diseases including infectious diseases, ischemia, immune disorders, neurodegenerative diseases, metabolic disorders, and cancer. With regards to these various disease condition above, our review focus on the role of HMGB1 and CNS Diseases.

Keywords: HMGB1; Central Nervous System Disease (CNS); pro-inflammatory cytokines; core body temperature; fever

1. Introduction

Inflammation is a reaction to the innate immune system that is initiated by infection or injury. It aims to defend and preserve the body by clearing and monitoring the initial stimulus, through the secretion of cells and mediators that fight foreign substances and thus help to inhibit infection [1,2]. Although inflammation is anticipated to be protective and useful, an extreme inflammatory response can cause auxiliary tissue damage. Once activated, primed inflammatory cells may target remote sites, indicating detrimental effects of long-term inflammation [2,3]. The brain has been seen as an immune privileged site due to the presence of extremely restrictive blood brain barrier (BBB). Though, "neuroinflammation," inflammation of the central nervous system (CNS) still happen [2].

High Mobility Group Box 1 (HMGB1) with about 106 molecules per cell, is the most highly secreted of all the High Motility Group family [4]. The name HMGB1 was coined out due to its rapid mobility on electrophoresis gels and function as a nuclear DNA binding protein. HMGB1 is greatly-secreted in various tissues and higher levels are found particularly in the spleen and thymus [5]. The threshold for the HMGB1 requirement to function in various biological processes may differ and may also depend on the cell type. Research has indicated that the secretion of HMGB1 in myeloid cells is higher than in lymphoid cells [6] and correlates with the differentiation stage of these cells [7]. It is clear that the secretion of HMGB1 is up regulated in cancer, but down regulated during aging [5,8] which indicate its critical role in development and cancer. It has also been indicated that over secretion of HMGB1 in cardiac tissue by transgenic methods significantly increases survival and protects mice against myocardial infarction by enhancing angiogenesis and cardiac function [9]. Studies have shown that conditional knockout of HMGB1 in the pancreas [10], liver [11], or macrophages [12] renders mice more sensitive to pancreatitis, liver ischemia/reperfusion injury and sepsis respectively. It is also indicated that HMGB1 conditional knockout strategies may cause substantially different functional phenotypes in the liver and heart [13].

Researchers have developed interest in exploring of the role of HMGB1 in the CNS very recently and HMGB1 has been studied extensively in patients affected with autistic disorders, anorexia nervosa, traumatic brain injury (TBI) in which HMGB1 levels are increased in cerebrospinal fluid (CSF), cell necrosis, bacterial and aseptic meningitis, epilepsy and febrile seizures where HMGB1 and pro-inflammatory cytokines (PIC) play a crucial pathogenic role. Research conducted with the intention of possible creation of a novel antiepileptic strategy based on pharmacological modulation of HMGB1-TLR/RAGE axis showed increased values of HMGB1 in both serum and CSF in patients with neuromyelitis optica and multiple sclerosis [14-16]. Initial studies have found out that HMGB1 mRNA levels are elevated in patients with TBI with most injuries located at the parieto-frontal cortex [17] and intracerebroventricular (ICV) injection of HMGB1 increases tumor necrosis factor-alpha (TNF-α) bioactivity in mouse brain and produces aphasia and taste aversion [18]. Current studies have also demonstrated the role of HMGB1 as a PIC with activity in the CNS. More studies have also been done on the various CNS disease. We review the cogent role of HMGB1 in these diseases and its therapeutic potentials as well as its PIC activities in the brain.

2. Structure of HMGB1

HMGB1 is made up of three cysteine residues. Two of which form a disulphide bond and all three are sensitive to oxidation status in the environment. HMGB1 now grouped into three isoforms and

these isoforms are named “disulphide HMGB1”, “thiol HMGB1” and “oxidized HMGB1” [19-21]. These isoforms have pleiotropic activities like any other cytokine and the activities depend on the cellular compartment of action, the reciprocal receptor and the specific molecular structure of the isoform. The principal isoform secreted during necrosis is thiol HMGB1 while the disulphide HMGB1 isoform is the main isoform that gathers in the extracellular space and serum compartment during acute and chronic inflammation. It is PIC-like molecule that activates macrophages/monocytes and other cells to produce cytokines and additional inflammatory mediators. The oxidized HMGB1 isoform is seen as noninflammatory, although the initial roles of this molecule is yet be known [21,22].

3. The role of nuclear HMGB1

HMGB1 acts a chaperone in the nucleus and regulates a number of key activities such binding and bending of DNA as well as chromatin replication and nucleosome assembly. Studies have shown that HMGB1 and linker histones (H1 and H5) are the important proteins that bind to linker DNA between successive nucleosomes in the chromatin fiber [23] which happens at their acidic and basic tails respectively [24]. Research has also demonstrated elevation of Circulating nucleosomes including histones and genomic DNA in patients with cancer, stroke, trauma, sepsis, and autoimmune diseases [25]. It is also now clear that the ability of HMGB1 to bind to DNA is also regulated by post-translational modifications (e.g., phosphorylation, acetylation, and oxidization) [26]. It is known that during V (D) J recombination, HMGB1 plays a vital role in the formation of RAG-RSS-HMG complexes to enhance RAG1/RAG2 activity [27].

It has also been indicated that during replication, the role of HMGB1 in DNA is regulated by post-translational modification in which the phosphorylated form of HMGB1 reduces the HMGB1-mediated polymerizing activity of DNA polymerase but does not influence its binding to single stranded DNA (ssDNA). Studies have also indicated that HMGB1 play a crucial role in transcription rates and gene expression by enhancing interaction with RNA polymerase (transcription by RNA polymerase II), promoting interaction with the TBP (TATA binding protein)/TATA-box complex [28] and long terminal repeat (LTR) [29] affecting recruitment of other general transcription factors, sustaining nucleosome dynamics and number at a global level, promoting assembly [30,31] and acting as an activator, enhancer, repressor, or silencer locally by interfering with several sequence-specific transcription factors to their cognate DNA. It is also demonstrated that HMGB1 has a dual role in DNA repair and cell death which depends on multiple factors were up or down regulation of HMGB1 enhance its translocation from the nucleus to the cytoplasm, increase DNA damage, decrease DNA repair efficiency and also increase cell death in response to chemotherapy, irradiation, and oxidative stress as a result of HMGB1 directly binding to a variety of bulky DNA lesions hence allowing it to participate in DNA repair pathways.

Yuang and colleagues reported involvement of HMGB1 in DNA mismatch repair initiation and excision [32] but Robertson et al. indicated that base excision repair is an evolutionarily-conserved pathway that corrects base lesions generated from oxidative, alkylation, deamination, and depurinatiation/depyrimidination damage [33]. It is now noted that two sub pathways, short-patch and long-patch are involved in base excision repair with short-patch pathway leading to insertion of a single nucleotide, while the long-patch pathway is involved in insertion of at least two nucleotides. The role of these two sub pathways are to initiate DNA glycosylase that recognizes a damaged base or a base in a specific DNA sequence and then removes the base by hydrolysis of the N-glycosylic bond.

HMGB1 is also now known to function as a regulator of the base excision repair pathway by its DNA binding and protein interaction activity [34].

Research again indicated that HMGB1 in yeast and mammalian cells promotes chromosomal instability and telomere aberrant events [35]. It is also indicated that a catalytic protein subunit (telomerase reverse transcriptase, TERT) and an RNA subunit (telomerase RNA, TR) are the two main core components in telomerase with shelterin; a six-subunit protein complex (TRF1, TRF2, TIN2, Rap1, TPP1, and POT1) as protecting agent. It has also been proven that HMGB1 acts as a cellular cofactor of Sleeping Beauty (SB) transposase, and physically interacts with SB to facilitate SB binding to the inner direct repeat element via its binding activity, which in turn stimulates synaptic complex formation and DNA recombination hence over secretion of HMGB1 by gene transfection has the ability to enhance SB mediated transposition efficiency, which provides a novel DNA transposition system for gene transfer [36]. It is clear that HMGB1 has the ability to enhance other DNA transposition systems such as herpes simplex virus/Sleeping Beauty (HSV/SB) amplicon vector platform [37] which means HMGB1 is an excellent candidate for improving gene transfer in gene therapy. Also HMGB1 promotes transfection efficiency in several systems by its nuclear localization signals and DNA binding ability [38,39] hence HMGB1 may be useful as a non-toxic gene delivery carrier in gene therapy [40]. Weber et al. indicated that extranuclear HMGB1 does not necessarily induce a proinflammatory cytokine response in the brain; rather, HMGB1 can potentiate the effects of a subsequent neuroinflammatory challenge [41].

4. Cytoplasmic HMGB1

Studies have shown that cytoplasmic HMGB1 binds many proteins involved in autophagy [42], cancer progression, and possibly the unconventional secretory pathway [43]. Lee et al. indicated that cytoplasmic HMGB1 is over-secreted and colonialized with lysosomal protein in colon, liver, and gastric cancer cells. They noted that among the cytoplasmic HMGB1-binding proteins, nine of them are related to protein translocation and secretion. Of these, annexin A2, myosin IC isoform A, myosin-9, and Ras related protein Rab10 are directly associated with the process of unconventional protein secretion which has been confirmed by an immunopreciptation experiment [43]. These identified HMGB1-binding molecules suggests new clues about the cytoplasmic functions of HMGB1 in cancer cells. HMGB1 not only binds to DNA, but also interacts with many none specific proteins by recognizing short amino acid sequence motifs [44]. Studies have indicated that HMGBI acts as an important biosensor of nucleic acid inside the cells and DNA or RNA derived from viruses, bacteria, or damaged cells trigger innate immune responses through HMGB1 which is required for subsequent recognition by specific pattern receptors [45].

5. Extracellular HMGB1

HMGB1 plays an important extracellular role in inflammation, immunity, cell growth, cell proliferation, and cell death. It is also massively secreted into the extracellular space by dead or dying cells [20]. We are now aware that extracellular HMGB1 acts as a DAMP to alert the innate immune system by recruiting inflammatory, smooth muscle cells, mesangioblasts, and stem cells [20]. In addition, extracellular HMGB1 acts as an immune adjuvant to trigger a vigorous response to activation or suppression of T cells, dendritic cells, and endothelial cells. Studies have shown that activated

immune cells (e.g., macrophages, monocytes, and dendritic cells) and endothelial cells also release HMGB1, which in turn forms a positive feedback loop that causes the secretion of additional cytokines and chemokines following inking of multiple receptors which means that HMGB1 sustains a long-term inflammatory state under stress [20]. Research has also demonstrated that extracellular HMGB1 has antibacterial, cell growth, and mitotic activity and are not only mediated by receptors, but also by its Redox state and structure [46].

6. HMGB1 as pro-inflammatory cytokine

It is well noted now that PIC is involved in a variety of immune and inflammatory responses, most notably, the initiation of an adaptive local inflammatory response that helps to contain and eliminate invading pathogens. Studies has now implicated HMGB1 as a PIC, an extracellular mediator of the innate immune system. Experimentally studies have demonstrated that bacterial lipopolysaccharide (LPS, endotoxin), a component of the cell wall of Gram-negative bacteria activates different kinds of cells to produce and secrete PICs. Researcher have shown that thermal (burn) injury increase secretion of PIC mRNA in various tissues, increases the release of HMGB1 mRNA in lung and liver [47].

In vitro studies has revealed that macrophages, monocytes, and pituicytes stimulated with LPS, interleukin-1(IL-1), or TNF-α secrete HMGB1 [48,49] and stimulation with HMGB1 increases the release of TNF-α mRNA and induces the secretion of PICs from monocytes [50,51]. Figure 1. It has also been revealed that high doses of TNF-α, IL-1, or HMGB1 are lethal, while lower doses produce signs of endotoxemia, including lethargy, piloerection and diarrhoea [48]. Further research has shown that Pathological quantities of LPS increase levels of IL-1 and TNF-α in serum and peripheral immune tissue (e.g. Lung and liver) and the pharmacological inhibition of any of these mediators significantly improves survival after a lethal dose of endotoxin [52,53]. Studies have also demonstrated that intratracheal administration of HMGB1 produces inflammatory injury to the lungs, with neutrophil accumulation, the development of lung oedema, and increased pulmonary production of IL-1 and TNF-α while anti-HMG antibodies protect against endotoxin-induced acute lung inflammation [54].

Many authors have indicated that Classic pro-inflammatory cytokines (cPICs) e.g. IL-1b and TNF-α are synergistic, redundant, and pleiotropic molecules produced by a variety of cell types including phagocytic cells such as monocytes/macrophages and CNS cells such as astrocytes and microglia. In comparison, administration of killed bacteria or TNF-α near healthy peripheral nerves creates exaggerated pain states such as mechanical allodynia [55,56] whereas HMGB1 administered over the sciatic nerve induces this enhanced pain state [57] which means that HMGB1 have similar potential as killed bacteria or TNF-α which are usually PICs. Further studies have demonstrated that Peripheral administration of PICs induces a constellation of CNS-orchestrated alterations that include fever, increased non-rapid eye movement sleep, mechanical allodynia, adipsia, aphasia, and reduced social and exploratory behaviours [55,58-60]. Furthermore, central administration of PICs also produces mechanical allodynia, learning impairments, adipsia, aphasia, and reduced social and exploratory behaviours [61-64].

Research has also indicated that Peripheral LPS administration also produces this CNS-orchestrated sickness response [61,65,66], markedly elevates PIC mRNA, IL-1, TNF-α and protein levels but HMGB1 mRNA was unchanged in the CNS [67,68]. The action of PICs within the CNS is crucial for the manifestation of these CNS coordinated components of host defence. It is also indicated

that the central administration of inhibitors of PICs inhibits the CNS mediated effects of peripheral immune stimulation and other cytokine-elevating stimuli [69,70]. Most recent studies have indicated elevation of HMGB1 mRNA in the parieto-frontal cortex in traumatic brain injury [17] and intracerebroventricular (ICV) injection of HMGB1 increases TNF-α bioactivity in mouse brain and produces aphasia and taste aversion [18] which confirms the role of HMGB1 as a PIC with activity in the CNS.

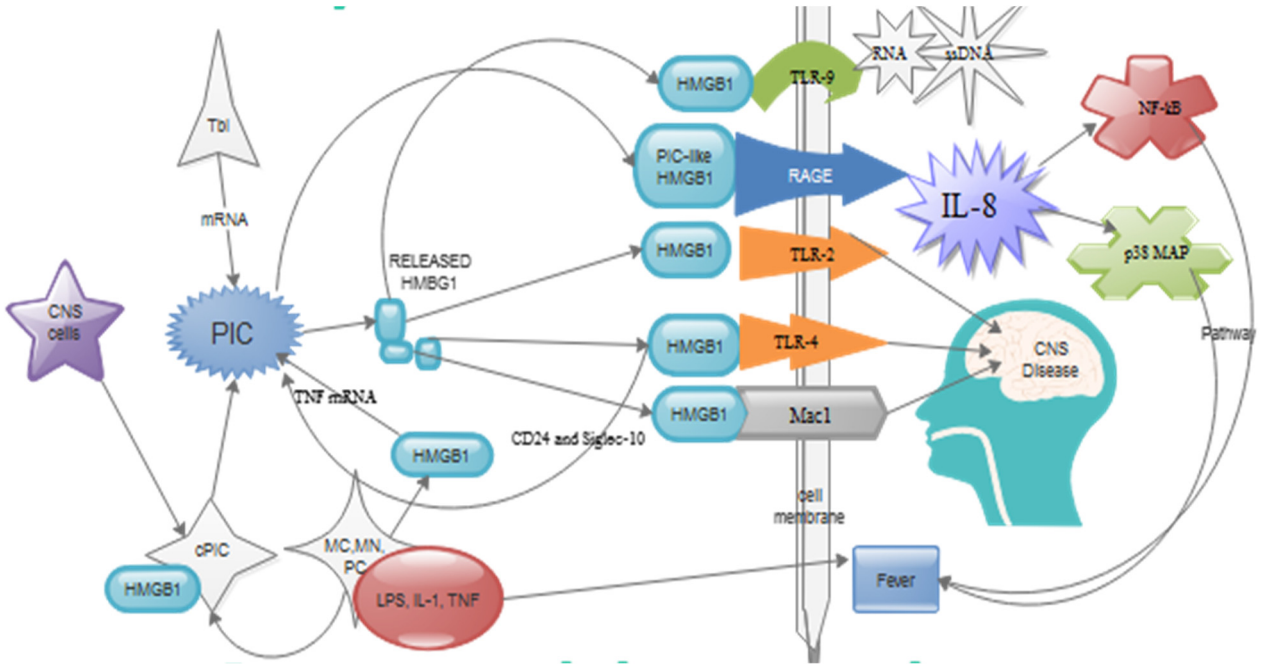

Figure 1. HMGB1 as a PIC and LPS activates CNS cells to produce and secrete PICs. Thermal (burn) injury increase secretion of PIC mRNA in tissues. A complex formed by macrophages, monocytes, and pituicytes stimulated with LPS, interleukin-1(IL-1), or tumour necrosis factor-a (**TNF-α**) to secrete HMGB1 and stimulation with HMGB1 increases the release of **TNF-α** mRNA and induces the secretion of PICs from monocytes. Membrane-bound HMGB1 (PIC-like) can bind to the receptor for RAGE and their interaction induce IL-8 production and activate NF-kB and p38 MAP kinase pathways leading fever in the CNS. LPS, interleukin-1 (IL-1), or tumour necrosis factor-a (**TNF-α**) complex can also produce fever directly with HMB1. HMGB1 may also suppress PIC release induced by HMGB1-TLR4 signalling, binding, and signalling through a bimolecular cell surface receptor complex formed by CD24 and Siglec-10 (in humans) or Siglec-G (in mice).HMGB1 act by TLR9 signalling, presenting several ligands, such as ssDNA or branched RNA structures, to its receptor.HMGB1 once released from neuronal death, binds to several receptors such as RAGE, TLR-2, TLR-4, and Mac1 in microglia, which in turn facilities neuroinflammation injury (CNS Diseases) and further HMGB1 release.

Abbreviations: CNS cells: Central nervous system cells, PIC: pro-inflammatory cytokine, TbI: Thernal Burns Injury, cPIC: Classic pro-inflammatory cytokines, MC: Macrophages, MN: Monocytes, PC: Pituicytes, IL-1: interleukin-1, TNF-α: tumour necrosis factor-a, LPS: lipopolysaccharide.

Recent studies has implicated IL-1 and TNF-α to increase core body temperature (CBT) when administered directly into the brain [71-73] (Figure 1). Some researcher have argued that while many PICs exhibit pyrogenic activity and increase IL-1 levels when injected directly into the brain, the effect of HMGB1 on CBT and hypothalamic IL-1 levels was unknown but current finding indicates that HMGB1 increased CBT and hypothalamic IL-1 levels and produced mechanical allodynia, confirming that HMGB1 can exert PIC-like effects in the CNS [74]. It is known that cytokine-induced fever is often marked as prostaglandin-dependent or prostaglandin-independent (i.e. via certain chemokines such as IL-8). It is also clear that synthesis of prostaglandins, which regulates several functions in the CNS such as the generation of fever and the perception of pain, appears to be highly regulated by both NF-kB and p38 mitogen activated protein (MAP) kinase pathways [75,76]. With the recent finding of HMGB1 as a PIC peripherally and exerts cytokine-like activity in brain, we propose that further research should conducted to ascertain the role of HMGB1 in the CNS.

7. Signalling pathways of pro-inflammatory cytokine like HMGB1

The mechanism by which HMGB1 carry out its PIC-like effects within the CNS is still a matter of debate between researches as shown in Figure 1. It is suggested that membrane-bound HMGB1 (termed ‘‘amphoterin’’) can bind to the receptor for advanced glycation end products (RAGE) [77] and their interaction induce IL-8 production and activate NF-kB and p38 MAP kinase pathways [78,79]. Therefore, HMGB1 may produce PIC-like effects directly by activating signaling cascades utilized by cPICs (i.e. NF-kB and p38 MAP kinase pathways) or indirectly by inducing cPICs. It has been demonstrated that HMGB1 may also suppress PIC release induced by HMGB1-TLR4 signaling, binding, and signaling through a bimolecular cell surface receptor complex formed by CD24 and Siglec-10 (in humans) or Siglec-G (in mice) [80]. It’s now also clear that HMGB1 act by TLR9 signaling, presenting several ligands, such as ssDNA or branched RNA structures, to its receptor [81]. Gao et al. indicated that HMGB1 once released from neuronal death binds to several receptors such as RAGE, TLR-2, TLR-4, and Mac1 in microglia which in turn facilities neuroinflammation injury and further HMGB1 release [82].

8. HMGB1 and central nervous diseases

We highlight the relationship between the HMGB1 and the varies CNS disease below. We try to elaborate on the varies disease firstly my looking broadly at the neuroinflammation mechanisms described by varies authors and secondly the epochal neuroinflammatory role of HMGB1and its receptors in aging and diverse CNS diseases.

8.1. Aging

Fu et al. noted a significate association between serum levels of HMGB1 and MyD88 during aging process in healthy people and their association with cathepsin B [83]. HMGB1 initiates inflammatory pathways through TLR4 [84-86]. TLR4 signaling is mediated by two distinct intracellular adaptor proteins: one known as myeloid differentiation factor 88 (MyD88) [83]. Cathepsins (the member of lysosomal enzymes group) have a significant function in the aging process. During aging, lipofuscin buildup can stimulate lysosomal membrane rupture. The membrane damage

can lead to the release of cathepsin B, which is known to induce inflammasomes [87]. Fu et al. demonstrated that HMGB1 and MyD88 were positively linked with cathepsin B, which is known to have an essential role in aging (Table 1) [83]. Morinaga et al. have earlier on indicated that HMGB1 and MyD88 may be involved in the aging process not through inflammatory pathways, but through other pathways, such as poly (ADP-ribose) polymerase (PARP) cleavage [88] (Table 1).

Table 1. The various CNS diseases, serum or CSF levels as well as mechanisms by each HMGBI mediate with other receptors to cause pathology. Symbols: ↑ increased, ↓ decreased.

Aging	Histo-pathology ↓ Serum ↓	HMGB1 is widely secreted throughout the brain in the early phase (E14.5-E16) of growth, while in the late phase (E18), HMGB1 is secreted in the cortical plate and thalamic area in adults but limited secretion in the regions of neurogenesis. HMGB1 and MyD88 were positively linked with cathepsin B, which is known to have an essential role in aging. HMGB1 and MyD88 may be involved in the aging process not through inflammatory pathways, but through other pathways, such as poly (ADP-ribose) polymerase (PARP) cleavage.
Huntington's disease	Serum ↓	HMGB1 can direct bind to polyQ aggregates and then promote degradation by autophagy or lysosomal pathways. HMGB1 in the nucleus leads to DNA double-strand break(DDSB)-mediated neuronal damage in Huntington's disease. Activity of APE1 and FEN1 levels are increased in association with enhanced HMGB1 expression.
Alzheimer's disease	Serum ↑	HMGB1 binding to Aβ42 inhibits microglial phagocytosis of Aβ42. HMGB1 impairs memory via TLR-4 and RAGE. HMGB1 can cause accumulation of neurotic plaques and the binding of Aβ will in turn inhibits phagocytosis and degradation of Aβ by microglial cells.
Parkinson's disease	Serum ↑	HMGB1 binds to α-synuclein in Lewy bodies impairs the autophagy pathway by binding to HMGB1 in Parkinson's disease.
Multiple sclerosis	Serum and CSF ↑	HMGB1 and its receptors RAGE, TLR2, and TLR4 are highly released in active lesions of MS.
ALS	Serum ↑	TLR-2, TLR-4, RAGE, and HMGB1 are increased in reactive glia in the spinal cord of patients with amyotrophic lateral sclerosis.
Seizure	Serum ↑	HMGB1 promotes seizures in a TLR-4-dependent pathway. HMGB1 contributed to seizes vie receptors such as IL-1 receptor, TLR2, RAGE, and NMDAR.
Autism	Serum and CSF ↑	TLR and RAGE signalling pathways are altered with a dysfunction in monocyte pathogen recognition.
AN	Serum or CSF ↑	Not yet known hence need further investigation.
TBI	Serum and CSF ↑	HMGB1 is associated with RAGE, TLR-2 and TLR-4 receptors which are ubiquitously secreted by CNS resident microglia, astrocytes and neurons during TBI.
Meningitis	CSF ↑↑	HMGB1, massively released into the cerebrospinal fluid, acts as an inflammatory cytokine through TLR pathway, mediating meningeal inflammation. Meningococcal CpG-DNA-HMGB1 enters in the cells by endocytosis and then binds to TLR9, inducing activation of inflammatory cytokines.

Trigeminal Neuragia	Serum ↑	HMGB1 and IL-1b released during cortical spreading depression (CSD) triggers of the inflammatory response. NF-kB activation in astrocytes may induce formation of cytokines, prostanoids, and inducible NO which may be released to the subarachnoid space.
NMO	Serum and CSF ↑	The positive link between CSF HMGB1 and CSF GFAP levels indicates that the damage (necrosis or apoptosis) to astrocytes could be the origin of CSF HMGB1 and elevated CSF HMGB1 levels may be a consequence of initial cell destruction by anti-AQP4 antibody and an epiphenomenon.
CVA	Serum ↑	HMGB1 also has interrelationship with IL-6 and TNF-α levels in patients with ICH. HMGB1 acts as a link between brain tissue destruction by ischemic injury and the activation and Th1 priming of T-cells.
Neuropathic Pain	Serum ↑	HMGB1 is secreted from neurons and satellite cells during and after nerve injury and augments pain hypersensitivity via RAGE or TLR4. HMGB1-neutralizing antibody inhibited pain onset in aneuropathic pain model. Blockade of panx-1 channels by carbenoxolone inhibits HMGB1 secretion in neurons and macrophages, which usually involved in the PKR-signaling pathway.
Gliomas	Serum CSF ↑	HMGB1 in necrosis and malignancy in glioma is due to an autocrine factor which enhances the growth and migration of tumor cells. HMGB1 that is secreted into the extracellular environment may cause surrounding tumor cells to undergo constant proliferation and induce the regeneration of small blood vessels, thus bolstering tumor growth. HMGB1 may cause tumorigenesis by disordered gene secretion, resulting in glial cells obtaining a tumor phenotype and resistance to apoptosis.
Psychological Stress	Histo-pathology ↓	HMGB1 as a stress signal to prime microglia for the expression of proinflammatory mediators in the brain. Blocking of TLR2 and TLR4 prevented neuroinflammatory responses during stress exposure which further supported the notion of neuroinflammation during psychological stress.

Initial research implicated HMGB1 as a heparin-binding protein abundantly secreted in rat brain neurons promoting neurite outgrowth [89]. Guazzi et al. indicated that in the early phase (E14.5-E16), HMGB1 is widely secreted throughout the brain while in the late phase (E18) (Table 1), HMGB1 is secreted in the cortical plate and thalamic area adults but limited secretion in the regions of neurogenesis [90]. Enokido and co noted that total HMGB1 secretion is highest in the brains of young adults and gradually decline during aging in the brains of mouse models hence they proposed that this could be the cause of continuous breaks of double strand DNA in the aged brain [91]. They also demonstrated that whereas HMGB1 is down regulated in the neurons of the aged brain, it is up regulated in astrocytes, meaning that the secretion of HMGB1 during aging is distinctly regulated between neurons and astrocytes [91]. Also Fang and co demonstrated that HMGB1 flaw plays dual roles in several neurodegenerative diseases, which is initially as a result of polyglutamine (polyQ) expansions in diverse proteins [92].

Fonken et al. indicated that aged rats show a “primed” neuroinflammatory response. They argue that aged animals do not release more inflammatory molecules under basal conditions, but exhibit a boosted neuroinflammatory response to an immune challenge. They demonstrated that HMGB1 mediates this neuroinflammatory “priming” in aged animals. HMGB1 gene and HMGB1 protein

expression were elevated under basal conditions in the hippocampus of aged rats as well as their CSF. They indicated that HMGB1 was likely released from microglia in the aged brain and may interact with upregulated innate immune receptors to prime neuroinflammatory responses. Furthermore, increases in HMGB1 and upregulation of innate immune receptors occurred in the absence of immune stimulation in aged rats [93].

8.2. Huntington's disease

Huntington's disease (HD) is a CNS disorder that is usually progressive in nature and affects muscle coordination and resulting in uncontrolled movements, psychiatric problems, and cognitive decline. HD is an autosomal dominant neurodegenerative disorder that is associated with mutations in the huntingtin gene (htt) [94]. Throughout HD and HD-like pathology, inflammation arises in the CNS, increasing gliosis and release of inflammation related genes, including GFAP and complement proteins [95]. Expression of mutant "htt" in microglia itself is enough to increase the expression of proinflammatory genes such as TNF-α and IL-6 [96]. The proinflammatory signals are thought to stimulate microglia further in inducing neuronal death, and this, in turn, could lead to the activationof chronic "feed-forward loop" [97].

Furthermore, it is characterized by an expanded trinucleotide repeat (CAG) n encoding glutamine on chromosome 4p16.3. Min et al. have demonstrated that HMGB1 can direct bind to polyQ aggregates and then promote degradation by autophagy or lysosomal pathways (Table 1) [98] and induce neuronal cell toxicity. Qi and co proved that the secretion of HMGB1 is decreased when mutant polyQ proteins are secreted in HD [99]. The also indicated that down regulation of HMGB1 in the nucleus leads to DNA double-strand break(DDSB)-mediated neuronal damage in HD (Table 1) [99]. Further have shown that HMGB1 acts as a cofactor to base excision repair by increasing activity of apurinic/apyrimidinic endonuclease(APE1) and 5′-flap endonuclease-1 (FEN1) (Table 1) [34,100,101] which prevent the neuronal CAG repeat expansion associated with Huntington's disease. It therefore means that HMGB1 regulates somatic CAG expansion via two different mechanisms. Fascinatingly, HMGB1 seems to be neuroprotective against the polyglutamine repeats toxicity in the HD models by exhibiting chaperone-like activity [2,79].

8.3. Alzheimer's disease

Alzheimer's disease (AD) is the most common type of dementia characterized by death of brain cells leading to memory loss and cognitive decline. The disease is noted with the formation of extracellular senile plaques and global neuronal loss. It is also associated with the production and deposition of the amyloid-beta peptide (Aβ) and the presence of intracellular tau protein tangles. In AD, microglia and astrocytes were described to confine to amyloid plaques. Consequently, neuroinflammation has been linked with the pathology of AD [102,103]. While it is clear that not all microglial activation is harmful to neurons, it is widely believed that chronic stimulation of a microglial phenotype plays key part in the pathophysiology of AD [103]. Microglia and astrocytes in and around Aβ plaques release proinflammatory factors and proteases, signifying that innate immune response is a key promoter to plaque-induced toxicity [104]. Never the less TLR4 and RAGE have been suggested as a major mediator of AD [105,106] and release of HMGB1 impairs memory by RAGE and TLR4 (Table 1) [107]. Furthermore, the release of HMGB1 can cause accumulation of neurotic plaques and the binding of Aβ will in turn inhibits phagocytosis and degradation of Aβ by microglial cells (Table 1) [108,109].

8.4. Traumatic brain injury

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality and usually due to road traffic accidents and a result of acceleration and deceleration [110]. Shortly after traumatic injury, a vigorous inflammatory reaction is inducted in the injured brain, a squeal which involves the activation of resident glial cells (microglia and astrocytes) and the infiltration of blood leukocytes. Furthermore, cytokines (e.g., IL-1, TNF-α, and IL-6) and chemokines (MCP-1, MIP-1, and RANTES) drive the accumulation of parenchymal and peripheral immune cells in the injured brain regions [111].

Research has shown that TLR4 facilitates innate immune activation and edema development after TBI. It has been proven that, there is correlation between immune activation and the augmentation of post-traumatic brain edema and the release of neuronal HMGB1 may induce microglial activation [112,113]. There is time dependent increase in microglial TLR4 elucidation occurred within the peri-contusional cortex, exhibiting both a temporal and spatial overlap with edema formation [112,113]. Inhibition of TLR4 mitigated the delivery of AQP4 an astrocytic water channel involved in the evolution of cellular edema although the mechanism responsible for microglia interaction with astrocytes remained undetermined. Therefore, the unique involvement in HMGB1-TLR4 signaling is the regulation of AQP4 and promotion of cerebral edema, a primary cause of patient mortality after brain injury by establishing the mechanism responsible for microglial-astrocytic interactions increases acute neurovascular injury using pre-clinical models and human tissue cultures [112,113].

Studies have shown that HMGB1 contribute to the degree of necrosis and apoptosis observed after TBI which leads to cell death and neurological morbidity [114]. Further studies in adults reveals the correlation between Glasgow Coma Scale score and HMGB1 levels which can serve as prognostic information in patients with severe TBI [115]. Researchers have also demonstrated that increased CSF levels of HMGB1 are associated with poor outcome in a study conducted to evaluate HMGB1 levels in ventricular cerebrospinal fluid (CSF) after TBI [116]. Studies have also demonstrated that the main receptors associated with HMGB1 and brain injury are RAGE, TLR-2 and TLR-4 which are ubiquitously secreted by CNS resident microglia, astrocytes and neurons (Table 1) [117,118]. It is now clear that Anti-HMGB1 monoclonal antibodies could be a novel and effective therapy for TBI by protecting against blood–brain barrier disruption and reducing the inflammatory responses induced by HMGB1 [113,119]. We propose that targeting HMGB1 signalling may be a promising therapeutic approach for the treatment of TBI in the general population, but more studies are required to further understand the pathophysiological role of this molecule in TBI.

8.5. Parkinson's disease

Parkinson's disease (PD) is characterized by abnormal accumulation of alpha-synuclein filaments in Lewy bodies which leads to neuropathological of the disease as well as sequestration of cellular protein into these protein aggregates hence contribute to the degenerative process. A classic motor phenotype emanating from substantial loss of dopaminergic neurons from the substantia nigra pars compacta (SNPC) is evident in PD [120]. The presence of inflammatory mediators such as TNF-α, IL-1β, IL-6, and Interferon(IFNγ) in the cerebrospinal fluid and postmortem SNPC of PD patient confirmed the association between neuroinflammation and PD [103,121].

Studies have shown that alpha-synuclein binds to HMGB1 in Lewy bodies, but the outcome of the biding is not known [122]. Song et al. indicated that while the translocation of HMGB1 from the

cytosol is inhibited when it interacts with alpha-synuclein, its interaction with Beclin-1 limits autophagy (Table 1) [123]. They again observed that corynoxine B inhibits the interaction between HMGB1 and alpha-synuclein and salvaged the impaired autophagy [123]. They therefore concluded that alpha-synuclein impairs the autophagy pathway by binding to HMGB1 in Parkinson's disease. Furthermore, in animal models of PD, an interaction between a microglial Pattern-recognition receptors (PRRs), Mac1, and HMGB1 was recognized. The HMGB1-Mac1-NADPH oxidase signaling axis is known to induce chronic inflammation and progressive dopaminergic neurodegeneration, indicating the possible role of persistent inflammation and chronic neurodegeneration [2,92,122,124].

Recent studies have shown that HMGB1 is not only found to co-localize with a-synuclein filaments in brain autopsy [122] but also found elevated in cerebrospinal fluid and serum [125]. Furthermore, systemic administration of neutralizing antibodies to HMGB1 has also been established to inhibit the microglial activation, suppress secondary neuroinflammation and thus inhibit the dopaminergic cell death upon neurotoxin exposure in PD models [125,126]. Beclin1 (Atg6) is an evolutionarily conserved protein family that has been proven to function in autophagy process in a diverse variety of species [127]. In mammalian cells, Beclin1 function as a vacuolar protein sorting (Vps) protein and can bind to Class III PI3K Kinase (Vps34), thus forming a Beclin1-Vps34 complex which is of critical significance in autophagy modulation [128]. Accidentally, HMGB1, a novel endogenous Beclin1 binding protein, was recognized to compete with Bcl-2 to orient Beclin1 to autophagosome, thus contributing to the modulation of autophagosome development [129]. Huang et al. therefore proposed that HMGB1 and Beclin1-Vps34 complex may probably play an important role in autophagy modulation in the context of PD [130].

8.6. Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease involving the brain, spinal cord, and optic nerves. It is also referred to as disseminated sclerosis or encephalomyelitis disseminate. There are four fundamental pathological characters of MS: (a) inflammation, of complex pathogenesis, which is generally believed to be the key trigger of the events leading to CNS tissue damage in the majority of cases, although recent evidence suggests that initial damage to neuroglial elements can initiate secondary inflammation in some cases; (b) demyelination, the hallmark of MS, where the myelin sheath or the oligodendrocyte cell body is destroyed by the inflammatory process; (c) axonal loss or damage; and (d) gliosis (astrocytic reaction to CNS damage) [131].

The interaction between multiple components of the immune system and all elements of the CNS determine the pathogenesis of MS. T cells in the periphery become stimulated by a viral or another infectious antigen or a superantigen. These T cells are capable of producing inflammatory cytokines and may be differentiated or have the potential to differentiate on activation into Th1 (producing IFN-gamma) or Th17 cells (IL-17, IL-22, IL-21) or cells producing both [131,132]. Activated T cells up-regulate integrins such as VLA-4 and are capable of crossing the BBB. Through the permeabilized BBB, attracted by chemokine release, other immune cells including B cells and monocytes/macrophages migrate into the CNS. There, they encounter the cognate antigen, probably originated from myelin antigen, presented by CNS resident or immigrant antigen-presenting cells (APC). These can be macrophages/microglia and in certain cases dendritic cells or astrocytes. On encountering the antigen, such autoreactive T cells are reactivated and differentiate, producing their signature cytokines, which activate the neighbouring immune or neural cells and attract further

inflammatory cells into the CNS. Of these, it is especially activated macrophages that are thought to indirectly and directly damage the CNS [131].

Wang et al. demonstrated that serum HMGB1 levels are elevated in patients with MS as compared to patients with other neurological disorders [16]. Andersson and associates also noted higher numbers of macrophages and microglial cells with nuclear and cytoplasmic secretion of HMGB1 than in white matter derived from controls during immunohistochemically staining of brains with MS at autopsy. They also indicated that HMGB1 and its receptors RAGE, TLR2, and TLR4 are highly released in active lesions of MS as well as in its counterpart animal model EAE, while being secreted at normal levels in inactive lesions (Table 1). Hence they concluded that the potential interaction of these molecules in the inflammatory process involved in pathogenesis [133].

Sternberg et al. also confirmed elevation serum HMGB1 levels in patients with MS, as compared to healthy controls and proposed novel role of inflammatory-like cytokine in MS pathogenesis [134]. The origin of HMGB1 in MS patients' serum may be diverse. HMGB1 can find its way into the serum through intrathecal secretion [133] in patients with MS who often have BBB leakiness [135]. Further studies have indicated that the origin of HMGB1 in MS patients' serum may stem from both the secretion from immune-activated cells (macrophages/microglia) and from injured brain cells as well as neurons and astrocytes, where the protein is being synthesized [18].

8.7. Autistic disorders

Autism is a neurodevelopmental disability associated with impairments in verbal communications, reciprocal social interactions, and restricted repetitive stereotyped behaviours [119]. The disease is characterized by recurrent uncontrolled immune function, reactive antibodies, and altered cytokine levels in the brain as well as altered function of innate immune cells [136]. Autistic disorder (AD) brain transcriptome studies identify molecular abnormalities in synaptic and immune/microglia markers gene expression, with the former being downregulated and the latter upregulated [137,138]. Other genes related to inflammation (e.g., il-1raplp1, il-1r2, c4b, met, mch2, par2, mtor1, and μpar) have been reported to be differentially expressed in ASD as well [137,139]. Furthermore, Genes involved in synapse formation or brain connectivity (e.g., fmr1, mecp2, shank3, tsc, neuroligin, and cntnap2) have been repeatedly linked to ASD [137,140,141].

Studies have shown HMGB1 levels are higher in Autistic children as compare with healthy controls [142] and a high incidence of A-allele homozygosis in the GLO1 gene with reduction in Glo1 activity [143]. It has been suggested that HMGB1 receptors are involved in the pathophysiological mechanisms of autism. Research has shown evidence dysfunction in monocyte pathogen recognition and/or TLR signalling pathways when a study was conducted to determine abnormal sensitivity of peripheral blood monocytes, isolated from children with and without autism (Table 1) [144]. Studies have also indicated that autism is associated with accumulation of methylglyoxal in the brain which leads to the formation of advanced glycosylated end products (AGE), which ultimately induces the RAGE mediated downstream signalling cascade (Table 1) [145]. We therefore suggest that further studies should carried to determine the correction between HMGB1 and this neurodevelopmental disorder since serum levels of HMGB1 could become a crucial biomarker in this disease.

8.8. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder caused by loss of motor neurons and extensive astrogliosis and microglial activation in the motor cortex and spinal cord. Most ALS cases are sporadic in origin; however, 5–10% cases are caused by an autosomal dominant mutation [2]. It is generally fatal within 5yr of diagnosis due to a progressive generalized paralysis, weakening respiratory muscles, and initiating respiratory failure [13]. In ALS patients and mouse models of ALS, areas with degenerating motor neurons are evident by the presence of abundant cytokines (e.g., TNF, MCP-1, TGF-β, and IFN-γ) and inflammatory cells (e.g., T cells, activated microglia, and astrocytes) [146,147].

HMGB1 and its receptors such as TLR2, TLR4, and RAGE are increased in reactive glia, whereas they are decreased in degenerating motor neurons in patients with amyotrophic lateral sclerosis, suggesting a possible role in the progression of inflammation and motor neuron degeneration (Table 1) [148,149]. In addition, serum HMGB1 autoantibody is increased in patients with amyotrophic lateral sclerosis compared with patients with Alzheimer's disease and Parkinson's disease [150]. These findings suggest that HMGB1 autoantibody may be a biomarker for amyotrophic lateral sclerosis [150].

8.9. Trigeminal neuralgia

During trigeminal nerve injury, inflammatory process leads to the secretion of pro-inflammatory cytokines, growth factors, hydrolytic enzymes and nitric oxide (NO), with resulting decrease in nociceptors activation threshold and increase in nervous fiber excitability [151,152]. Besides, inflammation and inflammatory mediators' secretion, neuropeptides and neutrophic factors, degenerative nervous fibers changes caused by direct damage, such as axonal injury and demielination, are also relevant peripheral mechanisms. Cytokines like TNF-α, IL-1β and IL-6 have been implied both in central and peripheral sensitization Trigeminal neuralgia: peripheral and central mechanisms [151,153]. TNF-α is able to promote neuronal hyperexcitability, to increase excitatory transmission and to promote inflammation in several nervous system levels, becoming an important mediator for chronic neuropathic pain, in addition to an excellent therapeutic target [151,153]. IL-1β produces systemic inflammation, induces substance P (SP) and NO production, having important function in pain development and maintenance. There are strong evidences that IL-1β reinforces synaptic transmission and neuronal activity in several nervous system sites [151,153]. IL-6, in turn, promotes neutrophils maturation and activation, maturation of macrophages and differentiation of cytotoxic T and natural killer lymphocytes [151]. IL-6 is predominantly pro-inflammatory in neuropathic pain, promoting inflammation exacerbation through the activation of glial cells in the central nervous system [151,153].

Karatas et al. hypothesize that stress-induced neuronal Pannexin1(Panx1) activation may cause headache by releasing pro-inflammatory mediators such as HMGB1 from neurons, which triggers a parenchymal inflammatory response leading to constant release of inflammatory mediators from glia limitans thereby prolonging trigeminal stimulation [154]. They indicated that while HMGB1 and IL-1b released during cortical spreading depression (CSD) may take part in triggering of the inflammatory response, NF-kB activation in astrocytes may induce formation of cytokines, prostanoids, and inducible NO which may be released to the subarachnoid space via glia limitans thereby stimulating trigeminal nerve endings around pial vessels (Table 1). Therefore suggested that by promoting constant headache, HMGB1 levels may serve biomarkers that can predict that the brain parenchyma has been

stressed by CSD or CSD-like events [154]. Other researchers are of the view that HMGB1 is most likely not the only mediator carrying out this function since other cytokines as well as microglia may also take part along the course of inflammatory response [155,156].

8.10. Neuromyelitis optica

Neuromyelitis optica (NMO) or Devic's disease, is a rare autoimmune disorder characterized by recurrent optic neuritis or myelitis and manifested clinically with loss of vision, muscle strength, and coordination, sensory impairment, as well as paraplegia or even tetraplegia. NMO-IgG from NMO-positive patients' serum was found to bind to distal urine-collecting tubules and to basolateral membranes of the epithelial cells of the gastric mucosa. This distribution suggested the water channel protein, AQP4 as the target autoantigen in NMO. AQP4 is an integral protein of astrocytic plasma membranes and is highly concentrated in the astrocyte foot processes [157]. In most NMO patients CSF analysis exhibits some abnormalities. Neutrophils are commonly found, and even the presence of eosinophils can be noted [158]. Protein content and some cytokines as interleukin (IL)-17 and IL-8, and the numbers of IL-5 and IL-6, IgG and IgM secreting cells are increased [158,159].

Many researchers have demonstrated elevation of HMGB1 in Serum and cerebrospinal fluid in patients with NMO which implies that HMGB1 could be a potential diagnostic marker for NMO in the early stages [15,16,160]. Uzawa et al. proved a marked elevation of CSF HMGB1 levels in NMO patients compared with those in MS and ONNDs patients. They also noted that CSF HMGB1 levels in NMO patients were also positively correlated with the CSF cell counts, CSF protein levels, CSF IL-6 levels, CSF GFAP levels and QAlb. They indicated that the elevation of CSF protein content and QAlb could be due to blood-brain barrier disruption, as increased permeability of the blood-brain barrier may have facilitated the access of anti-AQP4 antibody to astrocytes and further infiltration of the immune components into the CNS. They further explained that the elevation of CSF HMGB1 levels in NMO patients might be due to severe CNS inflammation or due to cell death by necrosis or apoptosis. They therefore concluded that the positive link between CSF HMGB1 and CSF GFAP levels indicates that the damage (necrosis or apoptosis) to astrocytes could be the origin of CSF HMGB1 and elevated CSF HMGB1 levels may be a consequence of initial cell destruction by anti-AQP4 antibody and an epiphenomenon (Table 1) [160].

8.11. Anorexia nervosa

Anorexia nervosa (AN) is an eating disorder primarily affecting girls and young women characterized by pathological fear of becoming fat, distorted body image, excessive dieting and emaciation.

The role of inflammation in AN is suggested by several lines of evidence [161]. Animal models proven that several pro-inflammatory cytokines lead to early satiety through interaction with hypothalamic neuropeptides. IL-6 and IL-1β have anorexigenic effects, interacting with leptin [162,163], while TNF-α stimulates the production of anorexigenic peptides [164]. Human data support this preclinical evidence. For example, different inflammatory mediators are known to reduce hunger leading to anorexia as observed in many chronic diseases [165], and case reports of patients affected by AN revealed significant weight gain and psychopathological improvement when inflammatory pathways were suppressed by immunosuppressive therapies [166]. Though, it remains unclear how

inflammation may interact with neuropeptide Y, an orexigenic peptide, which could play a part in binge-purging behaviors [167] and which has been reported to being elevated in AN [168], with cholecystokinin, a neuropeptide possibly playing a part in the adaptation of appetite to low food intake in AN [169], or with leptin, the "satiety hormone", which has been consistently reported being decreased in AN [170]. Finally, inflammation can be associated with depression, which is an important comorbidity in AN [171]. Since anorexia is a symptom of depression, the association between AN and depression could partially explain patients with AN can resist extreme starvation [161].

Studies have shown that administration of HMGB1 into cerebral ventricles in rats reduces food intake and in a model of endotoxemia, passive immunization with antiHMGB1 antibodies attenuated the development of hypoplasia [18]. When HMGB1 was evaluated in patients with AN at baseline, it was notes that high HMGB1 values recorded in AN patients who did not respond to nutritional rehabilitation and cognitive behaviour therapy [172]. We suggest that further studies are needed to determine the association between serum HMGB1 and signalling mechanisms involved in AN pathological process.

8.12. Seizure disorders

Seizure disorder, is characterized by a sudden change in behavior including loss of consciousness as result of increased electrical activity in the brain. Experimental and clinical findings support a significant responsibility of inflammation in the mechanisms underlying the generation of seizures [173]. Rodent studies showed that seizures stimulate high levels of inflammatory mediators in brain regions that are intricate in the generation and propagation of epileptic activities [174,175]. Proinflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α) are upregulated in activated astrocytes and microglia that activate a cascade of inflammatory events, involving neurons and vascular endothelial cells. Furthermore, inflammatory cytokines stimulate multiple pathways such as NF-κB, cyclooxygenase-2 (COX-2), complement system, chemokines, and acute phase proteins [176,177]. The rapid release of DAMPs from neurons, astrocytes, and microglia following proconvulsant injuries and activation of TLRs in astrocytes and neurons is considered as a critical event for initiating brain inflammation [178,179]. In seizure models, brain inflammation is thought to be elevated by BBB breakdown via the disruption of tight-junction organization [180-182].

Studies have confirmed elevation of Serum HMGB1 levels in child febrile seizure patients [183] and experimental models of seizures and in temporal lobe epilepsy showed that HMGB1 contributed to seizures in a TLR-4-dependent pathway by triggering tissue damage and the inflammatory response [178,184]. Current studies have demonstrated that HMGB1 contributed to seizes vie receptors such as IL-1 receptor, TLR2, RAGE, and NMDAR (Table 1) [185-189] which means that a complex receptor interaction is required for HMGB1-induced seizure.

8.13. Cerebrovascular accidents

Cerebrovascular accidents (CVA) is a sudden interruption of the blood supply to the brain caused by ruptured of an artery in the brain (cerebral haemorrhage) or the blocking of a blood vessel as by a clot of blood (cerebral occlusion). Hypoxia and energy deficiency cause Sudden cellular injury or death. The activation of microglia was seen in the penumbra after the first hour to days of ischemic event [190,191]. Several studies have directly linked inflammatory reactions with the degree of stroke associated brain

damage and infarct growth. Moreover, inflammation mediators, infarct size, and brain edema were markedly reduced by anti-inflammatory treatments [190,192]. The activation of innate immune responses has significant function in the generation of proinflammatory molecules. Additional, DAMPs such as heat shock proteins (HSPs) and adenosine triphosphate (ATP) are thought to be released from dying cerebral tissue after stroke that are sensed by putative receptors (e.g., TLR2, TLR4, and RAGE) to signal mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB) resulting the stimulation of inflammatory cascades, leading to the expression of TNF-α, IL-1β, ICAM-1, VCAM-1, E-selection, and iNOS [190].

Zhou and colleagues demonstrated that HMGB1 levels were elevated in patients with intracerebral haemorrhage (ICH) as compared to controls. They also indicated that the severity of stroke determines the level of expression of HMGB1 since patients with ICH and poor outcome had higher levels of HMGB1 than those with a favourable outcome. They further indicated that there is interrelationship between HMGB1 levels and the National Institutes of Health Stroke Scale (NIHSS) at day ten after stroke, and with the modified Ranking scale score at 3 months and that HMGB1 also has interrelationship with IL-6 and TNFα levels in patients with ICH (Table 1) [193].

Newburger et al. also observed elevation of HMGB1 levels in patients with cerebral vascular ischemia within 24 h after the onset of symptoms as compared to control subjects [194]. They also noted that elevation of HMGB1 levels in patients with stroke remain up to 14 days after the ischemic event as compared to normal controls while levels of the natural inhibitors of HMGB1, soluble RAGE (sRAGE) and esRAGE, remain unremarkable compare with control subjects within 48 h following stroke. Tang et al. observed the interrelationship between HMGB1 levels in patients with stroke and IL-6 levels but not with the extent of brain tissue destruction using CT morphometry. They indicated that patients with stroke has significate elevation of activated CD4+ T-cells in peripheral blood secreting CD25 or HLA-DR when compared to controls [195]. They proposed that due to the resemblance of the kinetics of serum HMGB1 and the kinetics observed for the absolute number of CD4+ T-cells secreting HLA-DR, they proposed a hypothesis that HMGB1 acts as a link between brain tissue destruction by ischemic injury and the activation and Th1 priming of T-cells (Table 1) [195].

8.14. Neuropathic pain

Neuropathic pain is caused by nervous system injury and persistent alterations in pain sensitivity. The crosstalk between glial cells and neurons is significant in the progress of neuropathic pain. Proinflammatory cytokines such as IL-1β, IL-6, and TNF produced by glial cells and neurons accelerate central pain sensitization, and inhibition of these cytokines in the CNS and PNS effectively reduces neuropathic pain [196,197]. Brain-derived neurotrophic factor (BDNF) derived from activated microglia potentiates the excitability of spinal neurons [198]. Microglial IL-18, a member of the IL-1 family, also plays a pivotal role in neuropathic pain [199]. IL-1β generated by macrophages and Schwann cells in injured nerves directly sensitizes nociceptors in primary afferent neurons [200]. IL-1 stimulates the secretion of substance P from DRG neurons [201] and neuropathic pain is reduced in IL-6 CCL2-knockout (KO) mice [202]. IL-6 can similarly contribute to pain by increasing the sensitivity of nerve endings [202]. IL-6 can increase neuropathic pain in the dorsal horn by activating STAT3 signaling in glial cells after peripheral nerve injury. The STAT-3 pathway is a fundamental mediator of signal transduction in neuropathic pain [203]. IL-17 is an essential regulator of immune responses and is involved in stimulating and mediating proinflammatory reactions in a wide range of

inflammatory and autoimmune diseases of the nervous system. Using IL-17 KO mice, it has been proven that IL-17 contributes to neuroinflammatory responses and pain hypersensitivity following neuropathic injury [196,204].

Initial studies implicated TNF-α as having toxic effects on myelin, Schwann cells, and endothelial cells, and may be involved in the pathogenesis of demyelination and the breakdown of the blood-nerve barrier in autoimmune neuropathies. Many researchers have demonstrated that HMGB1 is secreted from neurons and satellite cells during and after nerve injury and augments pain hypersensitivity via RAGE or TLR4 (Table 1) [205-207]. Further studies have demonstrated that HMGB1-neutralizing antibody inhibited pain onset in aneuropathic pain model [208,209]. Karatas et al. recently noted that Panx1 channel which is a mediator of migraine and depression also mediated HMGB1 secretion from neurons (Table 1) [154]. They indicated that blockade of panx-1 channels by carbenoxolone inhibits HMGB1 secretion in neurons and macrophages, which usually involved in the PKR-signaling pathway (Table 1) [154,210].

8.15. Neurological infectious diseases

Meningitis is an acute inflammation of the dura membranes covering the brain and spinal cord which may evolve in response to a number of pathogens such as bacteria, viruses, fungi, physical injury, cancer, or drugs. The binding of a cytokine or chemokine ligand to its cognate receptor during CNS infections results in the activation of the receptor, which in turn triggers a cascade of signaling events that regulate various cellular functions such as cell adhesion, phagocytosis, cytokine secretion, cell activation, cell proliferation, cell survival and cell death, apoptosis, angiogenesis, and proliferation [196,211].

Pneumococci can cross the BBB, so microglia may respond directly to intact bacteria or to pneumococcal cell wall antigens and produce a wide array of inflammatory mediators including TNF, IL-6, IL-12, keratinocyte-derived chemokine (CXCL1/KC), CCL2/MCP-1, CCL3/MIP-1α, CXCL2/MIP-2, and CCL5/RANTES, as well as soluble TNF-α receptor II, a TNF antagonist. The production of these inflammatory mediators is associated with the activation of the extracellular signal-regulated protein kinases ERK-1 and ERK-2 via a MAPK intracellular signaling pathway [212,213]. Homologous antibodies to TNF, IL-1α and IL-1β inhibited leukocytosis and brain edema and moderately decreased BBB permeability in this model of meningitis [214]. The anti-inflammatory cytokine IL-10 has been implicated in playing a role in modulating the immune response by downregulating TNF, IL-6, and keratinocyte-derived chemokine (KC), thereby reducing CSF pleocytosis in pneumococcal meningitis [215]. IL-8 appears to regulate CSF pleocytosis in pneumococcal meningitis from the systemic compartment, similar to that seen for TNF, IL-10, and TGF-β [216].

Resultant abscess formed at the site of infection may result in inflammation accompanied by edema, neuronal toxicity, seizures, and long-term cognitive loss [217]. Researchers proven that S. aureus not only induces brain abscesses but also elicits rapid and sustained expression of numerous proinflammatory cytokines and chemokines including IL-1β, TNF, IL-12 p40, CXCL2, CCL2, CCL3, and CCL4 [218-220]. Leukocyte recruitment elicited by microglia into the infected CNS facilitates bacterial clearance during abscess development. Microglia also exert S. aureus bactericidal activity. The organism is a potent inducer of numerous inflammatory molecules in microglia such as TNF, IL-1β, and CXCL1, among others [221,222]. Necrotic damage associated with brain abscesses and other CNS infections is accompanied by release of endogenous host molecules that could potentially exacerbate parenchymal necrosis in addition to that mediated by unchecked microglial activation. On

the other hand, cytokines like IL-1β, TNF, and IL-6 may exert beneficial effects on the establishment of host antibacterial immune responses. A study that assessed the relative significance of IL-1β, TNF, and IL-6 in experimental brain abscess using cytokine KO mice revealed that IL-1 and TNF play a key role in directing the ensuing antibacterial response, as bacterial burdens were significantly higher in both IL-1 and TNF-α-KO mice compared to wild-type mice which correlated with enhanced mortality rates in KO mice [223].

Tang et al. observed the elevation of HMGB1 levels in patients with bacterial meningitis as compared to controls [224]. Many studies have indicated the role HMGB1 in sustaining inflammation in CSF and brain damage during bacterial, aseptic, and tuberculous meningitis [224-226]. Studies have shown that tissue damage secondary to meningeal inflammation is induced by TLR signaling activation (Table 1) [227-229]. HMGB1, massively released into the cerebrospinal fluid, acts as an inflammatory cytokine through TLR pathway, mediating meningeal inflammation. Meningococcal CpG-DNA-HMGB1 enters in the cells by endocytosis and then binds to TLR9, inducing activation of inflammatory cytokines (Table 1). Alleva and co have also observed a pathogenetic role of HMGB1 in children showing cerebral symptoms as a result of severe falciparum malaria. They noted elevation of HMGB1 levels in patients with malaria as compare to controls, and proposed that HMGB1 levels are strictly related to patient's prognoses [230]. We propose that HMGB1 in the cerebrospinal fluid could become biomarkers for neurological infection diseases. However, further studies are required to find out the receptors needed in the pathogenesis between HMGB1 and neurological infections.

8.16. Gliomas

Human malignant brain tumor specimens including glioma, neuroblastoma, and medulloblastoma secret a high level of diverse cytokines that are involved in numerous pathways of cancer progression [231,232]. Obviously, IL6 has a significant relationship with brain cancer development. When it is released from astrocytes, IL-6 facilitates tumor development through induction of angiogenesis, cell proliferation and resistance to apoptosis [233]. IL-8, a powerful mediator of angiogenesis, is extremely over secreted in most brain cancers [234]. It stimulates the production of MMPs that play an essential part in angiogenesis and also stalls the apoptotic death of endothelial cells which in turn produces more MMPs. Another important role of IL-8 is its chemotactic attraction of diverse leukocytes, particularly neutrophil, which characterizes its involvement in various inflammatory responses and infectious disease. Upon secretion by monocytes and macrophages, IL-8 endorses migration of neutrophils, basophils, and T-lymphocytes [231].

Macrophages immensely insinuate brain tumor microenvironment, and its concentration correlates with tumor the grade in GBM. Therefore, IL-8 is mainly present in the perivascular areas of pseudopalisading cells near the necrosis. High-grade gliomas show amplified secretion of IL-8. The endogenous release of IL-8 is very low or almost undetectable in normal CNS areas because firmly regulated cytokine. The abnormal secretion of IL-8 in GBM is believed to be instigated by the activation of NF-κB. In glioma microenvironment TNF-α secretion lead to advancement tumor formation and angiogenesis [235]. It creates neovascularization through the stimulation of VEGF and IL-8. A study has discovered that TNF-α can activate phosphorylation of NF-κB and signal transducer and activator of transcription 3 (STAT3) which lead to augmented expression of IL-6 in tumor site [236]. Another study confirmed TNF-α stimulated increase in major histocompatibility complex class I (MHC-I) expression

and transcriptional activation which was synchronized with elevated HIF-1α, NF-κB, and β-catenin activities [237]. Therefore, TNF-α enables glioma cells to leak from immune response and grow aggressively in the inflammatory microenvironment. TNF-α additionally plays an important part in tumor growth by activating macrophages through SDF-1 stimulation to attack T-cells and other immunogenic factors [231].

In a study, using GBM tumor samples, TGF-β presented the highest mRNA expression levels out of 53 cytokines examined [238]. Nevertheless, all three isoforms of TGF-β (TGF-β1, TGF-β2, and TGF-β3) are profusely release in brain cancers, TGF-β2 is the primary isoform highly secreted in GBM and stimulate proliferation of cancer cells. TGF-β2 acts as immunosuppressive cytokine and negatively interferes with the DC maturation and downstream function by lowering MHC class II expression on CD4+ T-cells [239]. Subsequently, the IL-12 production by DC reduces, which is essential to stimulate subsequent T-cell proliferation and interferon (IFN) production. This cascade of events effectively results in GBM evading the host immune system. Macrophage Migration Inhibitory Factor (MIF) might act as a pro-inflammatory cytokine and take part in the regulation of immune and inflammatory responses [240]. It has functions in the pathophysiological process as well. The inflammatory function of MIF is mediated through improved secretion of Toll-like receptor-4 (TLR4) and amplifies production of inflammatory cytokines including IL-6, IL-1, and TNF-α [241]. IL-1β is produced in astrocytomas and other brain tumors and can contribute to tumor growth and metastasis [242]. It induces secretion of other pro-inflammatory cytokines and growth factors in astrocytoma and influence astrocytoma cell function and growth. IL-1β can also cause NF-κB activation through IκB [231].

Studies have shown that necrotic cells can secrete HMGB1 into the extracellular environment [243], and necrosis is a hallmark of malignant gliomas. It well noted that continues secretion of HMGB1 accelerates the growth and progresses of Gliomas leading to progressive necrosis of the lesions. This was supported by Jing and colleagues who explored the role of *HMGB1* gene in the U251 and U-87MG cells and also concluded that the up-regulated HMGB1 secretion plays a crucial role in the development of gliomas. Their result also indicated that early apoptosis eventuated in glioma cells and the percentage of apoptotic cells was higher than that in the untransfected group of mice after up-regulating the secretion of HMGB1 [244]. Further studies have indicated the degree of secretion of HMGB1 in different pathological grade of gliomas and noted gross difference between them. The fundamental role of HMGB1 in necrosis and malignancy in glioma is due to an autocrine factor which enhances the growth and migration of tumor cells (Table 1) [245,246]. Other authors are of the view that HMGB1 that is secreted into the extracellular environment may cause surrounding tumor cells to undergo constant proliferation and induce the regeneration of small blood vessels, thus bolstering tumor growth. HMGB1 may cause tumorigenesis by disordered gene secretion, resulting in glial cells obtaining a tumor phenotype and resistance to apoptosis (Table 1) [247]. studies have also indicated that the necrotic tumor cells which secrete HMGB1 facilities tumor growth and infiltration into the surrounding brain tissue hence presents a stronger resistance, which makes it difficult to attain whole resection leading to poor prognosis [246,248]. Also cells growth and migration in gliomas in vitro were suppressed when HMGB1 was inhibited [244]. Further studies have indicated that HMGB1 secretion is occurs in reactive astrocytes [249] and that GFAP and HSP27 proteins, markers for reactive astrocyte, were not changed, and because morphological change of GFAP-positive astrocytes could not be detected in aged brain it is unlikely that the increase of HMGB1 in astrocytes during aging corresponds to reactive gliosis [91].

8.17. Psychological stress

Innate immune reactions are now thought to be a general etiology of many psychiatric illnesses including posttraumatic stress disorder (PTSD), depression, and bipolar disorder [250,251]. Acute exposure to stressor induces a rapid increase of proinflammatory cytokines in stress-reactive areas of the brain such as hypothalamus and hippocampus [252]. Johnson et al. indicated that the rapid increase of IL-1β expression in glial cells is due to the release of norepinephrine in response to stressful events [253]. More recent Weber et al. implicated HMGB1 as a stress signal to prime microglia for the expression of proinflammatory mediators in the brain. They indicated that Blocking of TLR2 and TLR4 prevented neuroinflammatory responses during stress exposure which further supported the notion of neuroinflammation during psychological stress (Table 1) [254].

9. Conclusion

Intracellular and extracellular HMGB1 play significantly different roles in several diseases including CNS disease described above. The current function for HMGB1 is as an autophagy regulator, which has been linked to the pathogenesis several diseases and more importantly CNS diseases. In lined with the role of HMGB1 in the pathological process of CNS diseases we proposed HMGB1 could become a crucial biomarker and therapeutic target in these conditions. Although numerous strategies have been employed in the inhibition of HMGB1 expressions and activity in inflammation-associated diseases, more research is required to gain further insight into the association of HMGB proteins and signaling mechanisms involved in CNS disease.

Conflict of interest

The authors have no conflicts of interest to disclose.

References

1. Fernandes-Alnemri T, Yu J-W, Datta P, et al. (2009) AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. *Nature* 458: 509-513.
2. Banjara M, Ghosh C (2017) Sterile Neuroinflammation and Strategies for Therapeutic Intervention. *Int J Inflam* 2017: 8385961.
3. Lyman M, Lloyd DG, Ji X, et al. (2014) Neuroinflammation: the role and consequences. *Neurosci Res* 79: 1-12.
4. Romani M, Rodman TC, Vidali G, et al. (1979) Serological analysis of species specificity in the high mobility group chromosomal proteins. *J Biol Chem* 254: 2918-2922.
5. Prasad S, Thakur M (1989) Distribution of high mobility group proteins in different tissues of rats during aging. *Biochem Int* 20: 687-695.
6. Čabart P, Kalousek I, Jandová D, et al. (1995) Differential expression of nuclear HMG1, HMG2 proteins and H10 histone in various blood cells. *Cell Biochem Funct* 13: 125-133.
7. Seyedin SM, Pehrson JR, Cole RD (1981) Loss of chromosomal high mobility group proteins HMG1 and HMG2 when mouse neuroblastoma and Friend erythroleukemia cells become committed to differentiation. *Proc Natl Acad Sci U S A* 78: 5988-5992.

8. Muller S, Ronfani L, Bianchi ME (2004) Regulated expression and subcellular localization of HMGB1, a chromatin protein with a cytokine function. *J Intern Med* 255: 332-343.
9. Kitahara T, Takeishi Y, Harada M, et al. (2008) High-mobility group box 1 restores cardiac function after myocardial infarction in transgenic mice. *Cardiovasc Res* 80: 40-46.
10. Kang R, Zhang Q, Hou W, et al. (2014) Intracellular Hmgb1 inhibits inflammatory nucleosome release and limits acute pancreatitis in mice. *Gastroenterology* 146: 1097-1107.
11. Huang H, Nace GW, McDonald K-A, et al. (2014) Hepatocyte specific HMGB1 deletion worsens the injury in liver ischemia/reperfusion: A role for intracellular HMGB1 in cellular protection. *Hepatology (Baltimore, Md)* 59: 1984.
12. Yanai H, Matsuda A, An J, et al. (2013) Conditional ablation of HMGB1 in mice reveals its protective function against endotoxemia and bacterial infection. *Proc Natl Acad Sci U S A* 110: 20699-20704.
13. Huebener P, Gwak G-Y, Pradere J-P, et al. (2014) High-mobility group box 1 is dispensable for autophagy, mitochondrial quality control, and organ function in vivo. *Cell Metab* 19: 539-547.
14. Chirico V, Lacquaniti A, Salpietro V, et al. (2014) High-mobility group box 1 (HMGB1) in childhood: from bench to bedside. *Eur J Pediatr* 173: 1123-1136.
15. Wang K-C, Tsai C-P, Lee C-L, et al. (2012) Elevated plasma high-mobility group box 1 protein is a potential marker for neuromyelitis optica. *Neuroscience* 226: 510-516.
16. Wang H, Wang K, Wang C, et al. (2013) Cerebrospinal fluid high-mobility group box protein 1 in neuromyelitis optica and multiple sclerosis. *Neuroimmunomodulation* 20: 113-118.
17. Kobori N, Clifton GL, Dash P (2002) Altered expression of novel genes in the cerebral cortex following experimental brain injury. *Brain Res Mol Brain Res* 104: 148-158.
18. Agnello D, Wang H, Yang H, et al. (2002) HMGB-1, a DNA-binding protein with cytokine activity, induces brain TNF and IL-6 production, and mediates anorexia and taste aversion. *Cytokine* 18: 231-236.
19. Antoine DJ, Harris HE, Andersson U, et al. (2014) A systematic nomenclature for the redox states of high mobility group box (HMGB) proteins. *Mol Med* 20: 135-137.
20. Kang R, Chen R, Zhang Q, et al. (2014) HMGB1 in health and disease. *Mol Aspects Med* 40: 1-116.
21. Andersson U, Antoine DJ, Tracey KJ (2014) The functions of HMGB1 depend on molecular localization and post-translational modifications. *J Intern Med* 276: 420-424.
22. Su Z, Ni P, She P, et al. (2016) Bio-HMGB1 from breast cancer contributes to M-MDSC differentiation from bone marrow progenitor cells and facilitates conversion of monocytes into MDSC-like cells. *Cancer Immunol Immunother* 66: 391-401.
23. Thomas JO, Stott K (2012) H1 and HMGB1: modulators of chromatin structure. *Biochem Soc Trans* 40: 341-346.
24. Cato L, Stott K, Watson M, et al. (2008) The interaction of HMGB1 and linker histones occurs through their acidic and basic tails. *J Mol Biol* 384: 1262-1272.
25. Holdenrieder S, Stieber P (2009) Clinical use of circulating nucleosomes. *Crit Rev Clin Lab Sci* 46: 1-24.
26. Assenberg R, Webb M, Connolly E, et al. (2008) A critical role in structure-specific DNA binding for the acetylatable lysine residues in HMGB1. *Biochem J* 411: 553-561.
27. Little AJ, Corbett E, Ortega F, et al. (2013) Cooperative recruitment of HMGB1 during V (D) J recombination through interactions with RAG1 and DNA. *Nucleic Acids Res* 41: 3289-3301.

28. Das D, Scovell WM (2001) The binding interaction of HMG-1 with the TATA-binding protein/TATA complex. *J Biol Chem* 276: 32597-32605.
29. Naghavi MH, Nowak P, Andersson J, et al. (2003) Intracellular high mobility group B1 protein (HMGB1) represses HIV-1 LTR-directed transcription in a promoter-and cell-specific manner. *Virology* 314: 179-189.
30. Ellwood KB, Yen Y-M, Johnson RC, et al. (2000) Mechanism for specificity by HMG-1 in enhanceosome assembly. *Mol Cell Biol* 20: 4359-4370.
31. Mitsouras K, Wong B, Arayata C, et al. (2002) The DNA architectural protein HMGB1 displays two distinct modes of action that promote enhanceosome assembly. *Mol Cell Biol* 22: 4390-4401.
32. Yuan F, Gu L, Guo S, et al. (2004) Evidence for involvement of HMGB1 protein in human DNA mismatch repair. *J Biol Chem* 279: 20935-20940.
33. Robertson AB, Klungland A, Rognes T, et al. (2009) DNA repair in mammalian cells: Base excision repair: the long and short of it. *Cell Mol Life Sci* 66: 981-993.
34. Prasad R, Liu Y, Deterding LJ, et al. (2007) HMGB1 is a cofactor in mammalian base excision repair. *Mol Cell* 27: 829-841.
35. Giavara S, Kosmidou E, Hande MP, et al. (2005) Yeast Nhp6A/B and mammalian Hmgb1 facilitate the maintenance of genome stability. *Curr Biol* 15: 68-72.
36. Zayed H, Izsvák Z, Khare D, et al. (2003) The DNA-bending protein HMGB1 is a cellular cofactor of Sleeping Beauty transposition. *Nucleic Acids Res* 31: 2313-2322.
37. de Silva S, Lotta LT, Jr., Burris CA, et al. (2010) Virion-associated cofactor high-mobility group DNA-binding protein-1 facilitates transposition from the herpes simplex virus/Sleeping Beauty amplicon vector platform. *Hum Gene Ther* 21: 1615-1622.
38. Shen Y, Peng H, Pan S, et al. (2010) Interaction of DNA/nuclear protein/polycation and the terplexes for gene delivery. *Nanotechnology* 21: 045102.
39. Siu YS, Li L, Leung MF, et al. (2012) Polyethylenimine-based amphiphilic core-shell nanoparticles: study of gene delivery and intracellular trafficking. *Biointerphases* 7: 16.
40. Yi WJ, Yang J, Li C, et al. (2012) Enhanced nuclear import and transfection efficiency of TAT peptide-based gene delivery systems modified by additional nuclear localization signals. *Bioconjug Chem* 23: 125-134.
41. Weber MD, Frank MG, Tracey KJ, et al. (2015) Stress induces the danger-associated molecular pattern HMGB-1 in the hippocampus of male Sprague Dawley rats: a priming stimulus of microglia and the NLRP3 inflammasome. *J Neurosci* 35: 316-324.
42. Tang D, Kang R, Livesey KM, et al. (2010) Endogenous HMGB1 regulates autophagy. *J Cell Biol* 190: 881-892.
43. Lee H, Shin N, Song M, et al. (2010) Analysis of nuclear high mobility group box 1 (HMGB1)-binding proteins in colon cancer cells: clustering with proteins involved in secretion and extranuclear function. *J Proteome Res* 9: 4661-4670.
44. Dintilhac A, Bernues J (2002) HMGB1 interacts with many apparently unrelated proteins by recognizing short amino acid sequences. *J Biol Chem* 277: 7021-7028.
45. Kang R, Livesey KM, Zeh HJ, 3rd, et al. (2011) Metabolic regulation by HMGB1-mediated autophagy and mitophagy. *Autophagy* 7: 1256-1258.
46. Tang D, Billiar TR, Lotze MT (2012) A Janus tale of two active high mobility group box 1 (HMGB1) redox states. *Mol Med* 18: 1360-1362.

47. Fang WH, Yao YM, Shi ZG, et al. (2002) The significance of changes in high mobility group-1 protein mRNA expression in rats after thermal injury. *Shock* 17: 329-333.
48. Wang H, Bloom O, Zhang M, et al. (1999) HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 285: 248-251.
49. Wang H, Vishnubhakat JM, Bloom O, et al. (1999) Proinflammatory cytokines (tumor necrosis factor and interleukin 1) stimulate release of high mobility group protein-1 by pituicytes. *Surgery* 126: 389-392.
50. Andersson U, Wang H, Palmblad K, et al. (2000) High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. *J Exp Med* 192: 565-570.
51. Yang H, Wang H, Tracey KJ (2001) HMG-1 rediscovered as a cytokine. *Shock* 15: 247-253.
52. Alexander HR, Doherty GM, Venzon DJ, et al. (1992) Recombinant interleukin-1 receptor antagonist (IL-1ra): effective therapy against gram-negative sepsis in rats. *Surgery* 112: 188-193; discussion 193-184.
53. Libert C, Vink A, Coulie P, et al. (1992) Limited involvement of interleukin-6 in the pathogenesis of lethal septic shock as revealed by the effect of monoclonal antibodies against interleukin-6 or its receptor in various murine models. *Eur J Immunol* 22: 2625-2630.
54. Abraham E, Arcaroli J, Carmody A, et al. (2000) Cutting edge: HMG-1 as a mediator of acute lung inflammation. *J Immunol* 165: 2950-2954.
55. Wagner R, Myers RR (1996) Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. *Neuroreport* 7: 2897-2901.
56. Eliav E, Herzberg U, Ruda MA, et al. (1999) Neuropathic pain from an experimental neuritis of the rat sciatic nerve. *Pain* 83: 169-182.
57. Chacur M, Milligan ED, Gazda LS, et al. (2001) A new model of sciatic inflammatory neuritis (SIN): induction of unilateral and bilateral mechanical allodynia following acute unilateral peri-sciatic immune activation in rats. *Pain* 94: 231-244.
58. Shimommura Y, Shimizu H, Takahashi M, et al. (1990) Effects of peripheral administration of recombinant human interleukin-1 beta on feeding behavior of the rat. *Life Sci* 47: 2185-2192.
59. Crestani F, Seguy F, Dantzer R (1991) Behavioural effects of peripherally injected interleukin-1: role of prostaglandins. *Brain Res* 542: 330-335.
60. Dunn AJ, Antoon M, Chapman Y (1991) Reduction of exploratory behavior by intraperitoneal injection of interleukin-1 involves brain corticotropin-releasing factor. *Brain Res Bull* 26: 539-542.
61. Kluger MJ (1991) Fever: role of pyrogens and cryogens. *Physiol Rev* 71: 93-127.
62. Oka T, Aou S, Hori T (1993) Intracerebroventricular injection of interleukin-1β induces hyperalgesia in rats. *Brain Res* 624: 61-68.
63. Bluthe R-M, Michaud B, Kelley KW, et al. (1996) Vagotomy attenuates behavioural effects of interleukin-1 injected peripherally but not centrally. *Neuroreport* 7: 1485-1488.
64. Reeve AJ, Patel S, Fox A, et al. (2000) Intrathecally administered endotoxin or cytokines produce allodynia, hyperalgesia and changes in spinal cord neuronal responses to nociceptive stimuli in the rat. *Eur J Pain* 4: 247-257.
65. Yirmiya R (1996) Endotoxin produces a depressive-like episode in rats. *Brain Res* 711: 163-174.
66. Coelho A, Fioramonti J, Bueno L (2000) Brain interleukin-1beta and tumor necrosis factor-alpha are involved in lipopolysaccharide-induced delayed rectal allodynia in awake rats. *Brain Res Bull* 52: 223-228.

67. Turrin NP, Gayle D, Ilyin SE, et al. (2001) Pro-inflammatory and anti-inflammatory cytokine mRNA induction in the periphery and brain following intraperitoneal administration of bacterial lipopolysaccharide. *Brain Res Bull* 54: 443-453.
68. Gabellec M-M, Griffais R, Fillion G, et al. (1995) Expression of interleukin 1α, interleukin 1β and interleukin 1 receptor antagonist mRNA in mouse brain: regulation by bacterial lipopolysaccharide (LPS) treatment. *Mol Brain Res* 31: 122-130.
69. Laye S, Gheusi G, Cremona S, et al. (2000) Endogenous brain IL-1 mediates LPS-induced anorexia and hypothalamic cytokine expression. *Am J Physiol Regul Integr Comp Physiol* 279: R93-98.
70. Bluthe RM, Dantzer R, Kelley KW (1997) Central mediation of the effects of interleukin-1 on social exploration and body weight in mice. *Psychoneuroendocrinology* 22: 1-11.
71. Rothwell NJ (1988) Central effects of TNFα on thermogenesis and fever in the rat. *Biosci Rep* 8: 345-352.
72. Dascombe MJ, Rothwell NJ, Sagay BO, et al. (1989) Pyrogenic and thermogenic effects of interleukin 1 beta in the rat. *Am J Physiol* 256: E7-11.
73. Walter JS, Meyers P, Krueger JM (1989) Microinjection of interleukin-1 into brain: separation of sleep and fever responses. *Physiol Behav* 45: 169-176.
74. O'Connor KA, Hansen MK, Pugh CR, et al. (2003) Further characterization of high mobility group box 1 (HMGB1) as a proinflammatory cytokine: central nervous system effects. *Cytokine* 24: 254-265.
75. Fiebich BL, Schleicher S, Spleiss O, et al. (2001) Mechanisms of prostaglandin E2-induced interleukin-6 release in astrocytes: possible involvement of EP4-like receptors, p38 mitogen-activated protein kinase and protein kinase C. *J Neurochem* 79: 950-958.
76. Newton R, Kuitert LM, Bergmann M, et al. (1997) Evidence for involvement of NF-kappaB in the transcriptional control of COX-2 gene expression by IL-1beta. *Biochem Biophys Res Commun* 237: 28-32.
77. Hori O, Brett J, Slattery T, et al. (1995) The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. *J Biol Chem* 270: 25752-25761.
78. Fiuza C, Bustin M, Talwar S, et al. (2003) Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. *Blood* 101: 2652-2660.
79. Park JS, Arcaroli J, Yum HK, et al. (2003) Activation of gene expression in human neutrophils by high mobility group box 1 protein. *Am J Physiol Cell Physiol* 284: C870-879.
80. Chen GY, Tang J, Zheng P, et al. (2009) CD24 and Siglec-10 selectively repress tissue damage-induced immune responses. *Science* 323: 1722-1725.
81. Tian J, Avalos AM, Mao S-Y, et al. (2007) Toll-like receptor 9–dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. *Nat Immunol* 8: 487-496.
82. Gao H-M, Zhou H, Zhang F, et al. (2011) HMGB1 acts on microglia Mac1 to mediate chronic neuroinflammation that drives progressive neurodegeneration. *J Neurosci* 31: 1081-1092.
83. Fu GX, Chen AF, Zhong Y, et al. (2016) Decreased serum level of HMGB1 and MyD88 during human aging progress in healthy individuals. *Aging Clin Exp Res* 28: 175-180.
84. Tang AH, Brunn GJ, Cascalho M, et al. (2007) Pivotal advance: endogenous pathway to SIRS, sepsis, and related conditions. *J Leukoc Biol* 82: 282-285.

85. Park JS, Gamboni-Robertson F, He Q, et al. (2006) High mobility group box 1 protein interacts with multiple Toll-like receptors. *Am J Physiol Cell Physiol* 290: C917-924.
86. Imai Y, Kuba K, Neely GG, et al. (2008) Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell* 133: 235-249.
87. Salminen A, Ojala J, Kaarniranta K, et al. (2012) Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases. *Cell Mol Life Sci* 69: 2999-3013.
88. Morinaga Y, Yanagihara K, Nakamura S, et al. (2010) Legionella pneumophila induces cathepsin B-dependent necrotic cell death with releasing high mobility group box1 in macrophages. *Respir Res* 11: 158.
89. Rauvala H, Pihlaskari R (1987) Isolation and some characteristics of an adhesive factor of brain that enhances neurite outgrowth in central neurons. *J Biol Chem* 262: 16625-16635.
90. Guazzi S, Strangio A, Franzi AT, et al. (2003) HMGB1, an architectural chromatin protein and extracellular signalling factor, has a spatially and temporally restricted expression pattern in mouse brain. *Gene Expr Patterns* 3: 29-33.
91. Enokido Y, Yoshitake A, Ito H, et al. (2008) Age-dependent change of HMGB1 and DNA double-strand break accumulation in mouse brain. *Biochem Biophys Res Commun* 376: 128-133.
92. Fang P, Schachner M, Shen YQ (2012) HMGB1 in development and diseases of the central nervous system. *Mol Neurobiol* 45: 499-506.
93. Fonken LK, Frank MG, Kitt MM, et al. (2016) The Alarmin HMGB1 Mediates Age-Induced Neuroinflammatory Priming. *J Neurosci* 36: 7946-7956.
94. O'Donovan MC (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 72: 971-983.
95. Hodges A, Strand AD, Aragaki AK, et al. (2006) Regional and cellular gene expression changes in human Huntington's disease brain. *Hum Mol Genet* 15: 965-977.
96. Crotti A, Benner C, Kerman BE, et al. (2014) Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. *Nat Neurosci* 17: 513-521.
97. Crotti A, Glass CK (2015) The choreography of neuroinflammation in Huntington's disease. *Trends Immunol* 36: 364-373.
98. Min HJ, Ko EA, Wu J, et al. (2013) Chaperone-like activity of high-mobility group box 1 protein and its role in reducing the formation of polyglutamine aggregates. *J Immunol* 190: 1797-1806.
99. Qi M-L, Tagawa K, Enokido Y, et al. (2007) Proteome analysis of soluble nuclear proteins reveals that HMGB1/2 suppress genotoxic stress in polyglutamine diseases. *Nat Cell Biol* 9: 402-414.
100. Goula AV, Berquist BR, Wilson DM, 3rd, et al. (2009) Stoichiometry of base excision repair proteins correlates with increased somatic CAG instability in striatum over cerebellum in Huntington's disease transgenic mice. *PLoS Genet* 5: e1000749.
101. Liu Y, Prasad R, Beard WA, et al. (2009) Coordination between polymerase β and FEN1 can modulate CAG repeat expansion. *J Biol Chem* 284: 28352-28366.
102. McAlpine FE, Lee JK, Harms AS, et al. (2009) Inhibition of soluble TNF signaling in a mouse model of Alzheimer's disease prevents pre-plaque amyloid-associated neuropathology. *Neurobiol Dis* 34: 163-177.
103. Frank-Cannon TC, Alto LT, McAlpine FE, et al. (2009) Does neuroinflammation fan the flame in neurodegenerative diseases? *Mol Neurodegener* 4: 47.

104. Akiyama H, Arai T, Kondo H, et al. (2000) Cell mediators of inflammation in the Alzheimer disease brain. *Alzheimer Dis Assoc Disord* 14 Suppl 1: S47-53.
105. Buchanan MM, Hutchinson M, Watkins LR, et al. (2010) Toll-like receptor 4 in CNS pathologies. *J Neurochem* 114: 13-27.
106. Du Yan S, Chen X, Fu J, et al. (1996) RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease. *Nature* 382: 685-691.
107. Mazarati A, Maroso M, Iori V, et al. (2011) High-mobility group box-1 impairs memory in mice through both toll-like receptor 4 and receptor for advanced glycation end products. *Exp Neurol* 232: 143-148.
108. Takata K, Kitamura Y, Kakimura J, et al. (2003) Role of high mobility group protein-1 (HMG1) in amyloid-beta homeostasis. *Biochem Biophys Res Commun* 301: 699-703.
109. Takata K, Takada T, Ito A, et al. (2012) Microglial Amyloid-beta1-40 Phagocytosis Dysfunction Is Caused by High-Mobility Group Box Protein-1: Implications for the Pathological Progression of Alzheimer's Disease. *Int J Alzheimers Dis* 2012: 685739.
110. Richard SA, Wu M, Lin D (2014) Traumatic Subdural Effusion Evolving into Chronic Subdural Hematoma. *Open J Mod Neurosurg* 5: 12.
111. Woodcock T, Morganti-Kossmann MC (2013) The role of markers of inflammation in traumatic brain injury. *Front Neurol* 4: 18.
112. Laird MD, Shields JS, Sukumari-Ramesh S, et al. (2014) High mobility group box protein-1 promotes cerebral edema after traumatic brain injury via activation of toll-like receptor 4. *Glia* 62: 26-38.
113. Richard SA, Min W, Su Z, et al. (2017) High Mobility Group Box 1 and Traumatic Brain Injury. *J Behav Brain Sci* 7: 50.
114. Su X, Wang H, Zhao J, et al. (2011) Beneficial effects of ethyl pyruvate through inhibiting high-mobility group box 1 expression and TLR4/NF-B pathway after traumatic brain injury in the rat. *Mediators Inflamm* 2011.
115. Wang K-Y, Yu G-F, Zhang Z-Y, et al. (2012) Plasma high-mobility group box 1 levels and prediction of outcome in patients with traumatic brain injury. *Clin Chim Acta* 413: 1737-1741.
116. Au AK, Aneja RK, Bell MJ, et al. (2012) Cerebrospinal fluid levels of high-mobility group box 1 and cytochrome C predict outcome after pediatric traumatic brain injury. *J Neurotrauma* 29: 2013-2021.
117. Carty M, Bowie AG (2011) Evaluating the role of Toll-like receptors in diseases of the central nervous system. *Biochem Pharmacol* 81: 825-837.
118. Ding Q, Keller JN (2005) Evaluation of rage isoforms, ligands, and signaling in the brain. *Biochim Biophys Acta* 1746: 18-27.
119. Okuma Y, Liu K, Wake H, et al. (2012) Anti–high mobility group box-1 antibody therapy for traumatic brain injury. *Ann Neurol* 72: 373-384.
120. Litvan I, Halliday G, Hallett M, et al. (2007) The etiopathogenesis of Parkinson disease and suggestions for future research. Part I. *J Neuropathol Exp Neurol* 66: 251-257.
121. Gerhard A, Pavese N, Hotton G, et al. (2006) In vivo imaging of microglial activation with [11 C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Dis* 21: 404-412.
122. Lindersson EK, Hojrup P, Gai WP, et al. (2004) alpha-Synuclein filaments bind the transcriptional regulator HMGB-1. *Neuroreport* 15: 2735-2739.

123. Song J-X, Lu J-H, Liu L-F, et al. (2014) HMGB1 is involved in autophagy inhibition caused by SNCA/α-synuclein overexpression: a process modulated by the natural autophagy inducer corynoxine B. *Autophagy* 10: 144-154.
124. Zhang J, Niu N, Wang M, et al. (2013) Neuron-derived IgG protects dopaminergic neurons from insult by 6-OHDA and activates microglia through the FcγR I and TLR4 pathways. *Int J Biochem Cell Biol* 45: 1911-1920.
125. Santoro M, Maetzler W, Stathakos P, et al. (2016) In-vivo evidence that high mobility group box 1 exerts deleterious effects in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine model and Parkinson's disease which can be attenuated by glycyrrhizin. *Neurobiol Dis* 91: 59-68.
126. Sasaki T, Liu K, Agari T, et al. (2016) Anti-high mobility group box 1 antibody exerts neuroprotection in a rat model of Parkinson's disease. *Exp Neurol* 275 Pt 1: 220-231.
127. Furuya N, Yu J, Byfield M, et al. (2005) The evolutionarily conserved domain of Beclin 1 is required for Vps34 binding, autophagy, and tumor suppressor function. *Autophagy* 1: 46-52.
128. Funderburk SF, Wang QJ, Yue Z (2010) The Beclin 1–VPS34 complex–at the crossroads of autophagy and beyond. *Trends Cell Biol* 20: 355-362.
129. Kang R, Livesey KM, Zeh HJ, et al. (2010) HMGB1: a novel Beclin 1-binding protein active in autophagy. *Autophagy* 6: 1209-1211.
130. Huang J, Yang J, Shen Y, et al. (2017) HMGB1 Mediates Autophagy Dysfunction via Perturbing Beclin1-Vps34 Complex in Dopaminergic Cell Model. *Front Mol Neurosci* 10: 13.
131. Constantinescu CS, Farooqi N, O'brien K, et al. (2011) Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *Brit J Pharmacol* 164: 1079-1106.
132. McFarland HF, Martin R (2007) Multiple sclerosis: a complicated picture of autoimmunity. *Nat Immunol* 8: 913-919.
133. Andersson Å, Covacu R, Sunnemark D, et al. (2008) Pivotal advance: HMGB1 expression in active lesions of human and experimental multiple sclerosis. *J Leukoc Biol* 84: 1248-1255.
134. Sternberg Z, Sternberg D, Chichelli T, et al. (2016) High-mobility group box 1 in multiple sclerosis. *Immunol Res* 64: 385-391.
135. Leech S, Kirk J, Plumb J, et al. (2007) Persistent endothelial abnormalities and blood-brain barrier leak in primary and secondary progressive multiple sclerosis. *Neuropathol Appl Neurobiol* 33: 86-98.
136. Šestan N (2012) The emerging biology of autism spectrum disorders. *Science* 337: 1301-1303.
137. Madore C, Leyrolle Q, Lacabanne C, et al. (2016) Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. *Neural Plast* 2016: 3597209.
138. Voineagu I, Wang X, Johnston P, et al. (2011) Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 474: 380-384.
139. Odell D, Maciulis A, Cutler A, et al. (2005) Confirmation of the association of the C4B null allelle in autism. *Hum Immunol* 66: 140-145.
140. Oddi D, Crusio WE, D'Amato FR, et al. (2013) Monogenic mouse models of social dysfunction: implications for autism. *Behav Brain Res* 251: 75-84.
141. Shcheglovitov A, Shcheglovitova O, Yazawa M, et al. (2013) SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients. *Nature* 503: 267-271.
142. Emanuele E, Boso M, Brondino N, et al. (2010) Increased serum levels of high mobility group box 1 protein in patients with autistic disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 34: 681-683.

143. Junaid MA, Kowal D, Barua M, et al. (2004) Proteomic studies identified a single nucleotide polymorphism in glyoxalase I as autism susceptibility factor. *Am J Med Genet A* 131: 11-17.
144. Enstrom AM, Onore CE, Van de Water JA, et al. (2010) Differential monocyte responses to TLR ligands in children with autism spectrum disorders. *Brain Behav Immun* 24: 64-71.
145. Barua M, Jenkins EC, Chen W, et al. (2011) Glyoxalase I polymorphism rs2736654 causing the Ala111Glu substitution modulates enzyme activity--implications for autism. *Autism Res* 4: 262-270.
146. Henkel JS, Engelhardt JI, Siklos L, et al. (2004) Presence of dendritic cells, MCP-1, and activated microglia/macrophages in amyotrophic lateral sclerosis spinal cord tissue. *Ann Neurol* 55: 221-235.
147. Weydt P, Yuen EC, Ransom BR, et al. (2004) Increased cytotoxic potential of microglia from ALS-transgenic mice. *Glia* 48: 179-182.
148. Casula M, Iyer AM, Spliet WG, et al. (2011) Toll-like receptor signaling in amyotrophic lateral sclerosis spinal cord tissue. *Neuroscience* 179: 233-243.
149. Lo Coco D, Veglianese P, Allievi E, et al. (2007) Distribution and cellular localization of high mobility group box protein 1 (HMGB1) in the spinal cord of a transgenic mouse model of ALS. *Neurosci Lett* 412: 73-77.
150. Hwang C-S, Liu G-T, Chang MD-T, et al. (2013) Elevated serum autoantibody against high mobility group box 1 as a potent surrogate biomarker for amyotrophic lateral sclerosis. *Neurobiol Dis* 58: 13-18.
151. Costa GMF, Leite CMdA (2015) Trigeminal neuralgia: peripheral and central mechanisms. *Revista Dor* 16: 297-301.
152. Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. *Nature* 413: 203-210.
153. Austin PJ, Moalem-Taylor G (2010) The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. *J Neuroimmunol* 229: 26-50.
154. Karatas H, Erdener SE, Gursoy-Ozdemir Y, et al. (2013) Spreading depression triggers headache by activating neuronal Panx1 channels. *Science* 339: 1092-1095.
155. Kunkler PE, Hulse RE, Kraig RP (2004) Multiplexed cytokine protein expression profiles from spreading depression in hippocampal organotypic cultures. *J Cereb Blood Flow Metab* 24: 829-839.
156. Jander S, Schroeter M, Peters O, et al. (2001) Cortical spreading depression induces proinflammatory cytokine gene expression in the rat brain. *J Cereb Blood Flow Metab* 21: 218-225.
157. Lana-Peixoto MA (2008) Devic's neuromyelitis optica: a critical review. *Arq Neuropsiquiatr* 66: 120-138.
158. Correale J, Fiol M (2004) Activation of humoral immunity and eosinophils in neuromyelitis optica. *Neurology* 63: 2363-2370.
159. Ishizu T, Osoegawa M, Mei FJ, et al. (2005) Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis. *Brain* 128: 988-1002.
160. Uzawa A, Mori M, Masuda S, et al. (2013) CSF high-mobility group box 1 is associated with intrathecal inflammation and astrocytic damage in neuromyelitis optica. *J Neurol Neurosurg Psychiatry* 84: 517-522.
161. Solmi M, Veronese N, Favaro A, et al. (2015) Inflammatory cytokines and anorexia nervosa: A meta-analysis of cross-sectional and longitudinal studies. *Psychoneuroendocrinology* 51: 237-252.

162. Sadagurski M, Norquay L, Farhang J, et al. (2010) Human IL6 enhances leptin action in mice. *Diabetologia* 53: 525-535.
163. Senaris RM, Trujillo ML, Navia B, et al. (2011) Interleukin-6 regulates the expression of hypothalamic neuropeptides involved in body weight in a gender-dependent way. *J Neuroendocrinol* 23: 675-686.
164. Inui A (2001) Eating behavior in anorexia nervosa--an excess of both orexigenic and anorexigenic signalling? *Mol Psychiatry* 6: 620.
165. Scheede-Bergdahl C, Watt HL, Trutschnigg B, et al. (2012) Is IL-6 the best pro-inflammatory biomarker of clinical outcomes of cancer cachexia? *Clin Nutr* 31: 85-88.
166. Solmi M, Santonastaso P, Caccaro R, et al. (2013) A case of anorexia nervosa with comorbid Crohn's disease: beneficial effects of anti-TNF-alpha therapy? *Int J Eat Disord* 46: 639-641.
167. Hargrave SL, Kinzig KP (2012) Repeated gastric distension alters food intake and neuroendocrine profiles in rats. *Physiol Behav* 105: 975-981.
168. Sedlackova D, Kopeckova J, Papezova H, et al. (2011) Changes of plasma obestatin, ghrelin and NPY in anorexia and bulimia nervosa patients before and after a high-carbohydrate breakfast. *Physiol Res* 60: 165.
169. Cuntz U, Enck P, Frühauf E, et al. (2013) Cholecystokinin revisited: CCK and the hunger trap in anorexia nervosa. *PloS One* 8: e54457.
170. Terra X, Auguet T, Aguera Z, et al. (2013) Adipocytokine levels in women with anorexia nervosa. Relationship with weight restoration and disease duration. *Int J Eat Disord* 46: 855-861.
171. Hughes EK, Goldschmidt AB, Labuschagne Z, et al. (2013) Eating disorders with and without comorbid depression and anxiety: similarities and differences in a clinical sample of children and adolescents. *Eur Eat Disord Rev* 21: 386-394.
172. Yasuhara D, Hashiguchi T, Kawahara K, et al. (2007) High mobility group box 1 and refeeding-resistance in anorexia nervosa. *Mol Psychiatry* 12: 976-977.
173. Vezzani A (2014) Epilepsy and inflammation in the brain: overview and pathophysiology. *Epilepsy Curr* 14: 3-7.
174. Gorter JA, van Vliet EA, Aronica E, et al. (2006) Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. *J Neurosci* 26: 11083-11110.
175. Ravizza T, Vezzani A (2006) Status epilepticus induces time-dependent neuronal and astrocytic expression of interleukin-1 receptor type I in the rat limbic system. *Neuroscience* 137: 301-308.
176. Turrin NP, Rivest S (2004) Innate immune reaction in response to seizures: implications for the neuropathology associated with epilepsy. *Neurobiol Dis* 16: 321-334.
177. Vezzani A, French J, Bartfai T, et al. (2011) The role of inflammation in epilepsy. *Nat Rev Neurol* 7: 31-40.
178. Maroso M, Balosso S, Ravizza T, et al. (2010) Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. *Nat Med* 16: 413-419.
179. Liang Y, Lei Z, Zhang H, et al. (2014) Toll-like receptor 4 is associated with seizures following ischemia with hyperglycemia. *Brain Res* 1590: 75-84.
180. Allan SM, Tyrrell PJ, Rothwell NJ (2005) Interleukin-1 and neuronal injury. *Nat Rev Immunol* 5: 629-640.
181. Van Vliet E, da Costa Araujo S, Redeker S, et al. (2007) Blood–brain barrier leakage may lead to progression of temporal lobe epilepsy. *Brain* 130: 521-534.

182. Oby E, Janigro D (2006) The blood–brain barrier and epilepsy. *Epilepsia* 47: 1761-1774.
183. Choi J, Min HJ, Shin JS (2011) Increased levels of HMGB1 and pro-inflammatory cytokines in children with febrile seizures. *J Neuroinflammation* 8: 135.
184. Kleen JK, Holmes GL (2010) Taming TLR4 may ease seizures. *Nat Med* 16: 369-370.
185. Balosso S, Liu J, Bianchi ME, et al. (2014) Disulfide-containing high mobility group box-1 promotes N-methyl-D-aspartate receptor function and excitotoxicity by activating Toll-like receptor 4-dependent signaling in hippocampal neurons. *Antioxid Redox Signal* 21: 1726-1740.
186. Iori V, Maroso M, Rizzi M, et al. (2013) Receptor for Advanced Glycation Endproducts is upregulated in temporal lobe epilepsy and contributes to experimental seizures. *Neurobiol Dis* 58: 102-114.
187. Maroso M, Balosso S, Ravizza T, et al. (2011) Interleukin-1 type 1 receptor/Toll-like receptor signalling in epilepsy: the importance of IL-1beta and high-mobility group box 1. *J Intern Med* 270: 319-326.
188. Vezzani A, Maroso M, Balosso S, et al. (2011) IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. *Brain Behav Immun* 25: 1281-1289.
189. Zurolo E, Iyer A, Maroso M, et al. (2011) Activation of Toll-like receptor, RAGE and HMGB1 signalling in malformations of cortical development. *Brain* 134: 1015-1032.
190. Gelderblom M, Sobey CG, Kleinschnitz C, et al. (2015) Danger signals in stroke. *Ageing Res Rev* 24: 77-82.
191. Gelderblom M, Leypoldt F, Steinbach K, et al. (2009) Temporal and spatial dynamics of cerebral immune cell accumulation in stroke. *Stroke* 40: 1849-1857.
192. Kleinschnitz C, Kraft P, Dreykluft A, et al. (2013) Regulatory T cells are strong promoters of acute ischemic stroke in mice by inducing dysfunction of the cerebral microvasculature. *Blood* 121: 679-691.
193. Zhou Y, Xiong KL, Lin S, et al. (2010) Elevation of high-mobility group protein box-1 in serum correlates with severity of acute intracerebral hemorrhage. *Mediators Inflamm* 2010.
194. Goldstein RS, Gallowitsch-Puerta M, Yang L, et al. (2006) Elevated high-mobility group box 1 levels in patients with cerebral and myocardial ischemia. *Shock* 25: 571-574.
195. Vogelgesang A, May VE, Grunwald U, et al. (2010) Functional status of peripheral blood T-cells in ischemic stroke patients. *PLoS One* 5: e8718.
196. Ramesh G, MacLean AG, Philipp MT (2013) Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. *Mediators Inflamm* 2013.
197. Moalem G, Tracey DJ (2006) Immune and inflammatory mechanisms in neuropathic pain. *Brain Res Rev* 51: 240-264.
198. Coull JA, Beggs S, Boudreau D, et al. (2005) BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 438: 1017-1021.
199. Miyoshi K, Obata K, Kondo T, et al. (2008) Interleukin-18-mediated microglia/astrocyte interaction in the spinal cord enhances neuropathic pain processing after nerve injury. *J Neurosci* 28: 12775-12787.
200. Binshtok AM, Wang H, Zimmermann K, et al. (2008) Nociceptors are interleukin-1beta sensors. *J Neurosci* 28: 14062-14073.
201. Skoff AM, Zhao C, Adler JE (2009) Interleukin-1alpha regulates substance P expression and release in adult sensory neurons. *Exp Neurol* 217: 395-400.

202. Xu XJ, Hao JX, Andell-Jonsson S, et al. (1997) Nociceptive responses in interleukin-6-deficient mice to peripheral inflammation and peripheral nerve section. *Cytokine* 9: 1028-1033.
203. Dominguez E, Mauborgne A, Mallet J, et al. (2010) SOCS3-mediated blockade of JAK/STAT3 signaling pathway reveals its major contribution to spinal cord neuroinflammation and mechanical allodynia after peripheral nerve injury. *J Neurosci* 30: 5754-5766.
204. Kim CF, Moalem-Taylor G (2011) Interleukin-17 contributes to neuroinflammation and neuropathic pain following peripheral nerve injury in mice. *J Pain* 12: 370-383.
205. Feldman P, Due MR, Ripsch MS, et al. (2012) The persistent release of HMGB1 contributes to tactile hyperalgesia in a rodent model of neuropathic pain. *J Neuroinflammation* 9: 180.
206. Kuang X, Huang Y, Gu HF, et al. (2012) Effects of intrathecal epigallocatechin gallate, an inhibitor of Toll-like receptor 4, on chronic neuropathic pain in rats. *Eur J Pharmacol* 676: 51-56.
207. Maeda S, Hikiba Y, Shibata W, et al. (2007) Essential roles of high-mobility group box 1 in the development of murine colitis and colitis-associated cancer. *Biochem Biophys Res Commun* 360: 394-400.
208. Otoshi K, Kikuchi S, Kato K, et al. (2011) Anti-HMGB1 neutralization antibody improves pain-related behavior induced by application of autologous nucleus pulposus onto nerve roots in rats. *Spine (Phila Pa 1976)* 36: E692-698.
209. Shibasaki M, Sasaki M, Miura M, et al. (2010) Induction of high mobility group box-1 in dorsal root ganglion contributes to pain hypersensitivity after peripheral nerve injury. *Pain* 149: 514-521.
210. Li W, Li J, Sama AE, et al. (2013) Carbenoxolone blocks endotoxin-induced protein kinase R (PKR) activation and high mobility group box 1 (HMGB1) release. *Mol Med* 19: 203-211.
211. Devi LA (2000) G-protein-coupled receptor dimers in the lime light. *Trends Pharmacol Sci* 21: 324-326.
212. Hanisch UK, Prinz M, Angstwurm K, et al. (2001) The protein tyrosine kinase inhibitor AG126 prevents the massive microglial cytokine induction by pneumococcal cell walls. *Eur J Immunol* 31: 2104-2115.
213. Rock RB, Gekker G, Hu S, et al. (2004) Role of microglia in central nervous system infections. *Clin Microbiol Rev* 17: 942-964.
214. Saukkonen K, Sande S, Cioffe C, et al. (1990) The role of cytokines in the generation of inflammation and tissue damage in experimental gram-positive meningitis. *J Exp Med* 171: 439-448.
215. Zwijnenburg PJ, van der Poll T, Florquin S, et al. (2003) Interleukin-10 negatively regulates local cytokine and chemokine production but does not influence antibacterial host defense during murine pneumococcal meningitis. *Infect Immun* 71: 2276-2279.
216. Ostergaard C, Yieng-Kow R, Larsen C, et al. (2000) Treatment with a monocolonal antibody to IL-8 attenuates the pleocytosis in experimental pneumococcal meningitis in rabbits when given intravenously, but not intracisternally. *Clin Exp Immunol* 122: 207-211.
217. Kielian T, Barry B, Hickey WF (2001) CXC Chemokine Receptor-2 Ligands Are Required for Neutrophil-Mediated Host Defense in Experimental Brain Abscesses1. *J Immunol* 166: 4634-4643.
218. Kielian T, Phulwani NK, Esen N, et al. (2007) MyD88-dependent signals are essential for the host immune response in experimental brain abscess. *J Immunol* 178: 4528-4537.

219. Kielian T, Mayes P, Kielian M (2002) Characterization of microglial responses to Staphylococcus aureus: effects on cytokine, costimulatory molecule, and Toll-like receptor expression. *J Neuroimmunol* 130: 86-99.
220. Kielian T, Esen N, Bearden ED (2005) Toll-like receptor 2 (TLR2) is pivotal for recognition of S. aureus peptidoglycan but not intact bacteria by microglia. *Glia* 49: 567-576.
221. Gurley C, Nichols J, Liu S, et al. (2008) Microglia and astrocyte activation by toll-like receptor ligands: modulation by PPAR-agonists. *PPAR Res* 2008.
222. Esen N, Kielian T (2006) Central role for MyD88 in the responses of microglia to pathogen-associated molecular patterns. *J Immunol* 176: 6802-6811.
223. Baldwin AC, Kielian T (2004) Persistent immune activation associated with a mouse model of Staphylococcus aureus-induced experimental brain abscess. *J Neuroimmunol* 151: 24-32.
224. Tang D, Kang R, Cao L, et al. (2008) A pilot study to detect high mobility group box 1 and heat shock protein 72 in cerebrospinal fluid of pediatric patients with meningitis. *Crit Care Med* 36: 291-295.
225. Asano T, Ichiki K, Koizumi S, et al. (2011) High mobility group box 1 in cerebrospinal fluid from several neurological diseases at early time points. *Int J Neurosci* 121: 480-484.
226. Hohne C, Wenzel M, Angele B, et al. (2013) High mobility group box 1 prolongs inflammation and worsens disease in pneumococcal meningitis. *Brain* 136: 1746-1759.
227. Hemmi H, Takeuchi O, Kawai T, et al. (2000) A Toll-like receptor recognizes bacterial DNA. *Nature* 408: 740-745.
228. Koedel U (2009) Toll-like receptors in bacterial meningitis. *Toll-like Receptors: Roles in Infection and Neuropathology*. Springer. pp. 15-40.
229. Sanders MS, van Well GT, Ouburg S, et al. (2012) Toll-like receptor 9 polymorphisms are associated with severity variables in a cohort of meningococcal meningitis survivors. *BMC Infect Dis* 12: 112.
230. Alleva LM, Yang H, Tracey KJ, et al. (2005) High mobility group box 1 (HMGB1) protein: possible amplification signal in the pathogenesis of falciparum malaria. *Trans R Soc Trop Med Hyg* 99: 171-174.
231. Mostofa AG, Punganuru SR, Madala HR, et al. (2017) The Process and Regulatory Components of Inflammation in Brain Oncogenesis. *Biomolecules* 7: 34.
232. Albulescu R, Codrici E, Popescu ID, et al. (2013) Cytokine patterns in brain tumour progression. *Mediators Inflamm* 2013: 979748.
233. Goswami S, Gupta A, Sharma SK (1998) Interleukin-6-mediated autocrine growth promotion in human glioblastoma multiforme cell line U87MG. *J Neurochem* 71: 1837-1845.
234. Brat DJ, Bellail AC, Van Meir EG (2005) The role of interleukin-8 and its receptors in gliomagenesis and tumoral angiogenesis. *Neuro Oncol* 7: 122-133.
235. Yoshida S, Ono M, Shono T, et al. (1997) Involvement of interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor in tumor necrosis factor alpha-dependent angiogenesis. *Mol Cell Biol* 17: 4015-4023.
236. Tanabe K, Matsushima-Nishiwaki R, Yamaguchi S, et al. (2010) Mechanisms of tumor necrosis factor-alpha-induced interleukin-6 synthesis in glioma cells. *J Neuroinflammation* 7: 16.
237. Ghosh S, Paul A, Sen E (2013) Tumor Necrosis Factor Alpha-Induced Hypoxia-Inducible Factor 1α–β-Catenin Axis Regulates Major Histocompatibility Complex Class I Gene Activation through Chromatin Remodeling. *Mol Cell Biol* 33: 2718-2731.

238. Hao C, Parney IF, Roa WH, et al. (2002) Cytokine and cytokine receptor mRNA expression in human glioblastomas: evidence of Th1, Th2 and Th3 cytokine dysregulation. *Acta Neuropathol* 103: 171-178.
239. Grauer O, Poschl P, Lohmeier A, et al. (2007) Toll-like receptor triggered dendritic cell maturation and IL-12 secretion are necessary to overcome T-cell inhibition by glioma-associated TGF-beta2. *J Neurooncol* 82: 151-161.
240. Calandra T, Roger T (2003) Macrophage migration inhibitory factor: a regulator of innate immunity. *Nat Rev Immunol* 3: 791-800.
241. Mantovani A, Allavena P, Sica A, et al. (2008) Cancer-related inflammation. *Nature* 454: 436-444.
242. Apte RN, Dotan S, Elkabets M, et al. (2006) The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions. *Cancer Metastasis Rev* 25: 387-408.
243. Martins I, Kepp O, Menger L, et al. (2013) Fluorescent biosensors for the detection of HMGB1 release. *Methods Mol Biol* 1004: 43-56.
244. Zhang J, Liu C, Hou R (2014) Knockdown of HMGB1 improves apoptosis and suppresses proliferation and invasion of glioma cells. *Chin J Cancer Res* 26: 658-668.
245. Kostova N, Zlateva S, Ugrinova I, et al. (2010) The expression of HMGB1 protein and its receptor RAGE in human malignant tumors. *Mol Cell Biochem* 337: 251-258.
246. Seidu RA, Wu M, Su Z, et al. (2017) Paradoxical Role of High Mobility Group Box 1 in Glioma: A Suppressor or a Promoter? *Oncol Rev* 11: 325.
247. Jube S, Rivera ZS, Bianchi ME, et al. (2012) Cancer cell secretion of the DAMP protein HMGB1 supports progression in malignant mesothelioma. *Cancer Res* 72: 3290-3301.
248. Yang GL, Zhang LH, Bo JJ, et al. (2012) Increased expression of HMGB1 is associated with poor prognosis in human bladder cancer. *J Surg Oncol* 106: 57-61.
249. Kim JB, Lim CM, Yu YM, et al. (2008) Induction and subcellular localization of high-mobility group box–1 (HMGB1) in the postischemic rat brain. *J Neurosci Res* 86: 1125-1131.
250. Jones KA, Thomsen C (2013) The role of the innate immune system in psychiatric disorders. *Mol Cell Neurosci* 53: 52-62.
251. Frank MG, Weber MD, Watkins LR, et al. (2016) Stress-induced neuroinflammatory priming: A liability factor in the etiology of psychiatric disorders. *Neurobiol Stress* 4: 62-70.
252. Dantzer R, O'Connor JC, Freund GG, et al. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9: 46-56.
253. Johnson JD, Campisi J, Sharkey CM, et al. (2005) Catecholamines mediate stress-induced increases in peripheral and central inflammatory cytokines. *Neuroscience* 135: 1295-1307.
254. Weber MD, Frank MG, Sobesky JL, et al. (2013) Blocking toll-like receptor 2 and 4 signaling during a stressor prevents stress-induced priming of neuroinflammatory responses to a subsequent immune challenge. *Brain Behav Immun* 32: 112-121.

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