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HMGB1 in Development and Diseases of the Central Nervous System

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Abstract High mobility group box 1 (HMGB1) is widely expressed in cells of vertebrates in two forms: a nuclear "architectural" factor and a secreted inflammatory factor. During early brain development, HMGB1 displays a complex temporal and spatial distribution pattern in the central nervous system. It facilitates neurite outgrowth and cell migration critical for processes, such as forebrain development. During adulthood, HMGB1 serves to induce neuroinflammation after injury, such as lesions in the spinal cord and brain. Receptor for advanced glycation end products and Toll-like receptors signal transduction pathways mediate HMGB1-induced neuroinflammation and necrosis. Increased levels of endogenous HMGB1 have also been detected in neurodegenerative diseases. However, in Huntington's disease, HMGB1 has been reported to protect neurons through activation of apurinic/apyrimidinic endonuclease and 5′-flap endonuclease-1, whereas in other neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, HMGB1 serves as a risk factor for memory impairment, chronic neurodegeneration, and progression of neuroinflammation. Thus, HMGB1 plays important and double-edged roles during neural development and neurodegeneration. The HMGB1-mediated pathological mechanisms have remained largely elusive. Knowledge of these mechanisms is likely to lead to therapeutic targets for neurological diseases.

Keywords HMGB1 · Nervous system · Neural development · Neuroinflammation · Neurodegeneration

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Introduction

High mobility group box 1 (HMGB1), also called amphoterin and HMG1, is an abundant protein that is widely expressed in all tissues of vertebrates. Almost 40 years ago, HMGB1 was initially identified as a non-histone chromosomal protein in calf thymus [1]. HMGB1 contains an all α-helical fold in the form of a V-shaped arrowhead with two homologous HMG-box domains: A and B [2–4]. Differential localization functionally separates HMGB1 into an "architectural" factor vs. a secreted inflammatory factor. As an architectural factor in the nucleus, HMGB1 interacts with DNA nonspecifically to promote chromatin binding of distinct site-specific transcription factors, such as HOX proteins, RAG1/2 recombinase, and the tumor suppressor gene p53 [5, 6]. As a secreted inflammatory factor, many studies indicate that HMGB1 can be released by different kinds of cells, including monocytes, tissue macrophages, astrocytes, and neurons [7–10]. In addition, it is released from dying cells. HMGB1 can induce inflammation mainly through receptor for advanced glycation end products (RAGE), Toll-like receptor 4 (TLR-4), and Toll-like receptor 9 in many diseases, such as rheumatoid arthritis, systemic lupus erythematosus, hepatic ischemia and reperfusion injury, and nephritis [11–17]. Recently, important beneficial functions for HMGB1 in the cytoplasm have been described: HMGB1 can prevent mitochondrial abnormalities and promote autophagy in cancer chemotherapy [18, 19]. In the central nervous system, HMGB1 has been shown to be present in neurons, microglia, and astrocytes [8, 20, 21]. HMGB1 has also been detected in neurons and Schwann cells of the peripheral nervous system [22]. When present at the cell surface of neurons or in the extracellular matrix, HMGB1 promotes neurite outgrowth and cell migration and induces neuroinflammation after injury [21, 23–25]. Here, we aim at

a short review of the present knowledge on the implications of HMGB1 in ontogenetic development and diseases of the central nervous system.

HMGB1 and Central Nervous System Development

In central nervous system development, Rauvala and Pihlaskari provided pioneering evidence that HMGB1 is expressed in brain homogenates of embryonic days 17–18 (E17–18) rats [23]. Subsequently, a more precise localization of HMGB1 during embryonic central nervous system development demonstrated that HMGB1 is widely expressed throughout the brain during early phases and later appears in the cortical plate of the developing primary cortex in the presumptive thalamic region [26]. In E16 murine embryos, the cortical plate is more expanded as compared with E14 murine embryos, and a concomitant increase in the number of HMGB1-positive cells has been described. HMGB1 is present in the subplate and localized only in the cytoplasm and extracellular space. At late developmental stages (E18), HMGB1 levels decrease dramatically compared with E16 murine embryos, and most neural cells do not express HMGB1. However, it remains expressed at high levels in certain brain areas, where some degree of neurogenesis occurs, including the hippocampal dentate gyrus, olfactory bulb, and cells lining the telencephalic ventricles [26] (Fig. 1). The results of these studies indicate that HMGB1 contributes to neurogenesis during early development of the brain. In the rodent embryo, HMGB1 was detected not only in later stages of central nervous system development but also in the neural inducer, the notochord. For example, in the early development of amphioxus, HMGB1 is expressed in cerebral vesicles, neural tube, and notochord [27]. It is also detected in the embryonic lamprey during forebrain development [28]. It is noteworthy that until now, there has been no study on HMGB1 expression in the primate nervous system.

Functional studies in vitro have indicated that HMGB1 is involved in neurite extension: Coating of substrate surfaces with purified HMGB1 facilitates adhesion and neurite outgrowth of E17–18 rat neurons [23]. In vivo knockdown of HMGB1 in embryonic zebrafish by application of antisense morpholinos caused a shorter trunk with curled tail and a smaller head in 5 days postnatal fertilization zebrafish larvae, implicating a promoting role of HMGB1 in forebrain development [29]. Moreover, HMGB1 antisense morpholino treatment blocked the development of the catecholaminergic network and strongly reduced the number of tyrosine hydroxylase1-positive neurons in the telencephalon and anterior basal diencephalon, and very few proliferating cells could be detected in proliferating zones. Co-injection of HMGB1 cRNA with HMGB1 antisense morpholinos partially rescued this phenotype. These results suggest that HMGB1 is essential for forebrain development. However, the distribution of HMGB1 in the developing vertebrate brain and the effects of HMGB1 on neural stem cells and neural progenitor cells are not fully understood.

Yet, a function of HMGB1 in development in vivo may be inferred from its ability to promote neurite outgrowth and cell migration. For instance, postnatal day 4 (P4) to P7 rat cerebellar granule neurons, cultured on an HMGB1-coated substrate, showed more extensive neurite outgrowth compared with neurons cultured on laminin or bovine serum albumin substrates. It is noteworthy in this context that the human natural killer cell glycan HNK-1, which strongly binds to HMGB1, is beneficial for neurite outgrowth: HMGB1-stimulated neurite outgrowth in vitro is inhibited by addition of an HNK-1 antibody to the culture medium [30], suggesting that HMGB1 acts as a co-stimulant with HNK-1 to facilitate neurite outgrowth. These observations

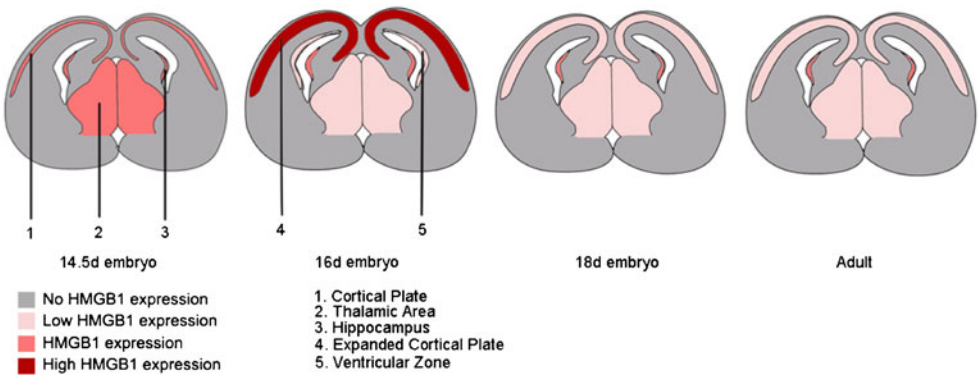

Fig. 1 Expression patterns of HMGB1 during brain development. In E14.5 mouse brains, HMGB1-positive cells are widely present in the developing cortex and thalamic region. In E16 brains, the cortical plate expands and the number of HMGB1-positive cells increases along with the appearance of scattered HMGB1-positive cells in the subventricular and ventricular zones. During later development at E18, the level of HMGB1 expression decreases. In the adult, expression of HMGB1 becomes restricted to regions of neurogenesis, such as the hippocampus and olfactory bulb [26]

are in agreement with the co-localization of HMGB1 with RAGE and RAGE with HNK-1 on granule cells migrating out of the core of microexplanted cultures from P5 rat cerebellum [31]. HMGB1, RAGE, and HNK-1 were co-localized at the cell surface, and interestingly, RAGE combines with HNK-1 and HMGB1 to stimulate cell migration and neurite outgrowth, with RAGE being a receptor for HMGB1 in promoting neurite outgrowth. Hori et al. purified RAGE ligands from bovine lung and found that each of the interacting peptides comprised sequences of HMGB1 [20]. Radioligand binding studies with ^{125}I-HMGB1 on cortical neurons isolated from E17 rat brain revealed that HMGB1 bound to RAGE specifically in a dose-dependent and saturable manner. RAGE was also highly expressed and co-localized with HMGB1 in histological sections of P5 rat cerebral cortex and hippocampus. Soluble RAGE or anti-RAGE IgG/(Fab′)$_2$ blocked HMGB1–RAGE interactions and prevented HMGB1-induced neurite outgrowth [20]. Similarly, HMGB1 was found to bind to RAGE-associated *N*-glycans and promoted neurite outgrowth. Furthermore, anti-carbohydrate antibody mAbGB3.1, which blocks RAGE-associated *N*-glycans, inhibited neurite outgrowth of N18 neuroblastoma cells cultured on surfaces coated with HMGB1 [32, 33]. Sulfoglucuronyl carbohydrate-binding protein 1, most likely identical with HMGB1, is widely expressed in cerebral cortex and cerebellum during rat brain development [30]; has the same binding site on HNK-1 as HMGB1; and displays functions similar to HMGB1 in promoting migration and neurite outgrowth of cerebellar granule cells in vitro [34, 35].

Experiments on the functions of HMGB1 show that it indeed plays a crucial role in neuronal migration. Western blotting of both N18 neuroblastoma cells and N18 neuroblastoma-conditioned medium revealed increased levels of HMGB1 in the culture medium, when cells were plated on laminin and when compared with heparin-binding glycan-associated molecules [25]. Inhibition of N18 neuroblastoma and C6 glioma cell migration on a laminin substrate was reduced in a dose-dependent manner by anti-HMGB1 antibodies in a haptotactic transfilter assay, verifying the involvement of HMGB1 in cell migration.

HMGB1 and Central Nervous System Injury

Unlike the beneficial roles of HMGB1 in early CNS development, it displays a high propensity to be a neuroinflammatory factor after CNS injury. It has been confirmed that HMGB1 protein expression is enhanced and HMGB1 is released from cells after a variety of injuries, such as spinal cord and brain injuries [24, 36]. Levels of the secreted HMGB1 correlated with apoptosis and degeneration of neurons [24]. After injury, most studies support a role of HMGB1 as an inflammatory factor which inhibits functional recovery. For instance, in a rat acute spinal cord injury model, increasing HMGB1 levels were found up to 72 h after lesion in the cytoplasm of dying cells. The expression of RAGE and tumor necrosis factor (TNF) was also upregulated by HMGB1, implicating a role for HMGB1 in the induction of apoptosis via inflammatory reactions [24]. Research on a rat spinal nerve ligation model also showed that HMGB1 expression in neurons was markedly enhanced in dorsal root ganglia at 7 days after ligation. Almost all HMGB1-positive non-neuronal cells at the lesion site and in the spinal nerve co-localized with glial fibrillary acidic protein (GFAP), a marker for satellite glial cells in dorsal root ganglia and non-myelin-forming Schwann cells in the peripheral nerve, suggesting that glial cells secrete HMGB1 and contribute to the neuroinflammation. Behavioral testing confirmed that HMGB1 contributed to the pathogenesis of neuropathic pain induced by neuroinflammation, since application of antibodies to HMGB1 prevented mechanical allodynia [37].

HMGB1 also mediates the apoptosis of motor neurons in a spinal cord ischemia model. HMGB1 can be released in an animal model of ischemia from the central nervous system into the blood stream due to disruption of the blood–brain barrier, reflecting the levels of HMGB1 expression in the central nervous system. Decrease of the serum concentrations of HMGB1 in this model was associated with better survival of motor neurons in the spinal cord [38, 39]. In other central nervous system ischemia models, HMGB1 levels were significantly increased in serum and cerebrospinal fluid and contributed to brain damage [36, 40]. Kim et al. injected a plasmid encoding HMGB1 shRNA to silence HMGB1 expression into the adult rat brain that had been made ischemic by middle cerebral artery occlusion. HMGB1 shRNA markedly suppressed infarct volumes, as shown by 2.3.5-triphenyl tetrazolium chloride staining [36]. In patients with ischemic stroke, serum concentrations of HMGB1 were higher than in age- and sex-matched control patients [40]. Furthermore, ischemia induced by oxygen–glucose deprivation in vitro induces HMGB1 release leading to neuronal cell death. In vivo, HMGB1 could be detected by immunocytochemistry in GFAP-positive astrocytes and Iba1-positive microglia after oxygen–glucose deprivation: In middle cerebral artery occlusion-induced ischemia, increased serum concentrations of HMGB1 were observed 4 h after occlusion, at which time immunostaining of nuclear HMGB1 in the cerebral cortex revealed loss of HMGB1 in the core of the infarct and a marked reduction in the peripheral areas, which was accompanied by a release of HMGB1 into the extracellular space. Intraperitoneal injection of anti-HMGB1 antibody 15 min before occlusion decreased the number of TdT-mediated dUTP-biotin nick end labeling-positive cells in the periphery of the ischemic area. Thus, HMGB1 was suggested to promote cell death in ischemia [40].

Secreted HMGB1 protein has been considered as a late inflammatory mediator following increases in levels of TNF and interleukin (IL)-1β [7]. However, other studies argued that HMGB1 is robustly released early after injury, subsequently leading to an increase in TNF levels [41]. HMGB1 could not evoke increases in levels of IL-1β, but strongly increased IL-6 and IL-8 levels through TLR-4 signaling [13]. In the process of mediating inflammation, secreted HMGB1 containing nucleosomes also stimulated inflammation through RAGE, TLR-2, and TLR-9 [42, 43]. Tian and colleagues found that application of HMGB1 in DNA-containing immune complexes to mouse bone marrow increased interferon (IFN)-α secretion in plasmacytoid dendritic cells compared with HMGB1 alone. In mice plasmacytoid dendritic cells deficient in RAGE and TLR-9, application of HMGB1 in DNA-containing immune complexes led to lower levels of IFN-α [43]. In agreement with this study, secreted HMGB1 alone could not stimulate inflammation or tissue damage, but only in a complex with lipid or DNA [44]. Such a trigger of the inflammatory reaction depended on both RAGE and TLRs [44]. In chronic neurodegeneration, HMGB1 cooperates with Mac1 to activate microglia, which drives progressive neuronal damage after injury, suggesting that HMGB1 may be a target in the therapy of acute and chronic central nervous system injuries [21] (Fig. 2).

HMGB1 and Neurodegenerative Diseases

Changes in HMGB1 levels have been observed during aging and in many neurological diseases. Here we mainly discuss Huntington's disease, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

In different brain regions of mice, including cortex, hippocampus, striatum, and cerebellum, HMGB1 expression is the highest in young adults and gradually decreases during aging. Its expression is clearly lower in aged neurons than in young ones, whereas it is higher in aged astrocytes than in young ones [8]. DNA double-strand breaks, which are mediators of neuronal damage in Huntington's disease, were found to accumulate in neurons with age, especially in the hippocampus and striatum. With increasing age, HMGB1 was described to be decreased in neurons and in parallel with increased DNA double-strand breaks, suggesting that reduction of nuclear HMGB1 is relevant for the accumulation of naturally occurring DNA damage leading to neuronal dysfunction in the aged brain [8].

In Huntington's disease models, HMGB levels were generally reduced in striatal neurons, and they co-localized with mutant huntingtin proteins in nuclear inclusion bodies. Reduction of HMGB1 in the nucleus is a frequent feature that is thought to promote neuronal dysfunction. Restoration of HMGB1 proteins reduced transcriptional repression and genotoxic stress signals induced by mutant polyQ proteins. Elevation of HMGB1 expression also improved neurite length and ameliorated neuronal death of primary cortical neurons in vitro and in *Drosophila* polyQ models [45]. Apurinic/apyrimidinic endonuclease (APE1) can cleave apurinic/apyrimidinic sites to help base excision repair, and 5′-flap endonuclease-1 (FEN1) can prevent neuronal CAG repeat expansion associated with Huntington's disease, suggesting that both enzymes help to prevent development of the disease. In experiments with $HMGB1^{+/+}$ cells and $HMGB1^{-/-}$ cells, Prasad et al. presented evidence that activities of APE1 and FEN1 are increased depending on the expression level of HMGB1 expression and that HMGB1 is the cofactor in base excision repair [46]. Further evidence in

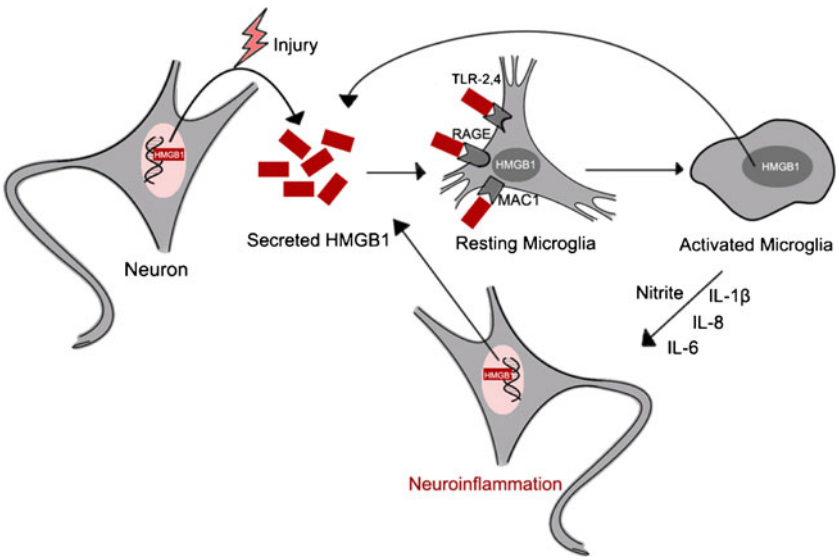

Fig. 2 HMGB1 induces progressive neuroinflammation when neurons are injured. When neurons die, HMGB1 is released and activates microglia through RAGE, TLR-2, TLR-4, and Mac1 receptors. Activated microglia mediate neuroinflammation by secreting, for instance, nitrite and cytokines, thereby inducing necrosis of other neurons, resulting in further HMGB1 release, thus upscaling neuroinflammation [21]

R6/1 mice, a transgenic mouse model for Huntington's disease, showed that levels of HMGB1 are 2- to 3-fold higher in the cerebellum (stable CAG repeat) than in the striatum (unstable CAG repeat). Similarly, the cerebellum of R6/1 mice contains higher levels of APE1 and FEN1, suggesting that HMGB1 helps stabilization of cerebellar functions through further activation of APE1 and FEN1 [47]. These data imply that HMGB1 ameliorates the symptoms of Huntington's disease, although the behavioral consequences of this amelioration have not been investigated in this context.

However, recent studies have suggested that HMGB1 is a risk factor for other neurodegenerative diseases. In Alzheimer's disease, extracellular HMGB1 may play a pathogenic role through inhibition of microglial phagocytosis and stabilization of Aβ42 oligomers, which are associated with the pathologic features of Alzheimer's disease. Mazarati and colleagues showed that HMGB1 added to rat microglial cultures in the presence of Aβ42 resulted in HMGB1 binding to Aβ42 and stabilized oligomerization of Aβ42 monomers in association with reduced microglial uptake of Aβ42 [48, 49]. In a test for novel object recognition, injection of HMGB1 into the lateral ventricle of wild-type mice led to impairment of encoding long-term memory, when compared to age-matched TLR-4 and RAGE null mice. Injection of LPS-RS, a TLR-4 antagonist, into RAGE null mice before administration of HMGB1 blocked HMGB1-mediated memory impairment. These data indicate that HMGB1 elicits memory impairment via both TLR-4 and RAGE [48].

In Parkinson's disease, HMGB1 specifically binds to aggregated α-synuclein in Lewy bodies isolated from rat brain, suggesting HMGB1's promoting roles during neurodegeneration in the chronic phase of the disease [50]. In primary cultures of mouse neurons and glial cells, HMGB1 was found to bind to Mac1, a microglial membrane receptor, and to activate the NF-κB pathway and NADPH oxidase expression, thus inducing chronic progressive neuroinflammation and dopaminergic neurodegeneration [21].

Increased HMGB1 expression was also found in white matter of patients with multiple sclerosis and in mice with myelin oligodendrocyte protein-induced experimental autoimmune encephalomyelitis [51]. In the mouse study, an elevated HMGB1 expression correlated with an increased expression of HMGB1-binding receptors, including RAGE, TLR-2, and TLR-4 in spinal cord tissue and in mononuclear cells of the cerebrospinal fluid. It is, thus, conceivable that HMGB1 and its receptors amplify inflammatory responses and thereby promote the neuroinflammatory processes in demyelination [51].

In other nervous system diseases, HMGB1 has been found to contribute to generating and perpetuating seizures in humans through TLR-4 signaling [52]. For instance, in human amyotrophic lateral sclerosis, progression of inflammation and motor neuron degeneration have been suggested to be induced by HMGB1 through the TLR/RAGE signaling pathway [53] (Table 1).

Perspectives

Dual roles of HMGB1 have been described in the nervous system of vertebrates: promotion of ontogenetic development, on the one hand, and neuroinflammation following injury, on the other. However, the principal receptors of HMGB1 responsible for inflammation remain to be defined. In addition, the roles of HMGB1 in response to nervous

Table 1 Overview of HMGB1 functions in neurological diseases

CNS diseases	Main findings	References
Huntington's disease	HMGB1 ameliorates the transcriptional repression and genotoxic stress signals induced by polyQ.	[45]
	Activity of APE1 and FEN1 levels are increased in association with enhanced HMGB1 expression.	[46]
	HMGB1 concentrations are 2- to 3-fold higher in the cerebellum than in the striatum of Huntington's disease mouse models.	[47]
Alzheimer's disease	HMGB1 binding to Aβ42 inhibits microglial phagocytosis of Aβ42.	[49]
	HMGB1 impairs memory via TLR-4 and RAGE.	[48]
Parkinson's disease	HMGB1 binds to α-synuclein in Lewy bodies.	[50]
	HMGB1 binds to Mac1 to activate microglia and induce chronic neuroinflammation.	[21]
Multiple sclerosis	Increased HMGB1 levels are found in brains of patients with multiple sclerosis and mice with experimental allergic encephalomyelitis.	[51]
Seizure	HMGB1 promotes seizures in a TLR-4-dependent pathway.	[52]
	Higher IL-1β in serum is correlated with increased levels of HMGB1, IL-6, and TNF in febrile seizure patients.	[54]
ALS	Degenerating motor neurons exhibit reduced immunostaining for HMGB1.	[55]
	TLR-2, TLR-4, RAGE, and HMGB1 are increased in reactive glia in the spinal cord of patients with amyotrophic lateral sclerosis.	[53]

system injury require further investigation. Presently, HMGB1 is regarded to play a deleterious role during neurodegeneration. However, beneficial effects of HMGB1 on neuroregeneration should not be ruled out, since regeneration after acute and during ongoing injury and neural development share some common features in functions of neurotrophic factors [56] and axon guidance molecules [57]. Thus, further exploring the functions of HMGB1 in neuroinflammation in different neurological diseases, including polyneuropathies, where the HNK-1 glycan can be an autoimmune target, will contribute to our understanding of the mechanisms by which HNGB1 ameliorates neurodegeneration. It will be interesting to intercross HMGB1 null mice as models for neurodegenerative diseases with mouse models of neurological diseases to explore the role of HMGB1 in neurodegeneration. Also, transgenic mice overexpressing HMGB1 in neural cells should yield insights into the impact of HMGB1 in neurodegenerative diseases. The ability to influence the neuropathological phenotypes through several receptors confers HMGB1 with the potential of a therapeutic target for neurodegenerative diseases.

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Conflict of Interest The authors declare that there are no conflict interests.

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