Review

Regulation of neuroimmune processes by damage- and resolution-associated molecular patterns

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Abstract

Sterile inflammatory processes are essential for the maintenance of central nervous system homeostasis, but they also contribute to various neurological disorders, including neurotrauma, stroke, and demyelinating or neurodegenerative diseases. Immune mechanisms in the central nervous system and periphery are regulated by a diverse group of endogenous proteins, which can be broadly divided into the pro-inflammatory damage-associated molecular patterns (DAMPs) and anti-inflammatory resolution-associated molecular patterns (RAMPs), even though there is notable overlap between the DAMP- and RAMP-like activities for some of these molecules. Both groups of molecular patterns were initially described in peripheral immune processes and pathologies; however, it is now evident that at least some, if not all, of these immunomodulators also regulate neuroimmune processes and contribute to neuroinflammation in diverse central nervous system disorders. The review of recent literature demonstrates that studies on DAMPs and RAMPs of the central nervous system still lag behind the much broader research effort focused on their peripheral counterparts. Nevertheless, this review also reveals that over the last five years, significant advances have been made in our understanding of the neuroimmune functions of several well-established DAMPs, including high-mobility group box 1 protein and interleukin 33. Novel neuroimmune functions have been demonstrated for other DAMPs that previously were considered almost exclusively as peripheral immune regulators; they include mitochondrial transcription factor A and cytochrome C. RAMPs of the central nervous system are an emerging area of neuroimmunology with very high translational potential since some of these molecules have already been used in preclinical and clinical studies as candidate therapeutic agents for inflammatory conditions, such as multiple sclerosis and rheumatoid arthritis. The therapeutic potential of DAMP antagonists and neutralizing antibodies in central nervous system neuroinflammatory diseases is also supported by several of the identified studies. It can be concluded that further studies of DAMPs and RAMPs of the central nervous system will continue to be an important and productive field of neuroimmunology.

Key Words: Alzheimer's disease; astrocytes; DAMPs; HMGB1; microglia; neurodegeneration; neuroimmune responses; neuroinflammation; neurotrauma; oligodendrocytes; pattern-recognition receptors; RAMPs

Introduction

Damage-associated molecular patterns (DAMPs), also known as danger-associated molecular patterns and alarmins, are endogenous molecules that can be released into the extracellular space upon cellular stress or damage. DAMPs are an integral part of immune response; at low concentrations, these molecules regulate homeostasis and correct altered physiological states, but at high concentrations, they enhance and propagate inflammatory reactions. Excessive release of DAMPs as a result of trauma or inflammatory processes leads to immune activation of surrounding cells and recruitment of distant cells. This causes further tissue injury, thus establishing vicious cycles of damage, which may lead to chronic inflammation (Patel, 2018). The concept of DAMPs as immunoregulators was introduced in the 1990s, and since then the number of molecules included in this group has been steadily increasing. Molecules that are normally located intracellularly are most often considered DAMPs. They originate from the nucleus (e.g., genomic DNA, high-mobility group box 1 protein (HMGB1), interleukin (IL)-33), cytosol (e.g., heat-shock proteins (HSPs), S100 proteins), mitochondria (e.g., ATP, mitochondrial DNA, cytochrome C), endoplasmic reticulum (e.g., calreticulin), or granules (e.g., defensins). Some researchers also consider extracellular matrix components (e.g., heparan sulfate, fibrinogen) as DAMPs due to their excessive release from tissues under inflammatory conditions. Currently, more than 30 different DAMPs have been described and this list will most likely need to be expanded as more molecules are discovered and characterized as DAMPs (Hauser and Otterbein, 2018; Mihm, 2018; Patel, 2018; Roh and Sohn, 2018; Gong et al., 2020). DAMPs can activate and sustain immune responses in the absence of infectious agents, making them critical to the sterile inflammation seen in many pathologies (e.g., trauma, ischemia, allergies, cancers, neurodegenerative diseases).

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Once released from damaged or inflamed tissues, DAMPs activate innate immune cells, including neutrophils, tissue macrophages, and dendritic cells, but they can also interact with non-immune cells, such as endothelial cells, fibroblasts and astrocytes, which are the non-neuronal support cells in the central nervous system (CNS). The most established cellular sensors of DAMPs are the pattern-recognition receptors (PRRs) expressed by antigen-presenting cells, including several different toll-like receptors (TLRs), C-type lectin receptors, NOD-like receptors (NLRs), and absent in melanoma 2 (AIM2)-like receptors, among others. In addition, several different non-PRRs mediate interaction between DAMPs and their target cells, such as triggering receptors expressed on myeloid cells (e.g., TREM2), several G-protein-coupled receptors (e.g., N-formyl peptide receptors) and ion channels (e.g., purinergic receptor P2X7R). Receptor for advanced glycation end products (RAGE) is another prominent target of DAMPs, which is considered a PRR by some researchers (Roh and Sohn, 2018; Gong et al., 2020).

The initial studies of DAMPs were focused on peripheral immune responses and pathologies with only recent recognition that many of the same molecules also contribute to sterile neuroinflammatory processes seen in such diverse CNS pathologies as neurotrauma, demyelinating diseases, and neurodegenerative disorders. Most of the recent CNS-focused review articles list up to 20 different DAMPs as contributors to various physiological and pathological processes. DAMPs most commonly associated with neuroimmune responses are listed in **Table 1** together with the receptors they have been shown to interact with. Some researchers consider CNS pathology-specific structures, such as aggregates of amyloid β (Aβ) protein and α-synuclein, as DAMPs; however, this view is not universally shared (Gadani et al., 2015a; Venegas and Heneka, 2017; Earls et al., 2019; Gomes-Leal, 2019). Under physiological conditions, and in pathologies with relatively intact blood-brain barrier (BBB), the three glial cell types – microglia, astrocytes, and oligodendrocytes – are the main CNS targets of DAMPs. Microglia belong to the mononuclear phagocyte system and are the main innate immune cell type in the nervous system (Gomez Perdiguero et al., 2015). Astrocytes are the main non-neuronal support cells of the CNS, while oligodendrocytes form myelin sheaths critical for neurotransmission (Reemst et al., 2016; Sung et al., 2019). Under pathological conditions where the BBB is compromised, including neurotrauma, ischemic stroke, and active multiple sclerosis lesions, peripheral immune cells, including neutrophils, macrophages and lymphocytes, can infiltrate brain parenchyma and become targets of some DAMPs (Gharagozloo et al., 2017; Nakamura and Shichita, 2019). Over the last two decades, it has become apparent that DAMPs play a central role in neuroinflammation present in a wide range of CNS pathologies. The delayed start in studies exploring DAMPs of the CNS has led to the current discrepancy where a significantly larger number of DAMP-like molecules have been characterized for peripheral immune responses and pathologies, compared to neuroimmune processes. This discrepancy has also created an opportunity for neurobiologists to explore neuroimmune roles of DAMPs that have thus far only been recognized as contributors to peripheral immune mechanisms. This review illustrates the current trends in neuroimmunology whereby over the last five years more in-depth knowledge about already established CNS DAMPs (e.g., HMGB1, IL-33) has been generated. In addition, previously unknown DAMP-like CNS functions have been discovered for molecules thus far only recognized for their contribution to peripheral inflammation (e.g., several mitochondrial DAMPs) (Liew et al., 2016; Bajwa et al., 2019; Michetti et al., 2019; Nishibori et al., 2019).

Table 1 | **DAMPs and RAMPs in neuroimmune responses***

Intracellular location	DAMPs	Receptors	RAMPs	Receptors
Nucleus				
	HMGB1	TLR2, TLR4, RAGE	prothymosin α	TLR4
	IL-33	ST2 (IL-1RL1)		
	Genomic DNA	TLR9, AIM2		
Cytosol				
	ATP	P2Y2R, P2X7R	HSP10	TLR2, TLR3, TLR4, TLR6, TLR7, TLR9
	HSP27	TLR2, TLR4	HSP27	TLR2, TLR4
	HSP70 (BiP)	TLR2, TLR4,	HSP70 (BiP)	TLR4
	S100 proteins	TLR2, TLR4, RAGE	αB-Crystallin	TLR1, TLR2, CD14
	Chromogranin A	TLR, RAGE		
	Peroxiredoxins (Prx-1, Prx-2, Prx-4)	TLR2, TLR4		
	RNA	TLR3		
Mitochondria				
	ATP	P2Y2R, P2X7R	Cardiolipin	TLR4, CD36
	mtDNA	TLR9, RAGE		
	Cytochrome C	TLR4		
	TFAM	RAGE, Mac-1		
	Formyl peptides	FPR1		

*Table is based on recent reviews describing DAMPs and RAMPs associated with the neuroimmune responses (Gadani et al., 2015a; Gelderblom et al., 2015; Thundyil and Lim, 2015; Venegas and Heneka, 2017; Gulke et al., 2018; Bajwa et al., 2019), as well as articles illustrating the cellular receptors engaged by these signaling molecules (Shields et al., 2011; Schaefer, 2014; Guisasola et al., 2018; Hauser and Otterbein, 2018; Mihm, 2018; Patel, 2018; Roh and Sohn, 2018; Gong et al., 2020). AIM2: Absent in melanoma 2; BiP: binding immunoglobulin protein; CD: cluster of differentiation; DAMP: damage-associated molecular pattern; FPR1: N-formyl peptide receptor 1; HMGB1: high-mobility group box 1; HSP: heat-shock protein; IL: interleukin; IL-1RL1: interleukin 1 receptor-like 1; Mac-1: macrophage-1 antigen; mtDNA: mitochondrial DNA; P2X7R: purinergic P2X7 receptor; P2Y2R: purinergic P2Y2 receptor; RAGE: receptor for advanced glycation end products; RAMP: resolution-associated molecular pattern; TFAM: mitochondrial transcription factor A; TLR: toll-like receptor.

Search Strategy and Selection Criteria

The initial literature search was performed on March 20, 2020 within OVID Medline (PubMed) databases using the following combination of keywords: "microglia OR microglial OR astrocyte OR astrocytic OR oligodendrocyte OR oligodendroglia" AND "DAMP OR alarmin". All fields were included in the search, which was restricted to publications from the last five years. The above search strategy identified 50 primary research articles and 29 reviews. More targeted searches using the names of known resolution-associated molecular patterns (RAMPs), including "cardiolipin", "prothymosin α", "binding immunoglobulin protein OR BiP OR GRP78 OR HSP70", and "αB-crystallin OR HSPB5", were also performed. Abstracts of all primary research articles were screened for relevance, which identified 60 significant publications discussed in sections below.

High-Mobility Group Box 1 Protein

HMGB1 remains the most studied DAMP in the context of CNS physiology and pathology. While the chosen search strategy identified only 14 primary research articles focused on HMGB1, a more targeted search discovers a significantly greater number of publications, including recent reviews describing the role of HMGB1 in CNS pathology (Richard et al., 2017; Ye et al., 2019; Paudel et al., 2020). HMGB1 is expressed in all nucleated animal cells. It is a non-histone chromosome binding protein, which under physiological circumstances is located within the nucleus, where it binds to DNA stabilizing nucleosomes and assists with DNA replication

and transcription. HMGB1 is released into the extracellular space by cells that die traumatically. In addition, cells that are destined to die, stressed cells, and activated cells of the innate immune system can secrete HMGB1 through several different mechanisms (Bianchi, 2009). Extracellular HMGB1 acts as a prototypical DAMP by binding to a number of different cellular receptors. Its most established interactions are with TLR2 and TLR4 on peripheral immune cells and CNS glial cells, as well as with RAGE, which is expressed by glia, neurons, and endothelial cells (Ye et al., 2019). Binding of HMGB1 to the cell surface receptors activates associated intracellular signaling pathways, thereby triggering cellular responses (Rosciszewski et al., 2019). In addition, recent studies demonstrate intracellular DAMP-like effects of HMGB1 where its RAGE-mediated endocytosis leads to destabilization of lysosomes (Andersson et al., 2018). It is important to note that the oxidation-reduction (redox) and acetylation states of HMGB1 play a critical role in its subcellular localization, release mechanism and receptor binding. For example, it has been demonstrated that the disulfide form of HMGB1, which is formed when cysteines C23 and C45 are oxidized, upregulates hippocampal pro-inflammatory mediators after its intra-cisterna magna injection. Interestingly, this oxidised form of HMGB1 also primes the inflammatory response of isolated primary microglia to subsequent challenge by bacterial lipopolysaccharide. Meanwhile, the reduced form of HMGB1 has no effect in either of these two experimental systems (Frank et al., 2016b).

Studies published within the last 5 years have further established the central role of HMGB1 as a key neuroinflammatory molecule associated with several different physiological and pathological processes, as well as pharmacological interventions. Studies with unmanipulated aged rats demonstrate upregulated HMGB1 mRNA expression and protein levels in the hippocampus as well as elevated cerebrospinal fluid HMGB1 in 24-months old rats, compared to young (3-months old) animals, which indicates increased HMGB1 extracellular release with normal aging (Fonken et al., 2016). Elevated expression of mRNA for HMGB1 and its receptor RAGE can be detected in rat hippocampal microglia after exposure of animals to chronic stress (Franklin et al., 2018). These observations are consistent with data from other studies that record increased hippocampal and amygdalar HMGB1 protein levels immediately after exposure of animals to acute stress (Frank et al., 2018, 2019). Hippocampal HMGB1 protein levels are also elevated after hypoxia-ischemia-induced brain injury in neonatal mice. HMGB1 translocation from the nucleus to the cytoplasm can be demonstrated in hippocampal nerve cells indicating release of HMGB1 from these neurons after hypoxia-ischemia insult (Le et al., 2020). Elevated HMGB1 levels have been recorded in sera of Alzheimer's disease (AD) patients and subjects with mild cognitive impairment (Festoff et al., 2016). Similarly, increased plasma HMGB1 levels can be seen four hours after pilocarpine-induced seizures in mice; since a corresponding decrease of brain HMGB1 accompanies upregulated peripheral levels of this protein, translocation of HMGB1 from the brain into peripheral blood is implied (Fu et al., 2017). Striatal levels of HMGB1 protein are also upregulated four hours after intraperitoneal injection of methamphetamine (Frank et al., 2016a).

Increased HMGB1 levels, and its extracellular release, generally lead to detrimental effects, including upregulation of brain pro-inflammatory cytokines (Fonken et al., 2016), immune activation and priming of microglia and astrocytes (Fonken et al., 2016; Das et al., 2019; Rosciszewski et al., 2019), neuronal death (Rosciszewski et al., 2019), and disruption of BBB (Festoff et al., 2016). Intraperitoneal administration of recombinant, fully reduced HMGB1 for 7 days leads to neuroinflammation and memory loss in mice (Das et al., 2019). Recent studies have also replicated previously reported immune activation of cultured primary microglia by HMGB1 through signaling pathways associated with TLR2, TLR4, and RAGE. Interestingly, HMGB1 is not directly toxic to cortical neurons, and microglial activation is required for induction of neuronal death in mixed neuron-glial cultures by recombinant HMGB1 (Rosciszewski et al., 2019).

Since upregulated HMGB1 levels and increased extracellular release could lead to primed and chronically exaggerated inflammatory responses, as well as neuronal death, inhibiting the DAMP activity of this protein has been explored as a therapeutic strategy (Fonken et al., 2016). Anti-HMGB1 antibodies block the detrimental effects of this DAMP on the integrity of the BBB in an *in vitro* model (Festoff et al., 2016); they also lower BBB leakage and expression of inflammatory mediators in a pilocarpine-induced mouse model of seizures, which leads to a reduced number of apoptotic hippocampal neurons in these animals (Fu et al., 2017). Glycyrrhizin, a major active ingredient of the roots and rhizomes of licorice (Glycyrrhiza glabra), has been used as a selective inhibitor of HMGB1 translocation and secretion. Administration of this compound after hypoxia-ischemia injury reduces HMGB1 nucleocytoplasmic translocation in hippocampal neurons and their apoptosis as well as decreases inflammatory cytokine levels in the hippocampus (Le et al., 2020). Intraperitoneal administration of glycyrrhizin immediately after inducing status epilepticus by pilocarpine significantly reduces reactive microgliosis and neuronal loss in the piriform cortex of rats (Rosciszewski et al., 2019). Interestingly, one of the HMGB1 protein domains, called box A, can be used as an HMGB1 antagonist to inhibit methamphetamine-induced upregulation of IL-1β in three distinct areas of rat brains (Frank et al., 2016a). Due to the perceived central role of HMGB1 as the initiator of the neuroimmune reactions in a wide range of neuropathologies, anti-HMGB1 monoclonal antibody therapy has been proposed for diverse CNS and peripheral nervous system disorders such as stroke, traumatic brain injury, Parkinson's disease, epilepsy, AD, and neuropathic pain (Nishibori et al., 2019).

Interleukin-33

IL-33 is a nuclear DAMP, which belongs to the IL-1 family. It binds to histones and chromatin in the nuclei of producing cells (Cayrol and Girard, 2018). In the CNS, it is constitutively expressed in mature oligodendrocytes and astrocytes. Upon release from these cells, IL-33 binds to its receptor ST2 (also known as IL-1 receptor-like 1, IL-1RL1) initiating intracellular signaling involving myeloid differentiation primary response protein 88, mitogen-activated protein kinases and nuclear factor kappa-light-chain-enhancer of activated B cells (Gadani et al., 2015b; Cayrol and Girard, 2018). Recent studies have implicated IL-33 as a DAMP that is upregulated and released in response to injury. In human patients and animal models with traumatic brain injury, astrocytes and oligodendrocytes are the main source of IL-33, which recruits microglia and macrophages expressing ST2 to the sites of damage (Wicher et al., 2017). Chronic constriction injury of the sciatic nerve induces IL-33 production and release by oligodendrocytes in the spinal cords of mice, causing microglia and astrocyte activation (Zarpelon et al., 2016). The same study uses IL-33 receptor knockout animals ($ST2^{-/-}$) and administration of soluble IL-33 decoy receptors to demonstrate that IL-33 contributes to development of hyperalgesia in this animal model of neuropathic pain. Interestingly, mice fed a high fat diet for 3 to 4 months exhibit increased hypothalamic IL-33 levels accompanied by myelin disruption and appearance of reactive microglia and astrocytes (Huang et al., 2019); based on the previous studies, it can be speculated that IL-33 released from oligodendrocytes is responsible for hippocampal gliosis observed in these animals. Even though IL-33, as a

typical DAMP, is involved in CNS injury and neuropathologies, its role as a regulator of physiological processes is emerging. Thus, studies with IL-33 knockout mice demonstrate that this cytokine is critical for oligodendrocyte maturation (Sung et al., 2019), and may also regulate the development and maturation of neuronal circuits since animals lacking IL-33 exhibit multiple behavioural deficits (Dohi et al., 2017).

Mitochondrial Damage-Associated Molecular Patterns

Several recent reviews describe a group of DAMPs that, under physiological conditions, are located mainly within mitochondria, including ATP, cytochrome C, heme, mitochondrial transcription factor A (TFAM), cardiolipin, succinate, N-formyl peptides, and mitochondrial DNA. Mitochondrial DAMPs have been mainly studied in the context of the peripheral immune responses, but their possible contributions to various CNS pathologies are emerging (Dela Cruz and Kang, 2018; Hauser and Otterbein, 2018; Bajwa et al., 2019; Rodriguez-Nuevo and Zorzano, 2019).

ATP is among the molecules that are released by cell damage. Within injured tissues, it can reach high local concentrations and activate purinergic receptors (P2X or P2Y) on surrounding cells. It has been recently demonstrated that ATP can synergize with other DAMPs, which act through TLR4 and are released after brain injury, to induce NOD-like receptor protein 3 (NLRP3) inflammasome activation and caspase-1-mediated IL-1β secretion by microglia (Gaikwad et al., 2017). Activation and assembly of microglial NLRP3 inflammasomes is one of the critical mechanisms engaged by not only ATP, likely acting through the purinergic receptor P2X7R, but several other DAMPs, including HMGB1, HSP70, and chromogranin A, that are released from dying cells (Frank et al., 2016b; Qu et al., 2017; Venegas and Heneka, 2019). Interestingly, it has been suggested that high ATP concentration in the brain parenchyma leads to NLRP3 inflammasome activation in microglia, causing their release of other DAMPs (Ratajczak et al., 2019). The role of ATP as a DAMP contributing to CNS sterile inflammation in various neuropathologies is now well established; however, recent studies have demonstrated that ATP can also regulate several physiological functions of microglia, including oxidative phosphorylation, glycolysis, and production of intracellular reactive oxygen species (Hu et al., 2020).

Cytochrome C is a soluble heme-containing mitochondrial protein, which under physiological conditions functions as an electron carrier in the electron transport chain. Under the conditions of cellular stress, cytochrome C can be released from the mitochondrial intermembrane space into the cytosol, thereby initiating apoptosis. Extracellular release of this protein from damaged neurons and glial cells has been documented, as well as its elevated concentration in cerebrospinal fluid after head trauma in children (Ahlemeyer et al., 2002; Au et al., 2012; Wenzel et al., 2019). Recent *in vitro* studies demonstrate TLR4-dependent pro-inflammatory activation of microglia and astrocytes by extracellular cytochrome C, leading to increased secretion of cytokines and cytotoxins (Gouveia et al., 2017; Wenzel et al., 2019); however, *in vivo* confirmation of the DAMP-like activity of extracellular cytochrome C is still required.

Heme contains iron ions coordinated to a porphyrin. Heme is synthesized in the mitochondria and incorporated into dozens of proteins, including cytochrome C and hemoglobin. Once heme proteins are released into the extracellular space, heme can escape from its protein enclosure and perform DAMP functions by activating immune cells in a TLR4-dependent manner (Hauser and Otterbein, 2018). Heme-dependent activation of microglia has recently been demonstrated in a mouse model of spinal cord injury (Yoshizaki et al., 2019). The same study demonstrates upregulated TLR4 and tumor necrosis factor-α expression in primary microglia after their exposure to extracellular heme.

TFAM belongs to the highly conserved HMGB family of DNA-binding proteins. TFAM is localised to the inner mitochondrial membrane, but it can also be released by damaged cells into the extracellular environment, where it functions as a DAMP. Stimulation of several different types of peripheral immune cells by TFAM, alone or in combination with mitochondrial N-formyl peptides, has been reported (Crouser et al., 2009; Hauser and Otterbein, 2018; Bajwa et al., 2019). Recently, studies of the DAMP-like properties of TFAM have been extended by *in vitro* experiments showing that extracellularly applied TFAM upregulates pro-inflammatory cytokines in human and rat microglia as well as microglia-like human monocytic cells. In the latter cells, the pro-inflammatory activity of TFAM is partially mediated by RAGE and macrophage antigen complex 1; both of these PRRs are also known to mediate the effects of extracellular HMGB1. *In vivo* experiments show that intra-cisterna magna injection of TFAM upregulates the expression of several pro-inflammatory cytokines in the hippocampus and the frontal cortex of rats (Schindler et al., 2018).

Cardiolipin is a phospholipid of the inner mitochondrial membrane of mammalian cells. Cardiolipin can also redistribute to the outer mitochondrial membrane, which is an essential step in mitophagy, a cellular process used to destroy malfunctioning mitochondria (Pointer and Klegeris, 2017; Bajwa et al., 2019). The extracellular role of cardiolipin as a DAMP has been suggested in peripheral tissues where it upregulates the phagocytic activity of peripheral macrophages (Balasubramanian et al., 2015; Chakraborty et al., 2017). Recent studies with murine and human microglia indicate that this phospholipid may inhibit the inflammatory activity of these cells by downregulating the release of cytotoxins and inflammatory mediators, such as tumor necrosis factor-α, nitric oxide and reactive oxygen species. Extracellular cardiolipin also upregulates phagocytic activity of murine microglia *in vitro* (Pointer et al., 2019). Such anti-inflammatory and inflammation-resolving properties make cardiolipin similar to other members of an emerging group of molecules termed RAMPs (Shields et al., 2011). Signaling molecules that have been considered as RAMPs of the CNS, as well as the receptors they interact with, are listed in **Table 1**.

Resolution-Associated Molecular Patterns

RAMPs are a heterogeneous group of molecules, which are similar to DAMPs since they are released from damaged cells and often interact with PRRs on neighbouring cells; however, since their predominant cellular effect is inhibition of the release of cytotoxins and pro-inflammatory mediators by immune cells, most RAMPs contribute to immune regulation and resolution of inflammation. RAMPs were initially described in the context of the peripheral immune system, but recent studies have implicated several of these molecules as regulators of glial activation and inhibitors of neuroimmune responses. In addition to cardiolipin, the following molecules have been recently considered as RAMPs of the CNS: prothymosin α, binding immunoglobulin protein (BiP), and αB-crystallin. It is important to note that some of these molecules have also been described as DAMPs due to their interaction with TLRs, leading to upregulated secretion of pro-inflammatory mediators by several different types of immune cells. For example, prothymosin α induces maturation of dendritic cells and elicits T-helper type 1 immune responses *in vitro* and *in vivo* (Birmpilis et al., 2019). However, other studies have described anti-inflammatory properties of prothymosin α, which has already been studied

preclinically as a therapeutic agent in an animal model of cerebral ischemia; intravenous administration of prothymosin α increases survival of mice after transient middle cerebral artery occlusion (Maeda et al., 2016). Anti-inflammatory activity of BiP (also known as glucose-regulated protein 78 and HSP70), which is another RAMP, has also been confirmed in a clinical study with rheumatoid arthritis patients; single intravenous administration of BiP decreases serum levels of C-reactive protein, IL-8, and vascular endothelial growth factor (Kirkham et al., 2016). Even though a protective role of BiP in stroke, including its anti-inflammatory activity, has been suggested, studies with animal models of CNS trauma or neurological diseases have not been performed yet, but are clearly warranted (Mohammadi et al., 2018). αB-crystallin is yet another RAMP whose anti-inflammatory properties have been established by using cultured microglia as well as animal models of demyelinating diseases (Holtman et al., 2017). Intravenous administration of αB-crystallin has been shown to induce a progressive decline in multiple sclerosis lesion activity in a 48-week randomized, placebo-controlled, double-blind Phase IIa clinical trial with patients suffering from the relapsing-remitting form of the disease (van Noort et al., 2015).

Figure 1 illustrates the key receptors and associated signaling pathways regulated by RAMPs and DAMPs in microglia, which are the main professional immune cells of the CNS known to express PRRs, RAGE and purinergic receptors. This figure has been derived from the reports referenced in previous sections as well as several recent articles reviewing relevant signaling mechanisms in microglia and other types of mononuclear phagocytes (Collins et al., 2009; Schroder et al., 2012; Kierdorf and Fritz, 2013; Freeman and Grinstein, 2014; Schaefer, 2014; Banjara and Ghosh, 2017; Gulke et al., 2018; Hou et al., 2018; Leitner et al., 2019; McKenzie et al., 2020).

TLR2 and TLR4 emerge to be critical for the interaction between RAMP and DAMP signaling since multiple different RAMPs and DAMPs bind to these PRRs (**Table 1**), which can lead to competition at the receptor level. Furthermore, the multiple parallel and sequential signaling pathways triggered by TLR2 and TLR4 result in very complex changes in secretory profile of cells, where binding of different DAMPs and RAMPs could lead to either up- or down-regulation of pro- and anti-inflammatory cytokines (Schroder et al., 2012). Such a complexity of TLR2/4-dependent signaling most likely also explains why certain molecules interacting with these receptors, such as HSP27 and HSP70, have been considered as both DAMPs and RAMPs depending on the experimental and clinical outcomes in different studies. Furthermore, while the TLR downstream signaling pathways are highly conserved between species, expression of TLR4, for example, and the signaling mechanisms engaged by its activation depend on species, cell type, and cellular activation state (Schroder et al., 2012; Vaure and Liu, 2014; Leitner et al., 2019).

Figure 1 demonstrates that formation of the NLRP3 inflammasomes is a pro-inflammatory signalling mechanism that is relatively selectively induced in microglia by the DAMP ATP acting on P2X7R (Schaefer, 2014; Gaikwad et al., 2017). Activation of NLRP3 inflammasomes leads to secretion of the mature forms of pro-inflammatory cytokines IL-1β and IL-18. In addition, inflammasome activation promotes pyroptosis, a specific form of pro-inflammatory cell death, which leads to release of various DAMPs and RAMPs from all cellular compartments further fuelling inflammatory responses (Bortolotti et al., 2018; Frank and Vince, 2019; McKenzie et al., 2020). Cytokine secretion is a critical immune function of microglia that is regulated by most DAMPs and RAMPs through interaction with multiple receptors (e.g., ST2, FPR1, macrophage antigen complex 1, TLRs) and activation of the associated intracellular signaling pathways. Phagocytosis is another key immune function of microglia; upregulated

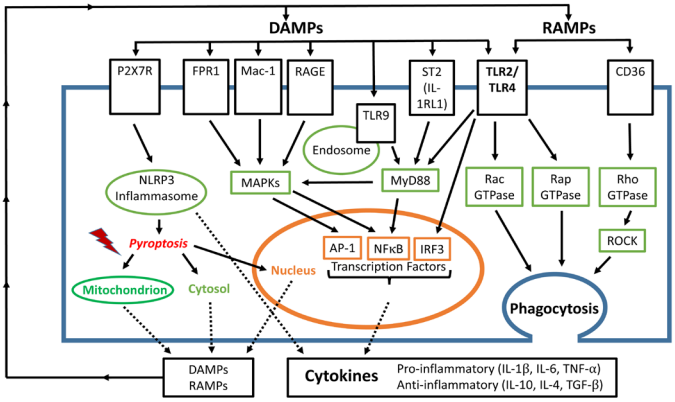

Figure 1 | Signaling mechanisms engaged by DAMPs and RAMPs in microglia.
AP-1: Activator protein 1; CD: cluster of differentiation; DAMP: damage-associated molecular pattern; FPR1: N-formyl peptide receptor 1; IL: interleukin; IL-1RL1: interleukin 1 receptor-like 1; IRF3: interferon regulatory factor 3; Mac-1: macrophage-1 antigen; MAPKs: mitogen-activated protein kinases; MyD88: myeloid differentiation factor 88; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-like receptor protein 3; P2X7R: purinergic P2X7 receptor; RAGE: receptor for advanced glycation end products; RAMP: resolution-associated molecular pattern; ROCK: Rho-associated protein kinase; TGF: transforming growth factor; TLR: toll-like receptor; TNF: tumour necrosis factor.

phagocytic activity is often considered to be a characteristic of the anti-inflammatory/resolution activation state of microglia (Reemst et al., 2016; Wolf et al., 2017). **Figure 1** illustrates that this microglial function can be regulated by both DAMPs and RAMPs interacting with TLR2/4, while CD36-mediated effect on phagocytosis has only been reported for the RAMP cardiolipin (Collins et al., 2009). Elucidation of the signaling mechanisms engaged by DAMPs and RAMPs in various CNS cell types is essential for the future development of specific RAMPs and/or DAMP inhibitors as therapeutic agents.

In addition to their general anti-inflammatory properties, such as inhibition of pro-inflammatory cytokine secretion and upregulation of phagocytic activity, cardiolipin, prothymosin α, BiP, and αB-crystallin display several disease-specific beneficial functions further supporting their RAMP-like activity in these pathologies. For example, they can either inhibit formation or facilitate removal of abnormal aggregates of tau and Aβ proteins, thereby preventing development of neurofibrillary tangles and senile plaques, respectively. Both of these pathological structures are hallmarks of the highly prevalent neurodegenerative AD (DeTure and Dickson, 2019). BiP and αB-crystallin have been shown to function as molecular chaperones that prevent oligomerization and aggregation of tau (Sahara et al., 2007). In addition, *in vitro* experiments demonstrate BiP binding to the amyloid precursor protein and reducing production of the Aβ oligomers (Yang et al., 1998). BiP also inhibits Aβ aggregation in its early stages (Evans et al., 2006).

At the cellular level, extracellular BiP enhances removal of Aβ by microglia *in vitro* (Kakimura et al., 2001). Furthermore, cardiolipin and prothymosin α upregulate phagocytic processes in murine microglia and human neutrophils, respectively (Samara et al., 2013; Pointer et al., 2019). Impaired microglial clearance of Aβ has been suggested to drive AD pathogenesis (Gabande-Rodriguez et al., 2020); therefore, it can be speculated that imbalanced regulation of microglial phagocytosis by extracellular signals, including RAMPs, contributes to this pathology. Interestingly, increased expression of αB-crystallin has been reported in AD brain areas with significant senile plaque and neurofibrillary tangle accumulations, which may indicate a compensatory response triggered by the disease mechanisms (Renkawek et al., 1994). Possible therapeutic application of RAMPs in AD

has been suggested based on a recent study demonstrating the beneficial effects of extracellular BiP in a *Drosophila melanogaster* model of AD (Martin-Pena et al., 2018).

Summary

Within the last 5 years, a significant effort has been aimed at further characterization of physiological and pathological roles of DAMPs in CNS inflammation. Considerable advances in our understanding of the pathophysiological roles of HMGB1 and IL-33 have been made along with discovery of novel DAMPs of the CNS. Some of these newly characterized molecules, such as TFAM and cytochrome C discussed above, represent already established DAMPs of the peripheral immune responses, which now have been implicated in CNS pathophysiology as potential pro-inflammatory stimuli of glial cells. While for other DAMPs, such as galectin-3 and peroxiredoxin-2, their CNS functions have been extended to a broader range of pathologies (Yip et al., 2017; Lu et al., 2018). And finally, a new group of anti-inflammatory RAMPs is emerging that could be essential for resolution of CNS inflammatory processes. It can be concluded that discovery of novel DAMPs and RAMPs of the CNS will be a productive field of neuroimmunology for the foreseeable future. In addition to expanding our basic knowledge about intercellular signaling during neuroinflammatory events, these studies could have significant translational value by identifying novel therapeutic approaches (e.g., DAMP receptor antagonists, DAMP signaling inhibitors, and anti-DAMP antibodies) for treatment of a wide range of CNS diseases. Even though human clinical trials with some of the RAMPs (e.g., BiP and αB-crystallin) have already been initiated, the potential of these and other RAMPs as therapeutics for various neuroimmune disorders of the CNS should be explored through further pre-clinical and clinical studies.

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