Sepsis and HMGB1 Release

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Sepsis remains a common cause of death in intensive care units, accounting for approximately 20% of total deaths worldwide. Its pathogenesis is partly attributable to dysregulated inflammatory responses to bacterial endotoxins (such as lipopolysaccharide, LPS), which stimulate innate immune cells to sequentially release early cytokines (such as tumor necrosis factor (TNF) and interferons (IFNs)) and late mediators (such as high-mobility group box 1, HMGB1). Below is a brief summary of the intricate mechanisms underlying the regulation of bacterial endotoxin-induced HMGB1 release.

sepsis pyroptosis innate immune cells

1. Introduction

Microbial infections and resultant sepsis syndromes are the most common causes of death in intensive care units, accounting for approximately 20% of total deaths worldwide [1]. The pathogenesis of sepsis remains poorly understood, but is partly attributable to immune over-activation or immunosuppression propagated by dysregulated innate immune responses to lethal infections [2][3]. Innate immune cells (such as macrophages, monocytes and neutrophils) constitute a front line of defense against microbial infections by eliminating invading pathogens via phagocytosis, and initiating inflammatory responses via various mediators. Upon detection of microbial products such as bacterial endotoxins (lipopolysaccharide, LPS), circulating neutrophils and monocytes immediately infiltrate into infected tissues [4]. After engulfing and killing pathogens, neutrophils exhaust intracellular enzymes and undergo apoptotic cell death. The cell debris of these apoptotic neutrophils are then removed by tissue macrophages (e.g., Kupffer cells, dendritic cells, and glia cells) [5] terminally differentiated from infiltrated monocytes.

Innate immune cells also carry various pattern recognition receptors (PRRs) to recognize distinct classes of molecules shared by a group of related microbes, which are collectively termed “pathogen-associated molecular pattern molecules” (PAMPs). For instance, Toll-like Receptor 2 (TLR2) [6], TLR4 [7] and TLR9 [8], respectively, serve as PRRs for distinct PAMPs such as peptidoglycans, bacterial endotoxins, and microbial un-methylated CpG-DNAs. The engagement of various PRRs by different PAMPs similarly activates innate immune cells to sequentially release early cytokines (such as tumor necrosis factor (TNF) and interferons (IFNs)) and late-acting pro-inflammatory mediators [such as high-mobility group box 1 (HMGB1) [9] and sequestosome 1 (SQSTM1)] [10].

HMGB1 is constitutively expressed by most types of cells to maintain a large “pool” of preformed protein in the nucleus, possibly due to the presence of two lysine-rich nuclear localization sequences (NLS) [11]. It carries two

internal repeats of positively charged domains (“HMG boxes” known as “A box” and “B box”) in the N-terminus, and a continuous stretch of negatively charged (aspartic and glutamic acid) residues in the C-terminus. These HMG boxes enable HMGB1 to bind chromosomal DNA, and fulfill its nuclear functions to maintain nucleosomal structure and stability, and regulate gene expression [12][13]. Once released, extracellular HMGB1 can bind many endogenous proteins, thereby modulating divergent innate immune responses to lethal infections [13].

2. Role of Cytoplasmic PRRs (Caspase-11/4/5/1) in the Regulation of Pyroptosis and HMGB1 Release

We and others demonstrated that ultra-pure LPS (free from any contaminating bacterial proteins, lipids, or nucleic acids) completely failed to induce HMGB1 release, unless the initial LPS priming was accompanied by a second stimulus (e.g., ATP) [14][15]. However, crude LPS that might carry trace amounts of bacterial proteins, lipids and nucleic acids, triggered a marked HMGB1 release [9]. It is possible that some contaminating bacterial proteins and lipids might enhance endocytosis of LPS, and consequently facilitate its innate recognition by cytoplasmic PRRs such as Casp-11/4/5. Indeed, when LPS was delivered to cytoplasmic Casp-11/4/5 either via CD14/TLR4 receptor-mediated endocytosis or bacteria-derived outer membrane vesicles (OMV) [16], it induced “non-canonical” inflammasome activation via oligomerization and proximity-induced activation of Casp-11/4/5 (**Figure 1**) [17]. The activated Casp-11/4/5 then catalyzes the cleavage of Gasdermin D (GSDMD) to form cytoplasmic membrane pores that cause immediate ionic gradient loss, osmotic burst and cell membrane rupture, a process aforementioned as “pyroptosis”. For the optimal activation of non-canonical inflammasome, both type I IFN-α/β and type II IFN-γ are needed to up-regulate Casp-11/4/5 [18][19] as well as guanylate-binding proteins [20] responsible for disrupting pathogen-containing vacuoles and releasing LPS. Coincidently, we and others demonstrated that LPS-inducible type I IFN-α/β [21][22] and type II IFN-γ [23] effectively stimulated innate immune cells to release HMGB1 in a time- and dose-dependent fashion.

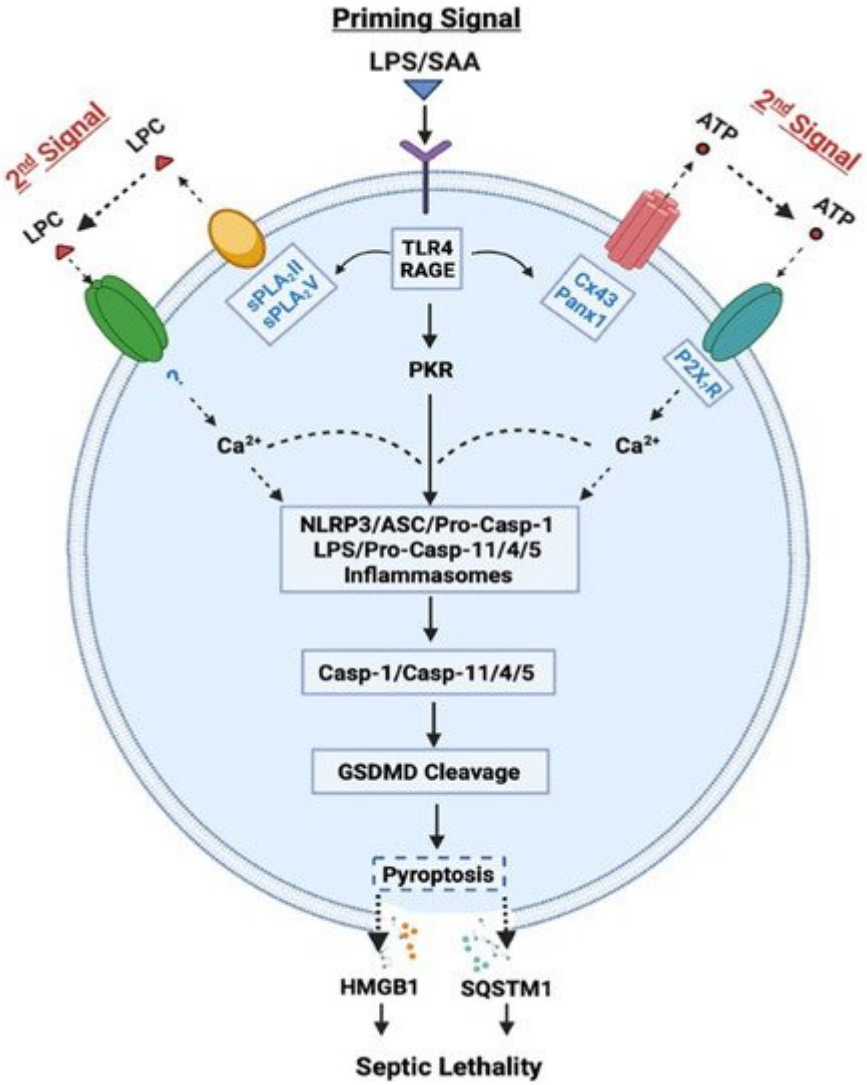

Figure 1. Role of Casp-1-mediated canonical and Casp-11/4/5-mediated non-canonical inflammasome activation in LPS- or SAA-induced pyroptosis and HMGB1 release. LPS or SAA may prime innate immune cells to up-regulate the expression of Cx43/Panx1 hemichannels, $sPLA_2$s and interferon-induced double-stranded RNA-activated protein kinase (PKR), thereby eliciting the release of ATP or LPC that may activate $P2X_7R$- or other receptor-mediated Ca^{2+} signaling. It then induces a feed-forwarding activation of PKR and inflammasome, cleavage of GSDMD, pyroptosis, and subsequent release of late mediators (such as HMGB1 and SQSTM1) of lethal infections.

In contrast, the “canonical” inflammasome activation is characterized by the oligomerization of intracellular “nucleotide-binding oligomerization domain (NOD)-like receptors” (NLRs such as NLRP1, NLRP3, and NLRC4) and the “apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain” (ASC) adaptor, as well as the recruitment and activation of pro-Casp-1 (**Figure 1**) [14]. Specifically, the pro-Casp-1 forms a heteromeric protein complex with an ASC adaptor and a NLR receptor, and the resultant protein complex, termed the “inflammasome”, is responsible for cleaving pro-Casp-1 to generate Casp-1, which triggers canonical inflammasome activation and pyroptosis via GSDMD cleavage [14]. Likewise, the optimal activation of canonical inflammasome also depends on a two-step process: (1) a priming signal elicited by extracellular PAMPs (e.g., LPS)

to up-regulate NLRP3 expression; and (2) a secondary signal elicited by extracellular damage-associated molecular pattern (DAMPs, e.g., ATP) to induce NLRP3 oligomerization with ASC and pro-Casp-1 (**Figure 1**). Notably, the cleavage of pannexin-1 (Panx1) hemichannel by Casp-11/4/5 might be needed for releasing ATP and activating the purinergic $P2X_7$ receptor ($P2X_7R$) and inflammasome signalings (**Figure 1**) [24][25]. Consistently, we found that crude LPS also markedly up-regulated Panx1 expression in macrophages and monocytes, and consequently elevated their hemichannel activities to release ATP [26], supporting a pathogenic role of Panx1 in LPS-induced HMGB1 release and animal lethality [24] (**Figure 1**).

It is thus possible that following cytoplasmic translocation, HMGB1 could be secreted extracellularly through Casp-1- or Casp-11/4/5-mediated inflammasome activation and pyroptosis (**Figure 1**). Recent evidence suggested that inflammasome-dependent HMGB1 release could not occur immediately after the formation of GSDMD membrane pores, but became prominent following the rupture of cytoplasmic membranes [27][28]. Consistently, pharmacological inhibition (with a broad-spectrum Caspase inhibitor Z-VAD-FMK) or genetic disruption of key inflammasome components (e.g., Casp-1 or Nlrp3) uniformly blocked the LPS/ATP-induced HMGB1 secretion [14][29]. Likewise, genetic disruption of interferon-induced double-stranded RNA-activated protein kinase (PKR) expression or pharmacological inhibition of its phosphorylation similarly reduced the LPS-induced inflammasome activation [15][30], pyroptosis [15][30], and HMGB1 release [15]. Thus, crude LPS may prime macrophages by simultaneously up-regulating PKR expression and eliciting Panx-1-mediated ATP release, thereby activating $P2X_7R$ [31] to induce a feed-forwarding PKR/inflammasome activation, pyroptosis and HMGB1 secretion (**Figure 1**).

In addition, HMGB1 can also be passively released by somatic cells undergoing cytoplasmic membrane destruction due to accidental mechanical events or regulated processes governed by other caspases or kinases. For instance, circulating levels of HMGB1 were rapidly elevated in critical ill patients with non-penetrating trauma [32][33][34], thereby contributing to trauma-induced dysregulated inflammation, immune paralysis or immunosuppression. Even following viral infections with influenza [35][36] or SARS-CoV-2 [37], proinflammatory cytokines such as TNF and IFN-γ can also induce necroptosis [38][39][40] or PANoptosis [37] via other caspases and kinases such as the Receptor-Interacting Serine/Threonine Kinase 3 (RIPK3) [35][36] and Casp-8 [40]. Thus, various cell death pathways can potentially lead to the passive release of HMGB1 following traumatic injuries or microbial infections. However, the possible roles of HMGB1 and various other cytokines in the pathogenesis of lethal infections such as COVID-19 remain controversial, because there is still a lack of clear association between many cytokine biomarkers and the severity of viral infections [41][42].

3. Pathogenic Role of Extracellular HMGB1 in Dysregulated Inflammation, Immunosuppression, and Immune Paralysis

Once released, extracellular HMGB1 can bind various PRRs and PAMPs to orchestrate divergent inflammatory responses. For instance, HMGB1 can bind TLR4 [43][44][45], TLR9 [46], receptor for advanced glycation end products (RAGE) [47], cluster of differentiation 24 (CD24)/Siglec-10 [48], Mac-1 [49], or single-transmembrane-domain proteins (e.g., syndecans) [50]. Due to its relatively higher affinity to TLR4 (K_D = 22.0 nM) [51] and lower affinity to RAGE (K_D = 97.7-710 nM) [52][53], HMGB1 might first bind TLR4 when it was actively secreted by innate immune cells at

relatively lower amounts [54]. Consequently, it could directly activate macrophages [55], neutrophils [56] and endothelial cells [57] to produce various cytokines and chemokines [43][57][58][59][60] partly through MyD88-IRAK4-dependent signaling pathways (**Figure 2**A).

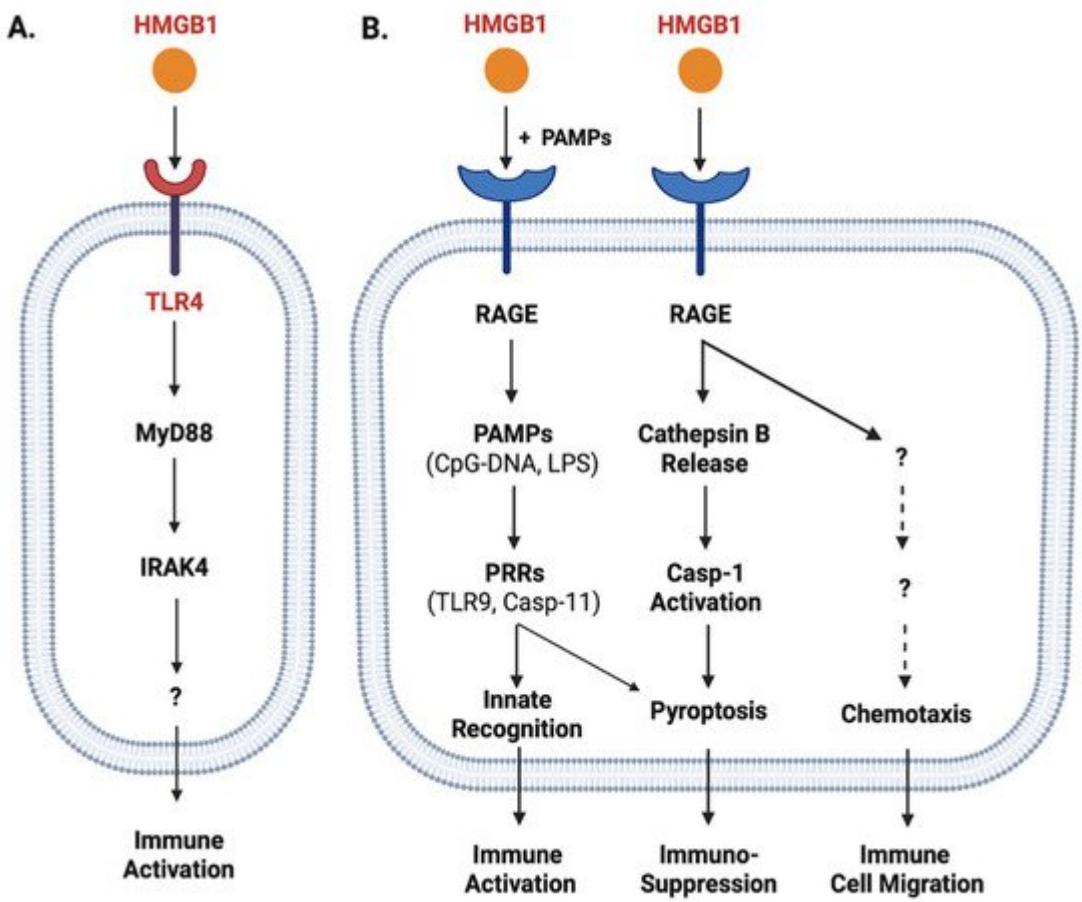

Figure 2. Role of TLR4 and RAGE in the regulation of HMGB1-mediated divergent inflammatory responses. HMGB1 can bind different PRRs such as TLR4 (Panel **A**) and RAGE (Panel **B**) with different affinities, and consequently induce divergent inflammatory responses such as immune cell migration, immune activation, or pyroptosis and resultant immunosuppression.

When HMGB1 was passively released by innate immune and somatic cells at relatively higher levels, it might also bind various microbial PAMPs (e.g., CpG-DNA or LPS) and RAGE [52][62] and consequently promoted RAGE-receptor-mediated endocytosis of these microbial products (**Figure 2**B) [63]. Upon reaching acidic endosomal and lysosomal compartments near HMGB1′s isoelectric pH, HMGB1 became neutrally charged and set free its cargos (LPS or CpG-DNA) [63], thereby facilitating their recognition by respective PRRs such as TLR9 [46] or Casp-11 [63] to augment inflammatory responses (**Figure 2**B). Furthermore, the engagement of RAGE with HMGB1 might also induce chemotaxis [64] and the migration of monocytes, dendritic cells [65][66] and neutrophils [49], thereby facilitating the recruitment of innate immune cells to site of the infection to orchestrate inflammatory responses [54] (**Figure 2**B). Finally, the engagement of HMGB1 with RAGE [52][62] might also induce TLR4 internalization and desensitization to subsequent stimulus (e.g., endotoxin), and might even trigger macrophage pyroptosis [63][67] via

a cascade of events including cathepsin B release from ruptured lysosomes followed by pyroptosome formation and Casp-1 activation (**Figure 2**B).

In neutrophils, HMGB1 can bind TLR4 to promote the formation of neutrophil extracellular traps (NETs), thereby amplifying neutrophil-mediated inflammatory responses [68]. In contrast, the engagement of RAGE by HMGB1 can adversely impair neutrophil NADPH-dependent production of reactive oxidation species (ROS) and associated bacterial killing, contributing to sepsis-induced immune paralysis and immuno-suppression [69][70]. Consistently, the blockade of extracellular HMGB1 activities with neutralizing antibodies even during a late stage of sepsis still restored neutrophil NADPH activity and anti-bacterial capacities [70]. Thus, excessive HMGB1 release contributes to the pathogenesis of lethal infections by posing divergent adverse effects such as immune tolerance [71][72], immune paralysis [69][70][73] and immunosuppression [71][74] (**Figure 2**B).

4. Positive Regulators of LPS-Induced HMGB1 Release

In addition to LPS-inducible type I IFN-α/β [21][22] and type II IFN-γ [23], human serum amyloid A (SAA) also effectively induced HMGB1 release by innate immune cells in a TLR4/RAGE-dependent fashion [75] (**Figure 3**). Consistent with its capacity in stimulating NLRP3 inflammasome activation [76][77], we observed that SAA also stimulated PKR expression and phosphorylation [75]. Conversely, pharmacological inhibition of PKR inhibited SAA-induced HMGB1 release [75], supporting an important role for PKR phosphorylation, inflammasome activation and pyroptosis in the SAA-induced HMGB1 release (**Figure 1**). In addition, some LPS-inducible enzymes [such as the 14 kDa type II secretory phospholipase A_2 ($sPLA_2$), inducible nitric oxide synthase (iNOS), and pyruvate kinase M2 (PKM2)] were also implicated in the regulation of LPS-induced HMGB1 release (**Figure 3**) [78][79][80][81]. In agreement with these findings, we found that human SAA effectively up-regulated the expression of $sPLA_2$-IIE and $sPLA_2$-V in murine macrophages (**Figure 1** and **Figure 3**) [82], and concurrently induced HMGB1 release [75]. Conversely, the suppression of $sPLA_2$-IIE expression by high density lipoproteins (HDL) also attenuated SAA-induced HMGB1 release, supporting a role of $sPLA_2$ in the regulation of HMGB1 release [82]. It is not yet known whether $sPLA_2$s facilitate HMGB1 release partly by catalyzing the production of lyso-phosphatidylcholine (LPC) and leukotrienes that are capable of activating NLRP3 inflammasome and pyroptosis (**Figure 1**) [83][84][85].

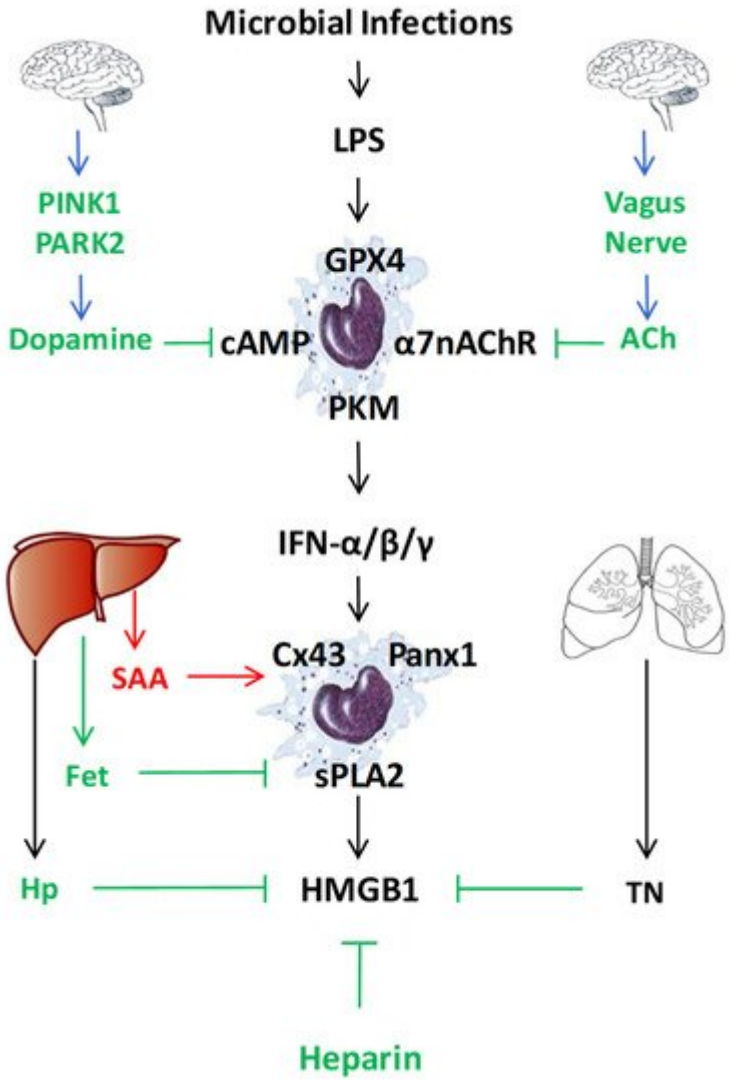

Figure 3. Endogenous regulators of LPS-induced HMGB1 release or action. To regulate the LPS-induced HMGB1 release or action, mammals have evolved multiple regulatory mechanisms that include neuro-immune pathways, liver-derived acute-phase proteins (e.g., SAA, Fetuin-A (Fet), Haptoglobin (Hp)), as well as other endogenous proteins (e.g., tetranectin (TN)) or polysaccharides (heparin).

Finally, both crude LPS and human SAA effectively up-regulated the expression of hemichannel molecules such as Panx1 [26] and Connexin 43 (Cx43) [86] in innate immune cells (**Figure 1** and **Figure 3**). The possible role of Cx43 in the regulation of LPS-induced HMGB1 release was supported by our findings that several Cx43 mimetic peptides, the GAP26 and Peptide 5 (ENVCYD), simultaneously attenuated LPS-induced hemichannel activation and HMGB1 release [86]. It was further supported by observation that genetic disruption of macrophage-specific Cx43 expression conferred protection against lethal endotoxemia and sepsis [87]. It is possible that Cx43 hemichannel provides a temporal mode of ATP release [88][89], which then contributes to the LPS-stimulated PKR phosphorylation, inflammasome activation, pyroptosis and HMGB1 secretion (**Figure 1** and **Figure 3**) [26][86]. Intriguingly, recent evidence has suggested that macrophages also form Cx43-containing gap junction with non-immune cells such as cardiomyocytes [90], epithelial [91][92] and endothelial cells [93]. It is possible that innate immune cells may communicate with non-immune cells through Cx43-containing gap junction channels to regulate

HMGB1 release and to orchestrate inflammatory responses [94][95]. Interestingly, recent studies have revealed an important role of lipid peroxidation [96] and cAMP immune-metabolism [97] in the regulation of Casp-11-mediated "non-canonical" inflammasome activation and pyroptosis (**Figure 3**). However, the possible role of these immunometabolism pathways in the regulation of LPS-induced HMGB1 release remains an exciting subject of future investigations.

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