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High-Mobility Group Box 1 Protein (HMGB1) in Systemic Lupus Erythematosus: Review Article

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ABSTRACT

Background: Recent studies have showed that high-mobility group box 1 (HMGB1), a proinflammatory cytokine, is well-received by many innate immune system cells. It was initially thought that this protein resided in the nucleus, where it was discovered. Systemic lupus erythematosus (SLE) is a chronic inflammatory illness characterized by the release of HMGB1 from both necrotic and apoptotic cells as a result of damage pattern. **Objective:** Review of the literature on role and correlations of High-Mobility Group Box 1 protein (HMGB1) among pathogenesis of Systemic Lupus Erythematosus.

Methods: We looked for data on High-Mobility Group Box 1 Protein, and Systemic Lupus Erythematosus, in medical journals and databases like PubMed, Google Scholar, and Science Direct. However, only the most recent or extensive study was taken into account between August 2000 and January 2023. References from related works were also evaluated by the writers. There are not enough resources to translate documents into languages other than English, hence those documents have been ignored. It was generally agreed that documents such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations did not qualify as legitimate scientific study.

Conclusion: Multiple disease mechanisms in SLE have been demonstrated to be influenced by HMGB1. Because of its dual role as a DAMP and a cytokine, HMGB1 can trigger harmful responses from both the adaptive as well as innate immunity systems. As the disease progresses in SLE, local cells in the damaged organs also interact with HMGB1. Understanding SLE and creating effective treatments will benefit greatly from research into the multiple roles HMGB1 plays in the immune system.

Keywords: HMGB1, Systemic Lupus Erythematosus.

INTRODUCTION

Autoantibody production and involvement of multiple body systems are hallmarks of SLE, an autoimmune disorder with a wide variety of clinical presentations. Fevers, arthritis, serositis, neuropsychiatric and renal involvements as well as skin lesions are the most prominent symptoms [(1)]. The autoimmune reaction is triggered by the body's immune system attacking its own nucleic acids and proteins that bind to them and ultimately leads to SLE when autoreactive B cells are abnormally activated. These bind to cells and trigger organ damage, usually by reacting with a tissue antigen [(2)]. Nucleic acid-containing immune complexes that are absorbed by Fc receptor contact can activate cells of the innate immune system. Pathologies associated with SLE are therefore influenced by neutrophils, dendritic cells (DCs), macrophages as well as monocytes [(3)]. DNA or RNA sensing in the cytosol contributes, as does a failure in the routine non-immunogenic clearance of apoptotic debris and changes in the cell's genetic makeup. It is believed that genes play a vital influence in response to environmental stimuli [(4)]. BLIMP1, IRF5, and C1q have all been identified as potential SLE risk gene loci [(5)]. To facilitate the removal of dead or dying cells, C1q attaches to opsonized cellular detritus. Having a C1q deficiency in your genes greatly increases your risk of developing SLE. Many studies have found that those with C1q deficiencies have a significantly increased risk of developing SLE (about 90%). Autoimmune illness of the central nervous system and kidneys manifests in these people in a serious way [(6–8)].**High-Mobility Group Box 1 Protein (HMGB1) correlation with SLE:** Like other high-mobility group (HMG) proteins, HMGB1 is found in the nucleus but is not a histone. Similar to amphoterin, HMGB1 is a 25-kDa protein with a negative C-terminal tail and two positively charged nucleic acid binding domains (called A boxes and B boxes). HMGB1's cellular role varies depending on the specific circumstances. HMGB1 has a crucial function in the nucleus, where it bends DNA and facilitates transcription factor binding. Outside the cell, HMGB1 can operate as a DAMP to stimulate the immune system and increase inflammation. It has an inflammatory effect because it is secreted by damaged or stimulated cells. Receptor for advanced glycation end-products (RAGE) and toll-like receptors 2 and 4 are bound by it. HMGB1's function is determined by the redox states of its three cysteine residues (C23, 45, and 106). Histone H1 has been found to be particularly effective at preventing oxidised HMGB1 from causing DNA to bend [(9-11)]. As an added note, oxidation of HMGB1 is known to affect its binding to extracellular receptors and subsequent activities. According to the literature study by Janko and colleagues, reducing HMGB1 to zero causes autophagy via its binding to RAGE and boosts cell migration via its binding to CXCR4 and CXCL12. The formation of a disulfide bond between residues of cysteine (C23 and 45) in HMGB1 allows it to send signals to TLR4 and trigger the release of pro-inflammatory cytokines [(11)]. It's well established that SLE patients experience elevated levels of oxidative stress, which plays a role in the immune system's dysfunction [(24)]. It is likely that disulfide HMGB1, which has been partially oxidised, plays a role in this process. Patients with SLE have higher than normal serum HMGB1 levels, and these levels are correlated with illness severity [(12)] (Figure 1).

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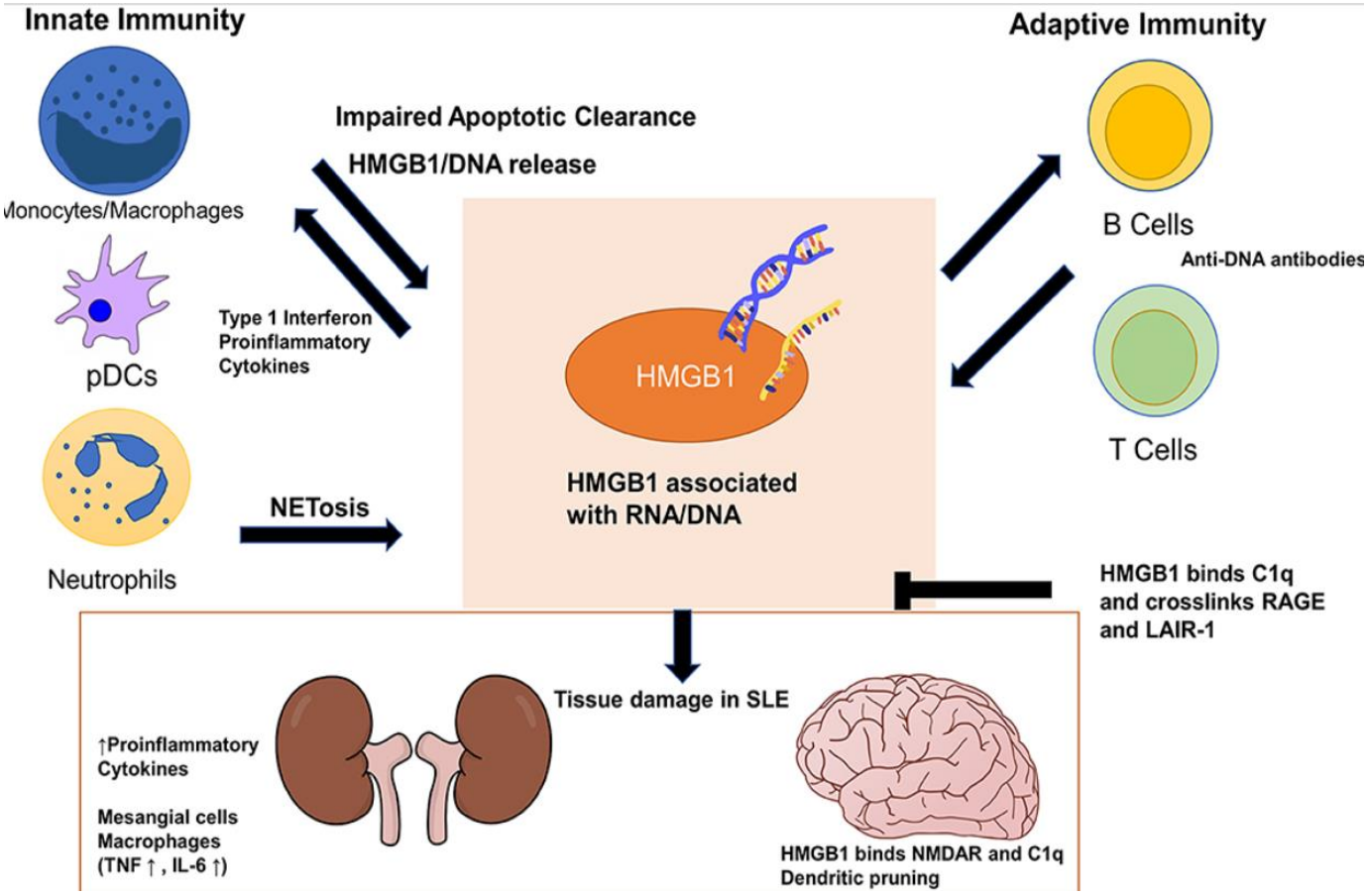

Figure (1): Showing High-mobility group box 1 pathogenesis effects among SLE [12].

Role of HMGB1 in SLE Pathogenesis:

Adaptive Immunity:

Antibodies against nuclear antigens are diagnostic of systemic lupus erythematosus. These autoantibodies cause tissue harm by binding to ubiquitous self-antigens and forming immune complexes that are then deposited in tissues. Defects in apoptosis play a crucial role in the development of SLE. Secondary necrosis occurs in apoptotic cells that are not removed properly, causing the contents of the cell to leak out. In SLE, the release of HMGB1 may serve as an autoadjuvant, impairing B cells tolerance and leading to the development of autoantibodies. Due to its ability to bind both RNA and DNA, upon entry to cells, HMGB1 can activate RAGE-dependent cytosolic nucleic acid receptors. In vivo studies have revealed that HMGB1-nucleosome complexes activate antigen presenting cells by way of toll-like receptor 2 (TLR2) and cause a response in the form of anti-dsDNA and anti-histone IgG [13].

Although anti-nuclear antibodies (ANA) normally bind to DNA and histones in nucleosomes, studies on SLE patients show that ANA also bind to HMGB1. Nevertheless, this may be evidence of HMGB1's DNA-binding activity. In SLE, higher anti-HMGB1 antibodies are seen, and their levels are correlated with illness severity. Increased levels of circulating HMGB1 are associated with SLE, suggesting that this may be a mechanism for the development of immunological complexes including nucleic acid linked to the HMGB1 [14, 15].

Innate Immunity:

The pathogenesis of SLE has been researched extensively, with a focus on the adaptive immune system's role in the production of autoreactive antibodies. However, the innate immune system is now also being recognized as having a significant part in this process [16]. Dendritic cells produced from monocytes (mo-DC) and macrophages both exhibit large levels of activating Fc receptors. These innate immune cells can be activated to perform their inflammatory functions by immune complexes generated from DNA or RNA/HMGB1 and IgG through their Fcγ receptors [17], among them being the release of cytokines like IL-6, type 1 interferon (IFN) as well as TNF-α. The Pathway of IFN is crucial to SLE progression in various animal models. Type I IFN contributes to the increase in autoreactive B cells and the decline in peripheral tolerance by suppressing dendritic cell maturation [18].

In SLE, monocytes are critical IFN producers despite the fact that plasmacytoid DCs (pDCs) produce the highest quantities of type 1 IFN per cell. For stimulation of the generation of IFNs, nucleic acids must be taken up by monocytes and transported to TLRs 7 and

9. It is through a RAGE-dependent route that HMGB1 chaperones nucleic acid to endosomal TLRs [19]. By binding and internalising with RAGE, HMGB1 delivers its nucleic acid cargo, which is one of two mechanisms by which SLE serum might activate monocytes, as described by **Porat *et al.*** [20] DNA mimetope binding to HMGB1 was demonstrated to block its interaction with RAGE, hence blocking the expression of the IFN hallmark genes [20].

As was noted before, PDCs are cells that are optimised for producing large quantities of interferons. Pseudotyped DCs (pDCs) upregulate RAGE expression as a part of their maturation in response to activation of Toll-like receptors 7 and 9. This sets up a self-sustaining cycle of type I IFN production, or autocrine loop. Scientists have long hypothesised that pDCs' malign role in SLE stems from these cells' inherent capacity to produce type I IFNs. Tissue pDCs are elevated, but circulating pDCs are reduced, in patients with systemic lupus erythematosus. In turn, IFN controls HMGB1 secretion by promoting its nuclear export to the cytoplasm, just before its release into the extracellular environment. This happens because stimulation of type 1 IFN activates the JAK/STAT1 signaling pathway [21]. It has also been shown that IFN-γ via a TNF-dependent mechanism, can promote HMGB1 release in a dose-dependent fashion [22]. Collectively, our observations emphasize the HMGB1's pivotal part in setting in motion the nucleotide-induced IFN signature among SLE patients.

Neutrophil extracellular traps (NETs) limit tissue damage and interferon (IFN) production. Nuclear autoantigens, immune complexes, and complement activation are all produced by NETs that remain uncleaned, keeping the inflammatory response going. Neutrophil extracellular traps (NETs) include HMGB1, and HMGB1 can also trigger NET release from neutrophils. Mice experiments have revealed that HMGB1 stimulates NET development in a TLR4-dependent fashion. We now know that NETs are a major contributor of HMGB1 in SLE patients and have a positive correlation with the development of lupus nephritis [23].

It should be noted, however, that macrophages, and in particular macrophages harboring SLE risk alleles, also play a role in the development of SLE. As a result of a delay in the clearance of apoptotic debris, autoantigens can remain exposed to the adaptive immune system for a longer period of time in individuals with systemic lupus erythematosus. Traditional M1 macrophages cause inflammation and tissue damage, while M2 macrophages help mend damaged tissues by phagocytosis and the elimination of inflammatory molecules [24].

It has been shown through gene expression patterns in SLE patients that there is a preference for M1 macrophage activation. The increased amounts of HMGB1 seen in SLE patients may help to explain this activation pattern. In order to reduce phagocytosis of apoptotic cells, HMGB1 is known to polarize monocytes into M1-like macrophage morphologies, shifting macrophage phenotype away from M2-like differentiation [25], putting people at risk for developing autoantibodies and having their peripheral B cells tolerance breakdown.

The classical complement pathway component C1q has been demonstrated to interact with HMGB1. Leukocyte-associated immunoglobulin-like receptor 1 is an inhibitory receptor for C1q found on the surface of many different types of immune cells (LAIR-1). Extremely elevated HMGB1 levels in lupus patients may lead to uncontrolled skewing to M1 macrophage polarization in the absence or presence of C1q. It's possible that immune complexes are to blame for this, as they consume complement. This causes the adaptive immune system to generate autoantibodies by exposing autoantigens due to the elevated inflammation and impaired clearance of apoptotic cells. Reduction in LAIR-1 expression on pDCs, together with elevated serum HMGB1 and type 1 IFN, has been linked to SLE in children, leading to a loss of LAIR-1's inhibitory function [26].

HGMB1 possible role among Lupus Nephritis

The significance of HMGB1 in integrating innate and adaptive components to generate the disease phenotype is best demonstrated by its role in lupus nephritis (LN). End-organ damage, such as lupus nephritis, is caused by immune complexes in SLE. This is a common issue that contributes greatly to the severe nature of this illness [27]. Similar to systemic lupus erythematosus, the root cause is polyclonal B cell activation and/or increased specific antigen exposure, which in turn causes a breakdown in immunological tolerance and the production of autoantibodies against nuclear autoantigens. Toll-like receptors (TLRs) and interferon (IFN) signaling are activated in the kidney when immune complexes attach to them. This causes glomerular endothelium, mesangial cells, and macrophages to produce proinflammatory cytokines in the local area. Chronic kidney failure and glomerulosclerosis are the end outcomes of a chain reaction triggered by injury to the renal parenchyma [27].

Anti-DNA antibodies were shown to upregulate proinflammatory genes and facilitate kidney injury in the MRL/lpr mouse model of systemic lupus erythematosus, according to research by Putterman *et al.* Furthermore, they showed that HMGB1 enhances the activity of anti-DNA antibodies in a RAGE/TLR2-dependent fashion. The presentation of HMGB1 to TLR2 has also been demonstrated to stimulate the growth of glomerular mesangial cells. Fibronectin and collagen IV levels fell after HMGB1 or TLR2 inhibition, while glomerular histological abnormalities and sclerosis increased [28].

High levels of TNF and IL-6 production by renal macrophages from SLE mice has been discovered. These cytokines are thought to be important pathogenic

cytokines in increasing kidney inflammation and injury in SLE. In a mouse model of lupus, the HMGB1 blocker glycyrrhizin alleviated disease severity by decreasing the inflammatory response of macrophages. Experiments in living organisms and test tubes showed that RAGE is the receptor HMGB1 uses to amplify the macrophage response. These findings reveal that HMGB1 has effects that are exclusive to the kidneys, in addition to its worldwide function in the etiology of SLE. Patients with SLE who have active LN can be distinguished from those who do not have the disease and from healthy controls based on the presence of HMGB1 in their urine [(29)]. This points to a somewhat high HMGB1 concentration in the immediate vicinity of the LN.

HGMB1 in Neuropsychiatric SLE:

Up to 80% of people with SLE will also experience a complication known as neuropsychiatric systemic lupus erythematosus (NPSLE). Most notably, it manifests as a decline in cognitive abilities and can damage either the brain or the rest of the nervous system. Some anti-DNA antibodies, known as DNRAbs, have been shown to react negatively with the N-methyl-D-aspartate receptor (NMDAR). Improved NMDAR signaling by DNRAbs leads to spatial memory deficits in SLE mice models and also correlates with memory loss in people. A two-step process, comprising excitotoxic cell death in stage 1 and microglia activation and neuronal pruning in stage 2, links transient exposure to DNRAb to long-term neuronal dysfunction. NMDAR-activated neurons, like all activated cells, can release HMGB1 in response to stress or activation. Intriguingly, HMGB1 can bind to NMDARs. Specifically, Nestor and colleagues demonstrated that dendrites linked to C1q are destroyed, leading to the spatial memory impairments observed in SLE. When it comes to communicating with the NMDAR, C1q employs HMGB1 as a bridge. Microglia are activated by HMGB1 via RAGE/TLR4 to damage dendrites that contain NMDAR-HMGB1-C1q complexes. Both in vitro as well as in vivo data supported this conclusion [(30)].

HMGB1 in Therapy:

Currently, corticosteroids and immunosuppressive medicines remain the gold standard for treating SLE, despite the many negative effects these therapies can have. In modern medicine, treatments aim to target particular pathways. It has been shown in several clinical trials that HMGB1 can be inhibited by small molecules such tashinone IIA derivatives and glycyrrhizin. Animal studies have looked into the therapeutic potential of HMGB1-specific antagonists in a number of different ways. The A box domain of HMGB1 is a powerful competitive inhibitor of HMGB1 due to its ability to bind to HMGB1 receptors such as TLR2/4 and RAGE without inducing proinflammatory responses [(31)].

Intramuscular HMGB1 injection therapy of HMGB1 antagonist, or "box," has been demonstrated to reduce mortality in a rat model of sepsis. Researchers have looked into the potential benefits of using monoclonal HMGB1-neutralizing antibodies to treat a wide variety of diseases. In some studies, monoclonal HMGB1 antibodies were demonstrated to ameliorate SLE clinical characteristics in MRL/lpr mice and BXSB mice, but in others, they had no effect on the course of illness in MRL/lpr mice [(31)]. As a result of contradictory clinical evidence, new approaches to HMGB1 inhibition have been explored. Anti-inflammatory actions of HMGB1 can be achieved by both direct suppression of HMGB1 and pathways involving HMGB1. Through its interactions with RAGE, LAIR-1, and C1q, HMGB1 is known to modulate macrophage polarization. Activated monocytes produce more specialized pro-resolving lipid mediators after exposure to HMGB1 and C1q, and HMGB1 also stimulates the production of leukotriene B4 via a positive feedback loop involving IRF5 [(32)].

Fusion proteins crosslinked HMGB1 and C1q, exerting pro-resolving effects both in vitro and vivo [(32)]. The realization that HMGB1 can be utilized to improve the immune system's tolerogenic capacities has opened up exciting new therapeutic possibilities.

CONCLUSION

Multiple disease mechanisms in SLE have been demonstrated to be influenced by HMGB1. Because of its dual role as a DAMP and a cytokine, HMGB1 can trigger harmful responses from both the adaptive as well as innate immunity systems. As the disease progresses in SLE, local cells in the damaged organs also interact with HMGB1. Understanding SLE and creating effective treatments will benefit greatly from research into the multiple roles HMGB1 plays in the immune system.

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