HMGB1 as a Therapeutic Target in Autoimmune Diseases: The Journey So Far.

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Although the adaptive immune system has been a focus of research on joint disease over the past decades, the critical role of innate immunity in the pathogenesis of many autoimmune diseases has been emphasized only in recent years. Treatment of these autoimmune diseases has been confronted with many challenges. There is therefore the need to target host pathogenic proteins that influence to a great extent a number of these autoimmune diseases. High-mobility group box-1 (HMGB1), a unique and important pathogenic protein, has been implicated as a pro-inflammatory cytokine in the pathogenesis of various inflammatory and autoimmune diseases. As an important inflammatory factor, HMGB1 is involved in many cardiovascular diseases, autoimmune disease pathogenesis, and CD4 T-cell differentiation and modulation. In this review, we will highlight recent evidence uncovering biological mechanisms of HMGB1 contribution to the pathological process of autoimmune immune diseases and as well as discuss emerging data on HMGB1 with the aim of unearthing novel therapeutic targets in autoimmune diseases.

Key Words: autoimmunity, HMGB1, experimental autoimmune encephalitis, rheumatoid arthritis, experimental autoimmune myocarditis.

INTRODUCTION

Autoimmune diseases are part of the leading causes of death among young and middle-aged women in the United States. Within the global population, autoimmune diseases have become the 3rd leading cause of morbidity and mortality following cardiovascular disease and cancer. An estimated 3% of the population in the United States is affected by a tissue-specific or systemic autoimmune disorder (Jacobson, Gange, Rose, & Graham, 1997). However, incidence rates may vary among the various autoimmune diseases. Many factors have been speculated to escalate autoimmune disease risk even though the cause(s) of autoimmune disorders remain largely unknown. Considerable evidence supports a role for environmental agents in inducing autoimmune disorders (Cooper, Miller, & Germolec, 2002; Hess, 1995). Actually, the approved therapies of autoimmune diseases initially focused on broad-based immunosuppression and numerous emerging therapies undertaking a more targeted immunomodulatory strategy. All of these strategies thus aimed to modulate the pathogenic immune response downstream of the initial oligodendrocyte damage and innate immune signaling that sustains the local inflammatory response. Currently, these immunosuppressive therapies have not been very impressive and still partly effective. Cytotoxic treatments including chemotherapy, radiation therapy, epigenetic drugs, oncolytic viruses, and immunotherapy, as well as stressed/dying immune cells often trigger the release of High-mobility group box-1 (HMGB1) and other pathogenic proteins to aggravate these autoimmune pathologies. This has necessitated quick identification of alternative immunotherapeutic targets to help address this global issue. An avenue that is receiving much attention and is being explored for treatment of acute tissue injury and autoimmunity in other organs targets where the intrinsic alarm signals or damage associated
molecular pattern molecules (DAMPs) drives the local inflammatory response. HMGB1 was originally defined in some of the most acute settings of medicine (that is, sepsis, shock) (Haichao Wang, Bloom, et al., 1999), but its intriguing immunological properties rapidly prompted the study of its role in chronic inflammatory and autoimmune conditions. Since then, HMGB1 has been implicated as a pro-inflammatory cytokine in the pathogenesis of various inflammatory and autoimmune diseases (Klune, Dhupar, Cardinal, Billiar, & Tsung, 2008). It is known to play an important role in the development and progression of autoimmune diseases such as RA (Komiyama et al., 2006), Myocarditis (Bettelli, Korn, & Kuchroo, 2007) and Multiple sclerosis (Kimura & Kishimoto, 2010). Elevated levels of HMGB1 have been found within the Synovial joints of Rheumatoid arthritis patients (Kokkola et al., 2002), the heart and serum of myocarditis patients (Steinman, 2007) as well as in the CNS and blood of multiple sclerotic patients (Steinman, 2007). HMGB1 has also been detected in the tissue and peripheral blood in various tumor histologies, including breast, colon, gastric, pancreatic and hepatocellular cancer (Chung et al., 2009; Kokkola et al., 2002; Kostova, Zlateva, Ugrinova, & Pasheva, 2010). Approximately one-third of patients with autoimmune diseases such as myocarditis, multiple sclerosis, and rheumatoid arthritis have shown dramatically beneficial response to the available novel therapies, whilst still a cohort of patients do not respond appropriately. These results warrant a search for modulation of additional inflammatory mediators to improve treatment for all patients with chronic autoimmune diseases. Therapeutic neutralization of excessive extracellular HMGB1 has been speculated to offer a new approach for managing various inflammatory diseases including rheumatoid arthritis, myocarditis, multiple sclerosis and many others. This paper seeks to review the various roles of HMGB1 in the pathogenesis of both human and animal disease models of rheumatoid arthritis, myocarditis and multiple sclerosis as well as the possibilities of using HMGB1 as a therapeutic target in treatment of the aforementioned diseases.

**Origin & Biochemical Structure of HMGB1**

High mobility group (HMG) proteins are a family of non-histone nuclear proteins that play a role in transcription, replication, recombination, repair, and other DNA-associated activities (Hasan & Hottiger, 2002). HMG-1/-2, HMG1/-Y, and HMG-14/-17 are three subfamilies of HMG proteins (Banks, Li, & Reeves, 2000; Bustin, 1999). HMGB1 which belongs to the subfamily of HMG-1/-2, was isolated three decades ago as an abundant chromosomal protein with important structural functions in chromatin organization (Goodwin & Johns, 1973). Biochemically, HMGB1 is a 30 kDa non-histone, chromatin-binding protein ubiquitously expressed in eukaryotic cells and highly preserved across mammalian species. It contains 215 amino acids and has a tripartite structure consisting of two DNA-binding domains, the A box (amino acid residues 9-79) and the B box (amino acid residues 95-163), and a C-terminal tail domain (Bianchi, Falciola, Ferrari, & Lilley, 1992; Müller, Ronfani, & Bianchi, 2004; Wen, Huang, Johnson, & Gerald, 1989). Unlike histones, HMGB1 binds to DNA with low affinity and can move from the nucleus to the cytoplasm depending upon cell cycle phase (Falciola et al., 1997). HMGB1 has a unique regional structure in which different sequences allow interaction with biochemically disparate molecules (Dintilhac & Bernués, 2002). The A and B boxes can bind to DNA; the C-terminal region can bind to histones, while the C-terminal region can also interact with the A and B boxes, modifying the 3-dimensional structure of HMGB1 and its molecular interactions. Containing three cysteine residues (C23, C45, and C106) that are redox-sensitive, HMGB1 can be modified into three isoforms termed “HMGB1” (all-thiol form), “disulfide HMGB1” (partially oxidized), and oxidized HMGB1 (Lu et al., 2014; Wu et al., 2015). The “all-thiol” HMGB1 is known to bind to other chemokines (e.g., CXCL12) and stimulates leukocyte recruitment via the CXCR4 receptor (Venereau, Schiraldi, Ugucioni, & Bianchi, 2013). The “disulfide” HMGB1 has the ability to activate immune cells to produce cytokines/chemokines via TLR4 or other receptors such as RAGE (Venereau et al., 2013; H. Yang et al., 2015), TLR2, TLR4 (Gill, Tsung, & Billiar, 2010), TLR9 (Gill et al., 2010; H. Yang et al., 2015), cluster of differentiation 24 (CD24)/Siglec-10 (H. Yang et al., 2015), Mac-1 (Haichao Wang, Ward, & Sama, 2014), thrombomodulin (H. Wang et al., 2014), or single transmembrane domain proteins (e.g., syndecans) (Lu et al., 2014). During binding to DNA, HMGB1 shows preferences for certain DNA structures such as bends or cruciforms, consistent with a role in modifying nucleosomal structure to regulate transcription, recombination or repair (Cato, Stott, Watson, & Thomas, 2008; Štros, 2010). The biological actions of HMGB1 are striking in their diversity, reflecting the unique biochemistry of this protein and its propensity for posttranslational modification.
Figure 1 The structure of the three isoforms of HMGB1. HMGB1 exists as oxidized, disulfide and reduced HMGB1. Structurally, HMGB1 consists of structure comprising of two DNA-binding domains, the A box and the B box, and a C-terminal tail domain which functions as transcription stimulatory domain. The A box also functions as p53 transactivation domain. The B box serves as TLR4 binding and cytokine activity domains.

Sources and function of HMGB1
HMGB1 can be released through three different mechanisms: (i) it is actively secreted from monocytes/macrophages, conventional dendritic cells (cDC) or pituicytes (Dumitriu et al., 2005; Haichao Wang, Bloom, et al., 1999; Haichao Wang, Vishnubhakat, et al., 1999) (ii) it is released passively from autophagic-stressed cells and (iii) by necrosis during cancer, injury or inflammation (Sims, Rowe, Rietdijk, Herbst, & Coyle, 2009).

Functionally, the role of HMGB1 depends on its location. When inside the nucleus, HMGB1 acts as an architectural protein that binds to DNA and can impact transcription. HMGB1 recognizes particular DNA conformations (e.g., bent DNA) rather than specific nucleic acid sequences and binds in the minor groove of the DNA helix. As a result, HMGB1 can distort DNA and thereby enhance interactions with several proteins, including p53, NF-κB, progesterone receptors, estrogen receptors and glucocorticoid receptors (Agresti, Lupo, Bianchi, & Müller, 2003; Jayaraman et al., 1998). HMGB1 plays an important role in transcriptional regulation neurite outgrowth, smooth muscle cell chemotaxis as well as promoting tumor cell metastasis.

HMGB1 in Experimental Autoimmune Encephalomyelitis (EAE)
Multiple sclerosis (MS) is an autoimmune-mediated inflammatory disease of the central nervous system (CNS) (Polman et al., 2005) characterized by localized areas with demyelination (Storch et al., 1998). Experimental Autoimmune Encephalomyelitis (EAE) is an animal model of MS. This disease is believed to be an autoimmune disorder mediated by activated immune cells such as T- and B-lymphocytes and macrophages/microglia. Lymphocytes are primed in the peripheral tissues by antigens, and clonally expanded cells infiltrate the CNS. HMGB1 is upregulated following brain ischemia and spinal cord injury (J.-B. Kim et al., 2006) and in one study it was shown to directly correlate with neuronal death (Kawabata et al., 2010), which supports the vital roles of HMGB1 in EAE disease. There is production of large amounts of inflammatory cytokines and nitric oxide (NO) that lead to demyelination and axonal degeneration. Several studies have shown that oligodendrocytes (OLGs), the myelin-forming glial cells in the CNS, are sensitive to cell death stimuli, such as cytotoxic cytokines, anti-myelin antibodies, NO, and oxidative stress (Kanwar, 2005). Extraneural (cytoplasmic) HMGB1 immunoreactivity has been found to be expressed in active MS lesions and, conversely, nuclear HMGB1 immunoreactivity was exhibited in inactive lesions (A. Andersson et al., 2008). Distribution of HMGB1 immunoreactivity suggests that HMGB1 is released from the cell nucleus when CNS inflammation occurs.

Previous research by Uzawa et al in 2013 identified that the protein CSF HMGB1 levels in MS patients were significantly higher than those in non-inflammatory neurological diseases patients, (Uzawa et al., 2013) and these levels in MS patients correlated with CSF cell counts (Ishizu et al., 2005), which is also reported by (Yonezu et al., 2014). Thus, there is a potential interaction among these molecules in the inflammatory processes involved in EAE and MS pathogenesis, which thus led to the conclusion that HMGB1 in the CNS may be a useful biomarker for CNS inflammation. The first study to demonstrate that HMGB1 inhibition by a specific monoclonal antibody could be used for EAE treatment was performed by Uzawa and his group. They evaluated the effects of an anti-HMGB1 mouse monoclonal antibody on EAE development. It was observed that anti-HMGB1 monoclonal antibody ameliorated the severity of EAE, as well as attenuated serum IL-17 up-regulation in EAE. It has been reported that prophylactic treatment with intravenous immunoglobulin at the time of EAE induction reduced disease symptoms and the underlying CNS pathology in EAE (Urbonaviciute et al., 2008). Uzawa et al. 2013 again found that anti-HMGB1 antibody attenuated CNS inflammation and demyelination in EAE. Again, treatment with an anti-HMGB1 monoclonal antibody (20 mg/day for 5 days) reduced IL-17 production in the peripheral circulation, which may contribute to the amelioration...
of the clinical and pathological severity of EAE. A reduction in IL-17 also resulted in the attenuation of the permeability of the blood–brain barrier, activation of microglia, suppression of the activity of matrix metalloproteinase-9 and an immune response and inflammatory cytokine release by immune cells such as IL-17, through neutralization of CNS HMGB1 with a specific antibody (Uzawa et al., 2013). This monoclonal antibody therapy would be novel from the perspective that it could be applied during acute disease exacerbations.

**HMGB1 in Experimental Autoimmune Myocarditis**

Myocarditis, which describes inflammatory disorders of the heart muscle of varied infectious and non-infectious origins, can lead to dilated cardiomyopathy (DCM) in young patients. Unfortunately, myocarditis lacks efficient and effective treatment. In view of this, more attention should be directed to the development of efficient immunomodulatory therapy. A mouse model for this CD4+ Th cell-mediated post-infectious myocarditis characterized by the infiltration of inflammatory cells into the myocardium, cardiomyocytes necrosis and deposition of collagen by cardiac fibroblasts/myofibroblasts (Su et al., 2014) is termed as Experimental autoimmune myocarditis (EAM). The cytokines and pathogenic proteins secreted by immune and cardiac cells contribute significantly to the pathogenesis of this disease in diverse forms. A previous data showed that HMGB1 was significantly up-regulated both in heart tissue and blood in EAM (Su et al., 2011). HMGB1 was found to have contributed to cardiac fibroblasts/myofibroblasts proliferation, migration and collagen deposition leading to EAM progression. It was also demonstrated that HMGB1 indirectly contributed Th17 cells expansion by facilitating macrophage reprogramming M1-like phenotype, but the detailed mechanisms need to be clarified. For example, M1-like phenotype macrophages has been observed to promote naïve CD4+ T cells differentiation into Th17 cells, effector Th17 cells proliferation or anti-apoptosis as well as its signal pathway. The same authors further established that Th17 cells mediated the EAM development and monocytes/macrophages infiltrated the heart ((Su et al., 2011; Su et al., 2014).

In this context, we reported that LPS increases HMGB1 production via TLR4/PI3K signaling pathway, and again plays a vital role in the LPS-induced myocardial contractile dysfunction in culture via a TLR4/PI3K signaling pathway (Xu et al., 2010). However, cardiac fibroblast/myofibroblast cells can secrete HMGB1 under stressed conditions (Su et al., 2014). In agreement, our studies and other reports have documented elevated levels of HMGB1 protein in the heart of EAM mice as well as in vitro proliferation of Th17 with the cells reported to contribute to the pathogenesis of EAM (Halwani, Al-Muhsen, Al-Jahdali, & Hamid, 2011; Rayavarapu, Coley, Kinder, & Nagaraju, 2013; Su et al., 2014).

To further identify whether HMGB1 contributes to autoimmune myocarditis development, it was reported that HMGB1 could directly lead to cardiac fibrosis. In addition, IL-17 secreted by Th17 cells also could directly lead to cardiac fibrosis. It was further reported that HMGB1 blockade attenuated cardiac pathological changes and reduced the number of infiltrating inflammatory cells in the heart during EAM (Su et al., 2011). Given the cardio-protective effects of HMGB1 silencing, inhibition of HMGB1 may improve myocardial fibrosis and undoubtedly provide new target for its intervention.

**HMGB1 in Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is characterized by uncontrolled hyperplastic synovium and inflammatory synovitis associated with the chronic production of proinflammatory cytokines and low oxygen tension. Synovial tissue inflammation in RA patients is maintained by sustained activation of multiple inflammatory positive-feedback regulatory pathways in a variety of cells including myeloid cells. During RA pathogenesis, it was observed that HMGB-1 is released from damaged or necrotic cells and interacts with toll-like receptors (TLRs) and receptors for advanced glycation end-products (RAGE) to induce inflammatory signals, as well as behave as an inflammatory cytokine to activate innate immune cells. Notably, RAGE interacts with HMGB-1, advanced glycation end-products, and innate immune cells to increase local inflammation. These alarmin proteins when released following cell damage, interact via TLRs to increase local inflammation and finally lead to cartilage degradation (Kokkola et al., 2003). Data from experimental mice models of arthritis have shown that HMGB-1 triggers arthritis with the inflammatory signs of synovitis possibly be neutralized by HMGB-1-specific monoclonal antibodies (Kokkola et al., 2003). The potential for HMGB1 to amplify the
effect of local cytokines has been suggested by its ability to stimulate macrophages derived from the synovial fluid of RA patients to release pro-inflammatory cytokines like TNF, IL-1β and IL-6 (Taniguchi et al., 2003). Intra-articular administration of HMGB1 induces the onset of arthritis in mice (Pullerits et al., 2003), suggesting an important role of HMGB1 in the pathogenesis of the disease (He et al., 2007; Kokkola et al., 2003). Extranuclear HMGB1 localization has been described in synovial tissue from osteoarthritic (OA) patients and in bovine osteoarthritic cartilage specimens (Hamada et al., 2008; Wåhåmaa et al., 2011). Evidence for an active role of HMGB1 in arthritis pathogenesis is provided by various studies which have demonstrated that a single injection of recombinant HMGB1 into knee joints of mice induced chronic synovitis (Wåhåmaa et al., 2011). Neutralization of HMGB1 by treatment with antibodies or with a specific HMGB1 peptide antagonist significantly suppressed arthritis development in several studies (U. Andersson, Erlandsson-Harris, Yang, & Tracey, 2002; Wåhåmaa et al., 2011; Hong Wang et al., 2004). HMGB1 promotes the release of proinflammatory cytokines (TNF-α, IL-1β, and IL-6) from macrophages in synovial fluid (Alghashom & Rasheed, 2014; Yan, Yan, Ramasamy, & Schmidt, 2009). Work by Hamada et al. (Hamada et al., 2008) depicted that hypoxia increases extracellular HMGB1, which localizes preferentially to regions of tissue hypoxia in arthritis lesions. HMGB1 upregulation plays significant roles in the development of arthritis. It has been established that synovial inflammation is accompanied by fibroblast proliferation and neutrophil infiltration as well as by angiogenesis in RA patients. The uncontrolled proliferation of the synovial lining layer leads to microenvironmental changes resulting in hypoxic conditions (Bosco et al., 2009; H. Y. Kim et al., 2014). In animal models of RA, anti-HMGB1 agents confer significant protection against joint tissue edema (Goldstein et al., 2007; Kokkola et al., 2003; H. Yang & Tracey, 2010), supporting a pathogenic role for HMGB1 in autoimmune diseases.

**HMGB1 influences Innate Immune cells during RA, EAE & EAM**

Recent studies have shown associations between HMGB1 and autoimmune diseases. High HMGB1 levels have been found in RA, Sjögren’s syndrome (SS), Churg–Strauss syndrome and systemic lupus erythematosus (SLE) (Ek, Popovic, Erlandsson Harris, Söderberg Nauclér, & Wahren-Herlenius, 2006; Taïra et al., 2007; Taniguchi et al., 2003). Important roles of HMGB1 in some autoimmune diseases have been described with one study reporting on that HMGB1 and its receptors, namely RAGE, TLR-2 and TLR-4 were up-regulated in active lesions of patients with MS and EAE (Urbonaviciute et al., 2008). The effect of HMGB1 on innate immune cells have been characterized and well documented. It has been reported to trigger the maturation of immature cDC, inhibits plasmacytoid DC response to TLR9 agonists and as well acts as a chemoattractant for neutrophils and macrophages (Messmer et al., 2004; Orlova et al., 2007; Popovic et al., 2006). Furthermore, HMGB1 is known to promote the survival and adherence of neutrophilic granulocytes (Lotfi et al., 2009). HMGB1 activates monocytes and neutrophils to release pro-inflammatory cytokines, including tumour necrosis factor (TNF-α), IL-1β, MIP-1α, MIP-1b, IL-6 and IL-8 (U. Andersson et al., 2000a; Park et al., 2003). HMGB1 can induce IL-6 and TNF-α release from macrophage-like cells (Haichao Wang, Yang, CZURA, Sama, & Tracey, 2001). Among its other functions, HMGB1 can also promote dendritic cell maturation and migration in vitro (Messmer et al., 2004; D. Yang et al., 2007). It has also been reported that RAGE and TLR are two major types of receptors mediating the inflammatory process triggered by HMGB1 (van Beijnum, Buurman, & Griffioen, 2008).

Thirteen TLRs (named TLR1 to TLR13) have been identified in mammalian species (Hans & Hans, 2011; Rauta, Samanta, Dash, Nayak, & Das, 2014; Temperley, Berlin, Paton, Griffin, & Burt, 2008). Actually, TLR4 is the first target activated by extracellular HMGB1 (U. Andersson & Tracey, 2011). HMGB1-TLR4 pathway can also trigger a second downstream pathway mediated by TRIF and leads to activation of type I interferon as well as a delayed activation of NF-kB (Vezzani, Maroso, Balosso, Sanchez, & Bartfai, 2011), resulting in the release of cytokine and activation of macrophages. IL-1β, IL-6 and TNF-α are always released during the early stage of inflammation. Notably, RAGE is another important receptor of HMGB1. It is expressed on a variety of cells, such as monocytes and belongs to the immunoglobulin superfamily (Long, 1999; Martin-Padura et al., 1998). Two major signaling pathways that are activated by RAGE are p38 MAPK and ERK1/2 pathways (van Beijnum et al., 2008). Both pathways can lead to the phosphorylation and degradation of inhibitors of NFκB by IkB kinase and thus activate NF-kB. Activated NF-kB then transfers to the nucleus and results in increase in NF-kB DNA binding, expression of various pro-inflammatory cytokines (e.g., TNF-α, IL-...
The roles of Adaptive immune cells are modulated in RA, EAE & EAM

The effects of HMGB1 on the function of different T-cell subsets have still remained elusive. Present evidence by Wild et al., reports that HMGB1 differentially impacts the biology of conventional and regulatory T cells. The authors further posited that HMGB1 is a potent chemoattractant for Treg, which might contribute to the infiltration and retention of Treg within damaged tissues (Wild et al., 2012). The effects of HMGB1 on Treg have been speculated to have the ability to alter immune reactivity in the setting of chronic inflammatory states such as cancer (Allavena & Mantovani, 2012). HMGB1 is known to modulate the biological activities of Treg as it can induce migration and prolongation of Treg survival. HMGB1 enhances suppressive capacity of T regulatory cells in cancers in a RAGE-dependent manner. In addition, it directly suppresses interferon-gamma (IFN-γ) release of conventional T cells (Tcon) and inhibits their proliferation via TLR4. It has been reported that enhanced proliferation of human CD4+ T lymphocytes is mediated by HMGB1, particularly when they are activated with limiting concentrations of αCD3 and αCD28 (Sundberg, Fasth, Palmblad, Harris, & Andersson, 2009). Additionally, HMGB1 is known to increase the proliferation of Th17 cells leading to the upregulation of IL-17, as well as lead to cardiac fibrosis. Endogenous or exogenous HMGB1 is established to play a role in DC activation and CD41 T-cell polarization (Su et al., 2011) as other studies also indicated that HMGB1 secreted by maturing DCs orchestrated priming, activation, and polarization of Th1 cells in vitro (Su et al., 2011; S. Zhang, Zhong, Yang, Gong, & Wang, 2010). Some studies have described that IL-17 had a predominant role in MS pathogenesis (Ishizu et al., 2005; Lock et al., 2002). However, most evidence was derived from EAE (Komiyama et al., 2006). In addition to IL-17, IL-6 plays crucial roles in EAE (Eugster, Frei, Kopf, Lassmann, & Fontana, 1998; Quintana et al., 2009). In EAM, HMGB1 has been found to indirectly contribute to Th17 cells expansion (Su et al., 2014). This confirms the immunomodulatory activities of HMGB1 on adaptive immune cells.

Therapeutic advances in targeting HMGB1 in RA, EAE & EAM

Many recent research have proven that targeting HMGB1 could be an important therapeutic approach in autoimmune diseases. It is also known that modification of HMGB1 and its interaction with various molecules are significant mediators of signaling pathways, suggesting that HMGB1 can serve as a new target for therapeutic purposes. Specific inhibition of endogenous HMGB1 reversed the lethality of established sepsis therapeutically, presumably by abrogating HMGB1-induced IL-6 and TNF-α release from macrophage-like cells (U. Andersson et al., 2000b). Antagonistic HMGB1 signals, based on small-molecule inhibitors such as ethyl pyruvate (Albayrak et al., 2010), HMGB1 silencing RAGE or TLRs knockout (Entezari et al., 2012; He et al., 2007; Leemans et al., 2009) have proven successful in a wide range of experiments, thereby resulting in reduced severity of autoimmune models. Anti-HMGB1 treatment, using HMGB1 antibodies or specific antagonist A box, has shown beneficial effects in collagen-induced arthritis in rodents (Kokkola et al., 2003). Therefore, an anti-HMGB1-based therapeutic strategy may also be useful in chronic inflammatory diseases such as arthritis. Anti-HMGB1 monoclonal antibody therapy partially prevented joint destruction and exhibited beneficial anti-arthritic effects in models of arthritis (Schierbeck et al., 2011), and attenuated cardiac pathological changes as well as reduced the number of infiltrating inflammatory cells in the heart induct by experimental autoimmune myocarditis via suppression of T helper type 17 (Th17) cells (Su et al., 2011). Inhibition of HMGB1 (A-box) ameliorated the induction of myocardial apoptosis (Xu et al., 2010). Besides, administration of HMGB1 dose-dependently increases the expression of collagen I and III, and TGF-β1, while pharmacological (neutralizing anti-HMGB1 antibody) or genetic (shRNA-HMGB1) inhibition of HMGB1...
in cardiac fibroblasts reduces HG-induced collagen production, MMPs activities, proliferation, and activates MAPK signaling (W.-k. Wang et al., 2014). Neutralizing extracellular HMGB1 in CNS with an anti-HMGB1 monoclonal antibody alleviated inflammation, which may have resulted in residual nuclear HMGB1 staining in anti-HMGB1 monoclonal antibody-treated EAE mice spinal cord sections. It has been reported that prophylactic treatment with intravenous immunoglobulin at the time of EAE induction reduced disease symptoms and the underlying CNS pathology in EAE (Jorgensen & Sorensen, 2005). Anti-HMGB1 monoclonal antibody therapy has been proven to be effective in the treatment of brain ischaemia as it inhibited the permeability of the blood–brain barrier, the activation of microglia, as well as the expression of TNF-a and inducible nitric oxide synthase coupled with its ability to suppress the activity of matrix metalloproteinase-9 by efficient clearance of circulating HMGB1 (Liu et al., 2007; J. Zhang et al., 2011) Further studies are recommended to define the immunological properties of HMGB1 and optimize strategies for blocking its abnormal activation in autoimmune diseases.

FUTURE PERSPECTIVES

HMGB1 is a ubiquitous protein that has diverse roles in mediating significant pathways of inflammation within and out of the microenvironment of cells. It plays a key role in controlling autoimmune responses by stimulating the release of inflammatory cytokines. The control of HMGB1 is considered to be a critical factor in the pathogenesis of many autoimmune diseases. Anti-HMGB1 monoclonal antibody therapy could be one of the best therapeutic options in the treatment of autoimmune diseases especially in this era where immunotherapy has been proven to be the best alternative in the treatment of cancers and autoimmune diseases. Future clinical trials will therefore help define whether HMGB1 will offer targets for therapeutic intervention, or whether targeted modulation of immune responses by HMGB1 can augment anti-inflammatory counter-reactions in autoimmune diseases.

DISCLOSURE OF CONFLICT OF INTEREST

None.

REFERENCES


(8) Andersson, U., & Tracey, K. J. (2011). HMGB1 is a therapeutic target for sterile inflammation and infection. Annual review of immunology, 29, 139-162.


nucleosome and DNA interactions. Biochemistry, 39(28), 8333-8346.


(14) Bianchi, M. E., Falciola, L., Ferrari, S., & Lilley, D. (1992). The DNA binding site of HMG1 protein is composed of two similar segments (HMG boxes), both of which have counterparts in other eukaryotic regulatory proteins. The EMBO journal, 11(3), 1055.


transient ischemia in rats. The FASEB Journal, 21(14), 3904-3916.
(72) Steinman, L. (2007). A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell–mediated tissue damage. Nature medicine, 13(1), 139-145.


American Journal of Respiratory and Critical Care Medicine, 164(10), 1768-1773.


