High Mobility Group Box 1 in the Pathogenesis of Inflammatory and Autoimmune Diseases

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Abstract

High mobility group box 1 is a nuclear protein participating in chromatin architecture and transcriptional regulation. When released from cells, HMGB1 can also act as a pro-inflammatory mediator or alarmin. Upon stimulation with lipopolysaccharides or tumor necrosis factor-alpha, HMGB1 is secreted from certain cells such as monocytes/macrophages and fosters inflammatory responses. In addition, HMGB1 is passively released from necrotic cells and mediates inflammation and immune activation. In contrast, during apoptotic cell death, nuclear HMGB1 becomes tightly attached to hypo-acetylated chromatin and is not released into the extracellular milieu, thereby preventing an inflammatory response. There is accumulating evidence that extracellular HMGB1 contributes to the pathogenesis of many inflammatory diseases, including autoimmune diseases. Increased concentrations of HMGB1 have been detected in the synovial fluid of patients with rheumatoid arthritis. In animal models of RA, HMGB1 appears to be crucially involved in the pathogenesis of arthritis since neutralization of HMGB1 significantly ameliorates the disease. Also, in the serum and plasma of patients with systemic lupus erythematosus we detected substantial amounts of HMGB1, which may contribute to the disease process. However, investigations of blood concentrations of HMGB1 and its relevance in human diseases are hindered by the lack of reliable routine test systems.

In addition, HMGB1 is passively released from necrotic cells, inducing an inflammatory response. In contrast, apoptotic cells retain HMGB1, which is tightly attached to hypo-acetylated chromatin. Therefore, HMGB1 is not released from apoptotic cells and does not induce inflammation.

Extracellular HMGB1 binds to cell surface receptors such as the receptor for advanced glycation end products, Toll-like receptors 2 and 4 and, possibly, to yet unknown receptors. Receptor binding leads to activation of the transcription factor nuclear factor-kappa B, inducing the transcription of multiple pro-inflammatory genes. Upon (co-)activation with HMGB1, macrophages produce pro-inflammatory cytokines such as TNFα, interleukin-1β, IL-6, IL-8, macrophage inflammatory protein-1α and MIP-2β. In addition, HMGB1 induces activation/maturation of dendritic cells with expression of major histocompatibility class II, CD83, CD80 and CD86.

There is increasing evidence that HMGB1 contributes to the pathogenesis of chronic inflammatory and autoimmune diseases due to its pro-inflammatory and immunostimulatory properties. Elevated levels of extracellular HMGB1 have been reported in experimental arthritis models. Similarly, in humans with rheumatoid arthritis increased concentrations of HMGB1 were detected within the synovial fluid from inflamed joints. In contrast to reports of HMGB1 in synovial fluid, we did not detect elevated concentrations of HMGB1 within serum or plasma of patients with RA. Importantly, collagen-induced arthritis in rodents was significantly ameliorated upon systemic application of either an antagonistic A box domain or neutralizing HMGB1-specific antibodies, indicating an important role in the pathogenesis of arthritis.

Within the lesional skin of cutaneous lupus erythematosus, increased amounts of cytoplasmic and extracellular HMGB1 have been detected, together with high expression of TNFα and IL-1β.

Using Western blot analysis and enzyme-linked immunosor-
bent assay we found increased concentrations of HMGB1 in the serum and plasma of a substantial number of patients with SLE [19]. Importantly, HMGB1 appears to be attached to circulating nucleosomes, most likely released from secondary necrotic cells [Urbonaviciute et al., submitted].

We propose the following model in which HMGB1 plays a crucial role in the immunopathogenesis of SLE. Normally, apoptotic cells are cleared swiftly in the early phases of apoptosis by phagocytes. As a result, apoptotic cells display a potent anti-inflammatory and immunosuppressive effect on monocytes/macrophages [22,23] that may prevent autoimmunity. However, in approximately 40% of SLE patients the phagocytosis of dead cells is impaired both in vitro and in vivo [24,25]. Hence, dying cells may enter late stages of apoptosis, i.e., secondary necrosis, and release HMGB1-containing nucleosomes since HMGB1 is tightly attached to the chromatin of apoptotic cells [13]. Nucleosomes as ubiquitously expressed abundant cellular components should establish profound central and peripheral tolerance, explaining their low immunogenicity under normal conditions. However, according to our recent data, HMGB1 complexed to “apoptotic” nucleosomes can activate dendritic cells and macrophages, thereby contributing to breaking the immunological tolerance to nucleosomes and double-stranded DNA, which represent key antigens in SLE [Urbonaviciute et al., submitted].

HMGB1 itself can be the target of an autoimmune response: anti-HMGB1 antibodies were found in patients with several autoimmune diseases including systemic sclerosis, ulcerative colitis, juvenile idiopathic arthritis, and SLE. However, the clinical relevance of these findings remains to be determined [13,26-28]. We also identified immunoglobulin G and M antibodies to HMGB1 in patients with SLE. Unexpectedly, most healthy blood donors displayed detectable amounts of anti-HMGB1 antibodies in their serum, although in lower concentrations than those of SLE patients. The presence of low titers of anti-HMGB1 antibodies in the majority of healthy subjects might be due to cross-reactivity or the sticky nature of HMGB1 [19]. HMGB1-binding antibodies might have physiological relevance by modulating the pro-inflammatory activity of HMGB1, thereby limiting overwhelming inflammatory responses caused by massive HMGB1 release in conditions such as sepsis and extensive necrosis. Importantly, anti-HMGB1 autoantibodies impede the reliable quantification of HMGB1 by ELISA [19]. Hence, the development of routine diagnostic methods for the reliable quantification of HMGB1 in serum and plasma is required to further elucidate the role of this multifunctional protein as a diagnostic and/or prognostic marker and as a potential therapeutic target in immune and inflammatory diseases.

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References


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In their study of 31 maternity hospitals and affiliated polyclinics in Belarus, Kramer et al. investigated whether exclusive and prolonged breast-feeding reduces the risk of childhood asthma and allergy by age 6.5 years. The participants were 17,046 mother-infant pairs, of whom 13,889 (81.5%) were contacted at age 6.5 years. The experimental intervention led to a large increase in exclusive breast-feeding at 3 months (44.3% vs. 6.4%, P < 0.001) and a significantly higher prevalence of any breast-feeding at all ages up to and including 12 months. The experimental group showed no reduction in risks of allergic symptoms and diagnoses or positive skin-prick tests. In fact, after exclusion of six sites (three experimental and three control) with suspiciously high rates of positive skin-prick tests, risks were significantly increased in the experimental group for four of the five antigens. The authors conclude that these results do not support a protective effect of prolonged and exclusive breast-feeding on asthma or allergy.


Eitan Israeli

Sex and antibodies to high mobility group proteins

Religion – freedom – vengeance – what you will. A word’s enough to raise mankind to kill

Lord Byron (1788-1824), British Romantic poet and controversial figure. He is regarded as one of the greatest European poets and remains widely read. Lord Byron’s fame rests not only on his writings but also on his life, which featured extravagant living, numerous love affairs, debts, separation, and allegations of incest and sodomy. He was famously described by Lady Caroline Lamb as “mad, bad, and dangerous to know.” Byron served as a regional leader of Italy’s revolutionary organization the Carbonari in its struggle against Austria, and later travelled to fight against the Turks in the Greek War of Independence, for which the Greeks consider him a national hero. He died from a febrile illness in Messolonghi. His daughter Ada Lovelace, notable in her own right, collaborated with Charles Babbage on the analytical engine, a predecessor to modern computers.

Capsule

Amateur boxing and risk of chronic traumatic brain injury

Loosemore and team retrospectively evaluated the risk of chronic traumatic brain injury from amateur boxing. They found 36 papers with relevant extractable data (from a detailed evaluation of 93 studies of 943 identified from the initial search). The quality of evidence was generally poor. The best quality studies were those with a cohort design and those that used psychometric tests. These yielded the most negative results: only 4 of 17 (24%) better quality studies found any indication of chronic traumatic brain injury in a minority of boxers studied. The authors conclude that there is no strong evidence to associate chronic traumatic brain injury with amateur boxing.


Capsule

Breast-feeding, allergy and asthma

In their study of 31 maternity hospitals and affiliated polyclinics in Belarus, Kramer et al. investigated whether exclusive and prolonged breast-feeding reduces the risk of childhood asthma and allergy by age 6.5 years. The participants were 17,046 mother-infant pairs, of whom 13,889 (81.5%) were contacted at age 6.5 years. The experimental intervention led to a large increase in exclusive breast-feeding at 3 months (44.3% vs. 6.4%, P < 0.001) and a significantly higher prevalence of any breast-feeding at all ages up to and including 12 months. The experimental group showed no reduction in risks of allergic symptoms and diagnoses or positive skin-prick tests. In fact, after exclusion of six sites (three experimental and three control) with suspiciously high rates of positive skin-prick tests, risks were significantly increased in the experimental group for four of the five antigens. The authors conclude that these results do not support a protective effect of prolonged and exclusive breast-feeding on asthma or allergy.


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