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SUPPLEMENT ARTICLE

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HMGB1: A pleiotropic activity

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Abstract

High-mobility group box 1 (HMGB1) is a nuclear protein involved in DNA replication, transcription, recombination, and repair. In the extracellular space, the HMGB1 plays an essential role in the onset and perpetuation of inflammation, belonging to the group of damage-associated molecular pattern (DAMP) molecules, also called alarmins. For this, HMGB1 has been studied in several acute and chronic inflammatory diseases as an early biomarker of inflammation. An increased concentration of HMGB1 has been detected in serum, as the expression of systemic inflammation, and in specific samples (such as stool, synovial fluid, nasal lavage fluid, sputum, and cerebrospinal fluid), as the expression of local production, in several infectious and/or inflammatory diseases. These data are particularly important because they open new futuristic possibilities for target therapies, potentially also for the COVID-19 treatment.

KEYWORDS

biomarker, HMGB1, inflammation, target therapy

High-mobility group box 1 (HMGB1) is a high conserved nuclear protein (215 residues, 30 kD) encoded by a gene located on chromosome 13 (13q12), and it is part of high-mobility group (HMG) superfamily.

The HMG proteins support chromatin structure in the nucleus and regulate DNA replication, transcription, recombination, and repair. This repair activity on damaged DNA, due to interactions with DNA repair enzymes, drew the attention of oncologists concerning chemotherapy-induced DNA adducts and the possible role of HMGB1 in radio-resistance of some types of cancer. HMGB1 plays an essential role in DNA repair for its high affinity for damaged DNA, both in nucleotide and base excision repair and in DNA double-strand break repair.[1]

The importance of HMGB1 in the inflammatory conditions comes from its role in innate immunity. Indeed, HMGB1 belongs to the group of damage-associated molecular pattern (DAMP) molecules called alarmins and plays an essential role in the onset and perpetuation of inflammation in response to infectious or sterile stimuli that may cause cell injury or death.[2]

The release of HMGB1 in the extracellular space may be a consequence of cellular necrosis or active secretion from more types of immune cells (such as monocytes, macrophages, endothelial cells, enterocytes, pituicytes, dendritic cells, and natural killer cells) in response to infectious agents and/or inflammatory cytokines. PAMPs (pathogen-associated molecular patterns), lipopolysaccharide, TNF-α (tumor necrosis factor-α), and IL-1 (interleukin-1) strongly stimulate the release of HMGB1 from immune cells. Type 1 and type 2 interferons induce intracellular localization of HMGB1 instead. In the extracellular space, the HMGB1 binds membrane receptors RAGE (receptor for advanced glycation end products) or TLRs (Toll-like receptors) such as TLR-2 and TLR-4. The activation of intracellular signaling cascade through TRAF6, NEMO, and IKK IKBα causes the induction of the transcription factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells). This causes the production and secretion of various pro-inflammatory cytokines (IL-12, IL-6, IL-1, IL-8, and TNF-α) and the amplification of the inflammation.[1-3]

The central role of HMGB1 in the onset and perpetuation of inflammation makes this cytokine a possible early marker for various

diseases characterized by systemic and/or local inflammation and opens new futuristic possibilities for target therapies. Indeed, more studies have shown a systemic and local increase of HMGB1 concentration in inflammatory conditions and a direct correlation between HMGB1 levels and disease severity. Besides, the HMGB1 action in the first phase of inflammation makes this alarmin one of the earliest markers of inflammation.

The possible use of serum HMGB1 as a biomarker for diagnosis and follow-up of inflammatory pathologies was demonstrated for various diseases: sepsis, obesity, tumor progression, and inflammatory and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and inflammatory bowel diseases (IBD).[2,3]

In IBD, arthritis, allergic rhinitis, bronchiolitis, asthma, cystic fibrosis, chronic obstructive pulmonary diseases, pneumonia, neuromyelitis optica, multiple sclerosis, and bacterial meningitis, increased HMGB1 levels in specific samples (respectively, in stool samples, synovial fluid, nasal lavage fluid, sputum, and cerebrospinal fluid) were also found and considered the expression of local HMGB1 production in the inflammation site.[3-5] The importance of HMGB1 recognition in a specific sample as the expression of local production comes from the aspecificity of this biomarker. Increased serum HMGB1 levels are an expression of systemic inflammation but do not give information about the apparatus initially involved in the inflammatory disease. In local samples, there is also an earlier and more substantial increase in HMGB1 concentration than in serum.

In epilepsy and febrile seizures, the HMGB1 plays an important pathogenetic role, with consequent possible creation of a novel antiepileptic strategy based on pharmacological modulation of HMGB1-TLR/RAGE axis. HMGB1 is an essential mediator of the neuroinflammation, and its role has been hypothesized in autism spectrum disorders.[3-6]

In some diseases, such as heart infarction, traumatic brain injury, pulmonary fibrosis, and acute lung injury, HMGB1 is passively released by damaged cells, and, for this, it may be considered the expression of cell necrosis degree in the early phases. In the extracellular space, HMGB1 causes the activation of NF-kB and other similar transcription factors with consequent local inflammation but also induction of genes that encode for inducible enzymes and growth factors that are important for the reparation process of damaged tissue.[7]

Of particular interest are data about the correlation between serum HMGB1 and severity of respiratory tract infections. For example, Wang et al studied differential alterations in serum HMGB1 of patients with community-acquired pneumonia (CAP) before and following antibiotic treatment, highlighting the directly proportional correlation between serum HMGB1 and the pneumonia severity index score ($P < .001$).[8]

Similar data about the direct relation between serum HMGB1 and severity of pneumonia have been found for several etiological agents such as mycoplasma pneumonia, mycobacterium tuberculosis, and viruses.[8]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may cause pneumonia with different degrees of severity, dependent on the efficiency of innate immunity and cytotoxic T lymphocyte activity. The immune system's inability to eliminate the virus causes an abnormal immunocytokine cascade with consequent lung and systemic inflammation, such as to lead to severe clinical pictures. Increased levels of inflammatory cytokines such as interleukin (IL)-1 and IL-6 are the expression of this inflammatory process and targets for the therapy. The recent data reported above on the relation between HMGB1 concentration and severity of pneumonia and the critical role of HMGB1 in innate immunity response and the onset and amplification of the inflammation make this alarmin a potential target for the treatment of SARS-CoV-2 disease (COVID-19). Besides, recent scientific studies show how HMGB1 stimulates leukocyte migration in the lung, playing an essential role in acute lung injury and becoming a potential biomarker. In the cytoplasm, the HMGB1 regulates the autophagic flux, and the autophagy is involved in SARS-CoV-2 entry and replication in cells. Finally, amyloidosis and thrombosis are autopsy findings from COVID-19 patients, and HMGB1 is increased in thrombosis-related diseases and sepsis-triggered amyloid-β accumulation of some central nervous system diseases. Although more pre-clinical studies show the effectiveness of HMGB1-specific antagonists in the reduction of inflammation in some models of acute or chronic inflammatory diseases, clinical trials are still missing. In consideration of the above, HMGB1 could be an excellent potential target for the treatment of various inflammatory diseases, including COVID-19.[9,10]

Key Message

HMGB1 may be considered an early biomarker of local and systemic inflammation in several acute and chronic inflammatory diseases. HMGB1-specific antagonists are a new potential target therapy, useful in the treatment of several infective and/or autoimmune diseases, including potentially COVID-19.

CONFLICT OF INTEREST

All authors (Laura Colavita, Giorgio Ciprandi, Annamaria Salpietro, Caterina Cuppari) declare no conflict of interest.

PEER REVIEW

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