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HMGB1: Exploring scaffolding factors that shape chromosomal organization

Bhumika Sureka[1] and Arianna Broad[2#]
[1]The International School Bangalore, India
[2]Weill Institute for Cell and Molecular Biology, Cornell University, USA

Abstract:

HMGB1 (High mobility group box 1) is a non-histone nuclear protein that is either passively released following cell damage or actively secreted in response to inflammatory stimuli. It is a non-histone chromatin-associated protein that is generally found inside cells; however, it can be secreted into the extracellular environment by passive or active release. Extracellular HMGB1 interacts with a variety of receptors and interactors to regulate hematopoietic stem cell (HSC) proliferation, differentiation, mobilization, and senescence. In this review, we comprehensively evaluate HMGB1's emerging roles and how it influences chromosomal arrangement, starting with its biological structure, which is an evolutionarily conserved multifunctional protein by nature. A quick glance at the timelines of findings linked with HMGB1 reveals that the assembly of histones with DNA to create nucleosomes is well recognized, but the nature of non-histone participation is less clear. Throughout this paper, we aim to systematically review the various hypotheses regarding the role and importance of HMGB1 in chromatin-related processes.

Key Words: Non-histone proteins, adaptive immunity, damage associate molecular pattern (DAMP), immunogenic cell death (ICD), inflammation, innate immunity, tissue repair

Introduction

High Mobility Group Box (HMGB) is a non-histone chromosome-binding protein in eukaryotic cells that is named after its low molecular weight and high gel mobility and is divided into three gene families. HMGB1, also known as amphoterin or HMG1, is the most abundant nonhistone nucleoprotein in the HMGB gene family. The HMGB1 gene is located on chromosome 13q12 and includes five exons and four introns. HMGB1 protein is a highly conserved nuclear protein consisting of 215 amino acids with a molecular weight of approximately 30 kD [1]. Structurally, HMGB1 is divided into three functional regions A-box (9-79 aa), B-box (89-162 aa), and acidic C-terminus (186-215 aa) [2]. The A-box and B-box are composed of 80–90 amino acid residues, with similar amino acid repeats and nonspecific DNA binding sites; the B-box is foundational to both the structure and function. [3] Its presence and specific structure allow HMGB1 to carry out its biological functions, including its role in eliciting an inflammatory response. [4] HMGB1 has dual functions as a nonhistone nucleoprotein and an extracellular inflammatory cytokine. Intracellular HMGB1 is extensively bound to DNA and involved in transcriptional regulation, DNA replication and repair, telomere maintenance, and nucleosome assembly. [5] Extracellular HMGB1 is passively released by necrotic tissue or stressed cells or actively secreted. As a chemokine or cytokine, it binds to pattern recognition receptors (PRRs) to play the role of a Damage-Associated Molecular Pattern (DAMP). [6]

HMGB1 directs the triggering of inflammation, innate and adaptive immune responses, and tissue healing after damage. It is a representative DAMP (Damage-Associated Molecular Patterns), a protein that is translocated and released extracellularly from different types of cells [7] Notably, cells undergoing severe stress actively secrete HMGB1 via a dedicated secretion pathway where it is relocated from the nucleus to the cytoplasm, then to the lysosome or to the extracellular space. Extracellular HMGB1 triggers inflammation and adaptive immunological responses by switching among multiple oxidation states, which direct the mutually exclusive choices of different binding partners and receptors. [8] Immune cells are first recruited to the damaged tissue where they are activated,

which initiates HMGB1 supportive tissue repair and healing by coordinating the switch of macrophage to the proliferation of stem cells and neo-angiogenesis. HMGB1 also orchestrates the support of stressed but illegitimate tissues, and tumors. Simultaneously, it enhances the immunogenicity of mutated proteins in the tumor (neoantigens), promoting anti-tumor responses and immunological memory. [9]

Timeline of findings associated with HMGB1

Numerous studies up until now, show a significant variation in the non-histone synthesis during the cell cycle, however, the aim of correlating changes in non-histone protein association with DNA and subsequent changes in the structure and function of interphase and metaphase chromatin has yet to be determined.

Prior to 2018, all that was known about mitotic chromosome composition was that about one-third of it was a highly heterogeneous and poorly characterized group known as nonhistone proteins. The idea that members of this group of proteins might have a role in determining the architecture and biochemical properties of mitotic chromosomes was developed most fully by Laemmli and co-workers, who established a method for the fractionation of chromosomes into a relatively soluble fraction, containing about 90-95% of the chromosomal proteins, and an insoluble fraction composed of a subset of the nonhistone proteins, termed the "chromosome scaffold". [10] It was suggested that this scaffold was composed of structural components that gave the mitotic chromosomes their characteristic shape and organized the interphase chromosome into loop domains of 50-100 kb.[11]

Following the discovery of HMGB1 potentially as a "chromosome scaffold", the proteins of the HMGB family are further elucidated through research, as "architectural factors" of chromatin, which play an important role in gene expression, transcription, DNA replication, and repair. However, as soon as HMGB1 goes outside the nucleus, it acquires completely different functions, post-translational modifications, and a change of its redox state. [12] Despite a lot of evidence of the functional its activity, there are still many issues to be solved related to the mechanisms of the influence of HMGB1 on the development and treatment of different diseases—from oncological and cardiovascular diseases to pathologies during pregnancy and childbirth. [13]

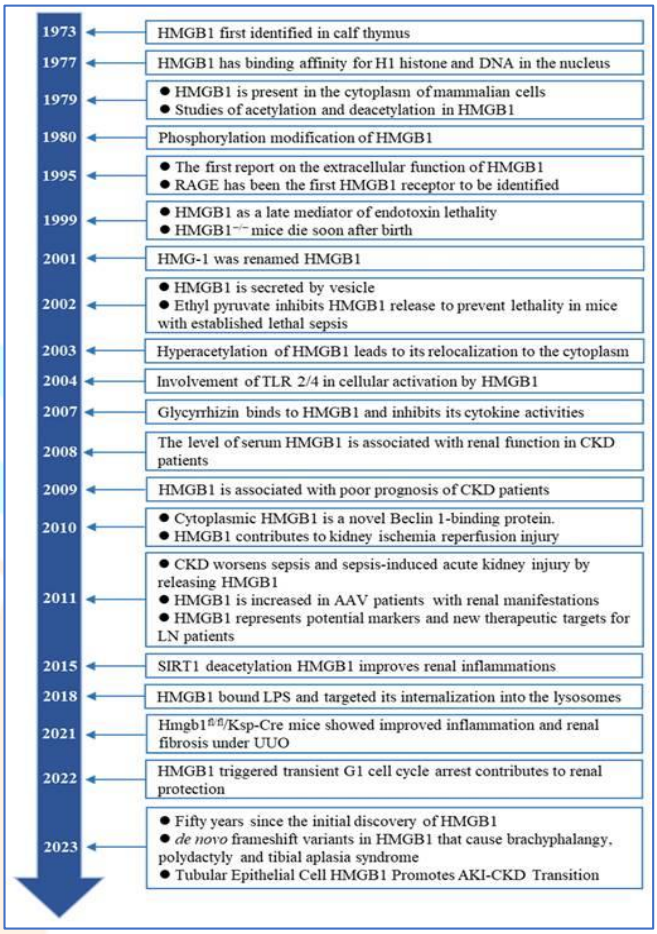

Fig 1: Timeline of findings associated with HMGB1 - *International Journal of Biological Sciences 19: 5020 image No. 001*

While HMGB1 and HMGB2 proteins have been implicated in numerous cellular processes including proliferation, differentiation, apoptosis, and tumorigenesis, it is unknown whether they are involved in regulating the typical functions of pluripotent human embryonic stem cells (hESCs) and/or those of the differentiated derivatives of hESCs. Using inducible, stably transfected hESCs capable of shRNA-mediated knockdown of HMGB1 and HMGB2, Alireza Jian Bagherpoor et al, 2017, demonstrated that downregulation of HMGB1 and/or HMGB2 in undifferentiated hESCs do not affect the stemness of cells and induces only minor changes to the proliferation rate, cell-cycle profile, and apoptosis [14]

Other components that modulate chromatin architecture include long-chain DNA molecules, which must be highly folded within the nucleus of the eukaryotic cell with some regularity. Information about the structure of chromatin has come from X-ray diffraction, physicochemical studies, electron microscopy, and nuclease digestion, which all suggest that chromatin from eukaryotes comprises a linear array of spherical particles in which DNA is supercoiled around a core of oligomers of histones.[15]. Furthermore, an orthologous approach assessed the structure of DNA in the nucleus of cultured mammalian cells and demonstrated that when all the histones and most of the non-histone proteins are removed from chromatin, DNA is supercoiled and folded by a few non-histone proteins [16]. While non-histone proteins are major components of metaphase chromosomes and interphase chromatin, their precise structural and functional roles are poorly understood. An approach to uncover a structural role for non-histones in the higher-order organization of metaphase chromosomes was to extract histones and other chromosomal proteins and to characterize the residual particles by polyacrylamide gel electrophoresis and electron microscopy [17].

It was elucidated that lysine acetylation (Kac), a Post-Translational Modification (PTMs), resulted in the loosening of heterochromatin [18]. This type of modification became one of the best characterized PTMs, with a specific role in several cellular functions including diversifying and regulating the cellular proteome [19]. In recent years, Kac has been shown to occur on histone and non-histone proteins involved in the regulation of transcription, metabolism, and cell signaling [20]. Recent studies on protein SET7/9 methylates (Lysine-specific methyltransferase 7), both lysine 4 of histone 3 (H3-K4) and the lysine(s) of non-histone proteins demonstrated that non-histone methylation of SET7/9, functions by contributing to tumorigenesis. [21] SET7/9 is an important methyltransferase, that can catalyze the methylation of a variety of proteins. Its substrates are tightly correlated to tumorigenesis mechanisms. [22]. Further, it plays a crucial role in tumorigenesis by adding a methyl group to specific proteins, modifying their function, hence impacting cell signaling pathways and gene expressions.

Recent research conducted in 2021 has shed light on the link between HMGB1 and cancer immunotherapy, yielding several key conclusions. HMGB1, identified as a single protein, plays a pivotal role in triggering inflammation, innate and adaptive immune responses, and tissue healing after damage [23]. Additionally, HMGB1 is characterized as a damage-associated molecular pattern (DAMP), which typically resides inside the cell but is released following cell death, (though DAMP is also associated with other molecules like DNA/RNA and is not limited to HMGB1) This release enables the immune system to discern between dangerous and non-dangerous antigens [24]. Notably, cells experiencing severe stress actively secrete HMGB1 through a dedicated secretion pathway. During this process, HMGB1 is relocated from the nucleus to the cytoplasm, then to secretory lysosomes, or directly to the extracellular space [25]. The extracellular form of HMGB1, either released or secreted, exerts its effects by switching among multiple oxidation states, leading to mutually exclusive choices of binding partners and receptors. This triggers inflammation and adaptive immunological responses [26].

In the context of tissue repair and healing, HMGB1 plays a crucial role. After immune cells are recruited to the damaged tissue and activated, HMGB1 coordinates the transition of macrophages to a tissue-healing phenotype, facilitates the activation and proliferation of stem cells, and promotes neoangiogenesis. [27] Furthermore, HMGB1 enhances the immunogenicity of mutated proteins in tumors, known as neoantigens, thereby fostering anti-tumor responses and immunological memory. [28] These findings underscore the potential significance of modulating HMGB1's activities in inflammation, immune responses, and tissue repair, offering promising rewards in the development of therapies for various medical conditions, including cancer.

Various contributing features of HMGB1 on DNA repair and regeneration

DAMPs are molecules released by dead or dying cells, particularly those that prematurely terminate. They are non-antigenic but recognized by Pattern Recognition Receptors (PRRs) with broad and often multiple specificities. Pathogen-Associated Molecular Patterns (PAMPs) are components of bacteria and viruses, while Damage-Associated Molecular Patterns (DAMPs) are molecules released by cells that prematurely terminate. The adaptive immune system exists to prevent infection by the same or related pathogens. DAMPs are molecules that are not antigens but prompt the immune system to react against antigens that it can recognize. They are similar to PAMPs, activating PRRs and eliciting the same early responses such as inflammation. HMGB1 is the first DAMP and is essential for tissue repair and the immune system's recognition of cancer. [29]

HMGB1 AS A DAMP

Based on the studies conducted in mice, (H Wang et.al 1999) HMGB1 is a DAMP that is released by mouse macrophages challenged with Lipopolysaccharide (LPS) and is a late mediator of endotoxin lethality. It is also adjuvanticity, exogenous HMGB1 activates Cluster of Differentiation (CDs) *in vitro* and i*n vivo* and controls the maturation of Dendritic Cells (DCs) and their migration to the closest draining lymph node and their interaction with T cells [30]. This activation of antigen-presenting cells and their signaling to T cells is so potent that countervailing suppressive mechanisms are required, including binding to the immuno-suppressive receptors CD2410 and TIM-3 [31].

To elaborate, HMGB1 is normally located in the cell nucleus, where it helps regulate the transcription of certain genes related to DNA repair. However, during conditions of cell stress, injury, or cell death (necrosis), HMGB1 can be actively released from cells into the extracellular space. This release can also occur passively when cells undergo necrosis, a form of cell death that leads to cell membrane rupture and release of intracellular contents. Once released into the extracellular environment, HMGB1 acts as a danger signal or an alarm to the immune system. It serves as a signal that there has been tissue damage or cellular stress. [32]

HMGB1 can interact with specific receptors on the surface of immune cells, such as Toll-like receptors (TLRs) and the Receptor for Advanced Glycation End-products (RAGE) [33]. Studies have demonstrated that RAGE is involved in the HMGB1-induced immune response of macrophages and in rat smooth muscle cells. HMG1 (and its individual DNA-binding domains) stimulated the migration of rat smooth muscle cells in chemotaxis, chemokinesis, and

wound healing assays. HMG1 induced rapid and transient changes of cell shape, and actin cytoskeleton reorganization leading to an elongated polarized morphology typical of motile cells. [34]

HMGB1 AS A SECRETED ALARMIN

HMGB1 is secreted by macrophages and has two Nuclear Localization Signals (NLSs). Acetylation of lysines or phosphorylation of serines in the NLSs preclude re-entry into the nucleus, and the protein accumulates in the cytoplasm. In hematopoietic cells, HMGB1 is loaded into secretory lysosomes, but non-hematopoietic cells can also secrete it. Acetylated HMGB1 is a biomarker for HMGB1 secretion. HMGB1 can be secreted in the presence of severe cell stress, but not necessarily cell damage, or in the presence of pathogens. Examples of this include ischemia and LPS detection, which activates NF-B and phosphorylates IRFs [35]. Phospho-STAT1 dimers translocate to the nucleus and recruit histone acetylases to acetylate HMGB1. [36]

FORMS AND FUNCTIONS OF EXTRACELLULAR HMGB1

HMGB1 has post-translational modifications that modify its function of ligand binding to different receptors. It forms a heterocomplex with the chemokine CXCL12, and the HMGB1-CXCL12 heterocomplex binds CXCR4, a 7-transmembrane G-protein-coupled receptor (GPCR) [37]. Both CXCL12 and the HMGB1-CXCL12 complex promote cell migration, extravasation from vessels, and tissue invasion. [38]

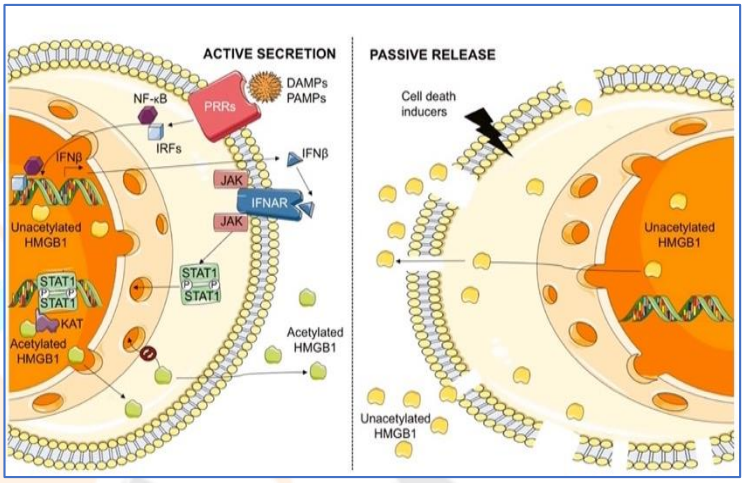

Figure 1. HMGB1 is both a DAMP that is passively released by dead cells (right) and a soluble protein (alarmin) that is actively secreted by severely stressed cells (left). In normal conditions, HMGB1 is mainly localized in the nucleus in a non-acetylated and reduced (thiol) form. Upon tissue injury, non-modified HMGB1 leaks out from dead cells and is later converted to disulfide-HMGB1 either by spontaneous oxidation or by the encounter with ROS that are abundantly produced by inflammatory cells. Leukocytes and many other cells can secrete HMGB1: HMGB1 is first translocated to the cytoplasm after being acetylated or phosphorylated and then to the extracellular space (after being loaded into secretory lysosomes in leukocytes, or by an unknown mechanism in non-hematopoietic cells). Secreted HMGB1 can be distinguished from passively released HMGB1 (yellow in the diagram) because it is acetylated (green in the diagram). Secreted HMGB1 also becomes oxidized. The diagram on the left represents the pathway of HMGB1 secretion induced by LPS (bacterial PAMP) and interferons (IFNs, produced in response to viral PAMPs). The cascade entails two consecutive steps, IFN-β synthesis and secretion upon LPS binding to TLR4, and HMGB1 secretion upon binding of IFN-β to IFN receptors (IFNAR). HMGB1 acetylation is believed to be executed by lysine acetyltransferases (KATs) recruited by phosphorylated STAT1 dimers bound to DNA

A different PTM of HMGB1, a disulfide-bonded HMGB1, binds the MD2-TLR4 complex and promotes the activation of NF-B and the transcription and secretion of multiple inflammatory mediators [39]. The HMGB1/TLR4 axis is involved in inflammation and immune regulation. It binds to Toll-like receptors (TLRs) and enhances cytokine production in macrophages, B cells, and plasmacytoid dendritic cells (DCs). It also binds to RAGE, a multifunctional single-transmembrane protein of the immunoglobulin superfamily. RAGE signaling leads to activation of the NF-B pathway and signal transduction through JNK, p38, and ERK MAP kinase pathways, inducing MMP-9 activation and resulting in allowing immune cells to migrate to the site of infection. (Activation of NF-κB is also involved in this process) [40]. It is also involved in many other HMGB1-dependent signaling pathways, such as thrombosis, migration of dendritic T cells to lymph nodes, T-cell activation, angiogenesis, and the spreading of brain damage after stroke. [41]

EXTRACELLULAR HMGB1 IN TISSUE DAMAGE AND HEALING

When a tissue is damaged, HMGB1 orchestrates two key events in inflammation: leukocyte recruitment and their induction to secrete inflammatory cytokines. When released in injured tissue, HMGB1 forms a heterocomplex with low concentrations of CXCL12 and promotes the production of more CXCL12 by binding the RAGE receptor on neighboring cells. HMGB1 also plays an important role in muscle regeneration after injury, recruiting monocytes, and local and mesenchymal stem cells, and promoting neoangiogenesis. HMGB1 secreted by leukocytes is important for the skeletal muscle to react to hypoxia and to initiate angiogenesis in response to injury (Figure 2). [42]

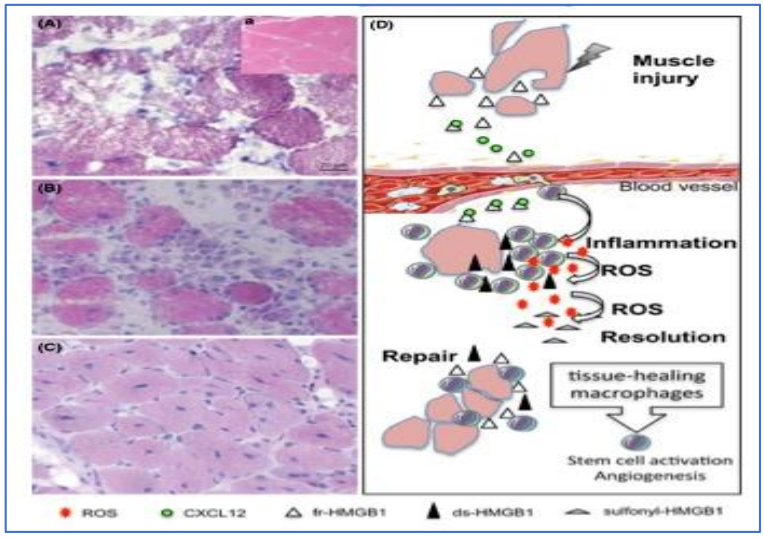

Figure 2. HMGB1 and tissue repair. Here, HMGB1 activities are illustrated during muscle injury. Reduced HMGB1is released by damaged/necrotic muscle cells **(A; inset a: normal muscle cells)** and promotes leukocyte recruitment by forming a heterocomplex with CXCL12. Leukocytes are recruited **(B)** and the damaged tissue is highly inflamed. HMGB1 is oxidized to the disulphide form by ROS originating from infiltrating leukocytes, activates them to release proinflammatory cytokines/ chemokines, but loses the ability to form a heterocomplex with CXCL12. ROS produced by leukocytes eventually cause the terminal oxidation of HMGB1 cysteines to sulfonates; sulfonyl HMGB1 no longer has chemoattractant nor proinflammatory activities. After inflammation resolution, macrophages with a tissue-healing phenotype release more HMGB1, which may activate stem cells (satellite cells) and promotes angiogenesis, leading to the repair of the damaged muscle **(C). (D)** Recapitulates the various steps in muscle damage and repair in a diagrammatic way.

HMGB1 IN TUMOR BIOLOGY

HMGB1 is a protein that is involved in inflammation and injury, as well as tumorigenesis. It is particularly associated with mesothelioma, a tumor of mesothelial cells lining the pleura and peritoneum, which is highly associated with exposure to asbestos and other mineral fibers. Macrophages recruited by secreted HMGB1 support the growth of colon carcinoma secondary lesions in the peritoneum, and melanoma and papilloma can be initiated or supported through the HMGB1/TLR4 axis. Many cancer tissues overexpress HMGB1, and many may secrete it, at least under some conditions. [43]

Immunogenic cell death (ICD) is a form of apoptotic death characterized by calreticulin, HMGB1, and ATP emission. This combination stimulates the cross-presentation of neoantigens from cancer cells to the immune system and the activation of CD4 T cells. ICD can be experimentally studied in mice, and the loss of HMGB1 from malignant cells negatively affects prognosis in patients with breast cancer treated with anthracyclines as adjuvant chemotherapy. ICD is an ancient response program to pathogens, as it activates response pathways similar to those activated by viruses. Calreticulin, a protein resident in the ER, is released in association with ER stress and detected via LRP1. ROS production that targets the ER is an upstream molecular event in ICD. HMGB1 is released before caspase 3 activation and must be released before caspase 3 activation (Figure 3). [44]

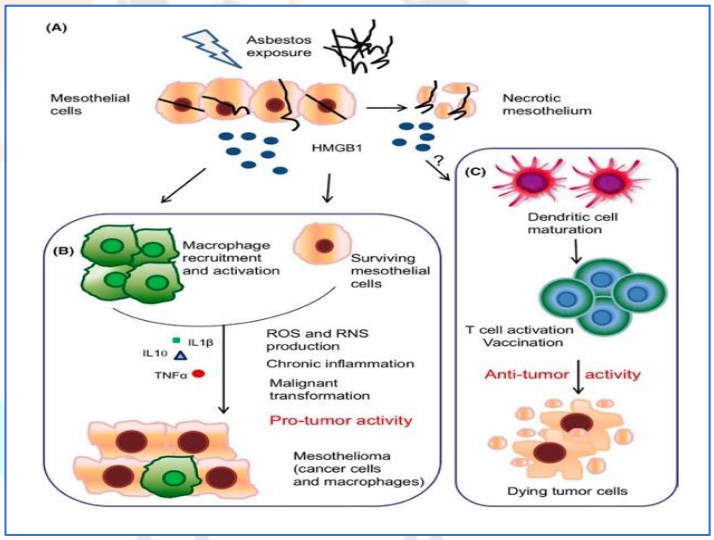

Figure 3. Schematic representation of pro-tumor and anti-tumor activities of HMGB1. (A) Pathogenesis of malignant mesothelioma is discussed as an example. Mesothelial cells injured by asbestos undergo a programmed necrotic death, with HMGB1 release. Extracellular HMGB1 recruits and activates macrophages. **(B)** Pro-tumor activities of HMGB1. HMGB1 binding to TLR4 generates a status of chronic inflammation that leads to malignant transformation. Macrophages with a tissue healing phenotype are part of the mesothelial tissue, and HMGB1 is constitutively secreted by mesothelioma cells. **(C)** Anti-tumor activities of HMGB1. The question mark denotes that the involvement of these in mesothelioma has not been investigated and might not be relevant; however, the involvement of HMGB1 in anti-tumor activities against several tumors and in ICD has been extensively documented. HMGB1 secreted by cells undergoing ICD activates DCs to cross-present neoantigens (mutated tumor proteins) to lymphocytes, which mount B- and T-cell responses that kill tumor cells and establish anti-tumor immunological memory.

Discussion

HMGB1, a non-histone protein, is a relatively understudied concept in Biology. Despite its significance, little is known about HMGB1, despite ongoing research aimed at elucidating its complex roles and potential applications in diagnosing and treating diseases. Numerous studies have demonstrated that HMGB1 plays crucial roles in cell death, immunity and inflammation, thrombosis, remodeling, and repair. In the early stages of cerebral infarction, HMGB1 is heavily implicated in the pathological injury process, whereas in the late stages, it promotes brain tissue repair and remodeling. In acute white matter infarction, it plays a neurotrophic role, whereas in chronic white matter ischemia, it causes sustained activation of inflammation and plays a harmful role. [45]

It also plays a complex role in cerebral infarction, which is related not only to the modification of HMGB1 and bound receptors but also to the various phases and subtypes of cerebral infarction. Future research on HMGB1 should focus on investigating its spatial and temporal dynamics following cerebral infarction. In addition, it should aim to incorporate the various stages and subtypes of cerebral infarction. [46]

While HMGB1 was initially identified as a chromatin protein with unknown function, it is now known to serve as a chaperone in the nucleus, facilitating DNA bending and nucleosome assembly. When a cell's integrity is compromised, HMGB1 has evolved an additional function as a DAMP that signals cell demise and stress [47]. HMGB1 from mussels has also been demonstrated to stimulate innate immunity [48]. Over such a long period of evolution, HMGB1 and its family members have been utilized in every biological process in which a cell has an interest in the (inducing apoptosis of itself or apoptosis of a neighboring cell death or potential death of a neighboring cell, for any reason ranging from being alerted to pathogens to supporting or rescuing the ailing cell to the process of replacing it. Inversely, some of these responsibilities might not be precisely coordinated, such as when immune cells from the innate arm aid tumors while immune cells from the adaptive branch seek to eliminate them.

Manipulation of HMGB1's multifaceted functions to direct a specific outcome would surely represent a scientific high point, particularly in the context of pathogenesis. HMGB1 regulates inflammation, immunity, and cell fate in pathogenic processes. When used to promote a desired outcome, it has the potential to revolutionize our ability to modulate disease progression, potentially leading to groundbreaking therapies for conditions where HMGB1 is implicated, such as cancer, autoimmune diseases, and sepsis. Attaining this level of control over HMGB1 functions promises to be a game changer in scientific research and medical interventions.

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Methods

Cited literature in this study was curated from scientific literature platforms such as the National Center for Biotechnology Information (NCBI) - National Library of Medicine, BioMedCentral, online seminar conducted by School of Medicine - San Raffaele University, MDPI, and Google Scholar.

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