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REVIEW

The Ambiguous Role of HMGB1 Across the Hallmarks of Aging: A Narrative Review

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Abstract: Aging is a complex, multifactorial process driven by interconnected biological mechanisms collectively known as the hallmarks of aging, which contribute to functional decline and the onset of age-related diseases. High-mobility group box 1 (HMGB1), a nuclear DNA chaperone and damage-associated molecular pattern (DAMP), plays a pivotal role in regulating these hallmarks through its dual functions: preserving genomic stability within the nucleus and promoting inflammatory responses when released extracellularly. This review examines the multifaceted involvement of HMGB1 in key aging hallmarks, such as genomic instability, telomere attrition, mitochondrial dysfunction, and chronic inflammation among others. Preclinical studies demonstrate that nuclear HMGB1 supports chromatin integrity and DNA repair, whereas its extracellular release triggers TLR4/RAGE signaling pathways, thereby intensifying inflammaging and senescence-associated secretory phenotypes (SASP). Emerging therapeutic approaches—such as HMGB1 inhibitors, neutralizing antibodies, and epigenetic modulators—show potential in restoring genomic homeostasis and mitigating age-related pathologies. Nevertheless, significant challenges remain, including elucidating HMGB1's roles in nutrient sensing and psychosocial stress, fine-tuning interventions to preserve its nuclear functions while minimizing extracellular toxicity, and establishing efficacy in human clinical settings. Addressing these gaps may position HMGB1 as a promising multifunctional target for delaying aging and translating preclinical findings into clinical applications.

Keywords: aging, HMGB1, hallmarks of aging, preclinical studies

Introduction

Aging is widely recognized as the progressive accumulation of cellular and tissue alterations that increase vulnerability to chronic diseases and mortality.[1] It is strongly linked to cardiovascular disorders, chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD), and degenerative diseases including arthritis.[2] Even in the absence of overt pathology, aging manifests through complex structural, functional, and molecular changes across multiple biological levels.[3]

The hallmarks of aging provide a unifying framework to describe these processes, encompassing fourteen interconnected mechanisms.[4] These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and chronic inflammation. Together, these hallmarks drive tissue degeneration by accumulating molecular damage, disrupting homeostasis, and impairing regenerative capacity. Importantly, preclinical studies indicate that interventions targeting these mechanisms can extend health span, underscoring the translational potential of mechanistic insights.[5]

Among the molecular regulators implicated in these hallmarks, high-mobility group box 1 (HMGB1) has attracted increasing attention as a potential modulator of aging biology.[6,7] HMGB1 is a highly conserved, non-histone chromatin-binding protein with diverse functions. In the nucleus, it safeguards genomic stability by maintaining chromatin architecture, facilitating DNA repair,[8] and coordinating transcriptional regulation. In the cytoplasm, it influences

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autophagy and innate immune responses. Once released into the extracellular space, HMGB1 acts as a prototypical damage-associated molecular pattern (DAMP), engaging receptors such as TLR4 and RAGE to activate NF-κB and MAPK signaling pathways, thereby amplifying inflammation. Through these context-dependent roles, HMGB1 has been implicated in multiple age-related pathologies, including neurodegenerative, cardiovascular, and metabolic disorders.

Nevertheless, the role of HMGB1 in aging remains incompletely defined and, in some contexts, controversial. On one hand, HMGB1 exerts protective nuclear functions that preserve genomic integrity; on the other, its extracellular release promotes chronic inflammation and tissue injury. These dual and seemingly opposing functions complicate interpretation and highlight unresolved questions. Moreover, most available evidence derives from preclinical studies, with limited validation in human aging, raising concerns about clinical relevance. Notably, several hallmarks—such as deregulated nutrient sensing, loss of proteostasis, and psychosocial influences—remain insufficiently connected to HMGB1 at a mechanistic level.

Clarifying these inconsistencies will be essential to define HMGB1's contribution to aging biology. This review synthesizes current evidence on HMGB1 in age-related processes, evaluates its dual context-dependent functions, and discusses its feasibility as a therapeutic target to modulate the hallmarks of aging, with the ultimate aim of translating mechanistic insights into strategies that promote healthy aging and alleviate the burden of age-associated diseases.

HMGB1 and the Hallmarks of Aging: A Mechanistic Link

As proposed by López-Otín and colleagues,[9] a number of fourteen interconnected hallmarks influence the process of aging by collectively driving functional decline and disease susceptibility:[4] (1) genomic instability, characterized by progressive DNA damage accumulation from endogenous and exogenous stressors;[10,11] (2) telomere attrition, marked by replication-dependent shortening and oxidative erosion of chromosomal termini;[12,13] (3) epigenetic alterations, involving dysregulated DNA methylation, histone modifications, and non-coding RNA networks;[14] (4) loss of proteostasis, reflecting impaired protein synthesis, folding, and degradation systems;[15,16] (5) disabled macroautophagy, driven by age-related declines in autophagic flux and lysosomal efficiency;[17,18] (6) deregulated nutrient sensing, encompassing mTOR, AMPK, and sirtuin pathway imbalances;[19,20] (7) mitochondrial dysfunction, featuring bioenergetic collapse, ROS over-production, and mtDNA mutations;[21,22] (8) cellular senescence, a state of irreversible growth arrest with dual roles in tumor suppression and tissue degeneration;[23,24] (9) stem cell exhaustion, defined by diminished regenerative capacity due to oxidative and epigenetic stress;[9,25] (10) altered intercellular communication, mediated by pro-inflammatory SASP factors and disrupted signaling cascades;[26,27] (11) chronic inflammation, a low-grade systemic state perpetuated by DAMPs and immune dysregulation;[28,29] (12) dysbiosis, involving gut microbial imbalance and metabolite-driven pathologies;[30,31] (13) extracellular matrix remodeling, characterized by AGE accumulation, collagen fragmentation, and mechanotransductive stress;[32,33] and (14) psychosocial isolation, linked to neuroendocrine dysregulation and accelerated inflammatory aging.[34] Emerging preclinical evidence indicates that HMGB1 contributes to eleven hallmarks of aging through its dual intracellular and extracellular functions. In contrast, direct mechanistic studies linking HMGB1 with psychological isolation, nutrient sensing, and proteostasis are still lacking. Accordingly, this review focuses on the interactions between HMGB1 and the remaining eleven hallmarks of aging. The following sections will delineate the mechanistic connections between HMGB1 and these hallmarks. Figure 1 illustrates three representative channels of HMGB1.

HMGB1 and Genomic Instability

HMGB1 plays a multifaceted role in maintaining genomic stability, primarily through its regulation of DNA damage repair pathways, particularly base excision repair (BER). HMGB1 inhibits single-nucleotide BER by competitively binding to the 5′-deoxyribose phosphate (dRP) group, thereby blocking the dRP lyase activity of DNA polymerase β (Pol β). Simultaneously, it stimulates long-patch BER by enhancing flap endonuclease 1 (FEN1)-mediated cleavage of displaced DNA flaps.[35] This dual regulation promotes long-patch BER, which is crucial for resolving complex lesions, but it may also contribute to trinucleotide repeat instability. Experimental evidence from HMGB1 knockout ($HMGB1^{-/-}$) mouse embryonic fibroblasts (MEFs) shows that HMGB1 enhances AP endonuclease 1 (APE1) incision activity under limiting conditions, leading to increased accumulation of single-strand breaks (SSBs) in the presence of methoxyamine

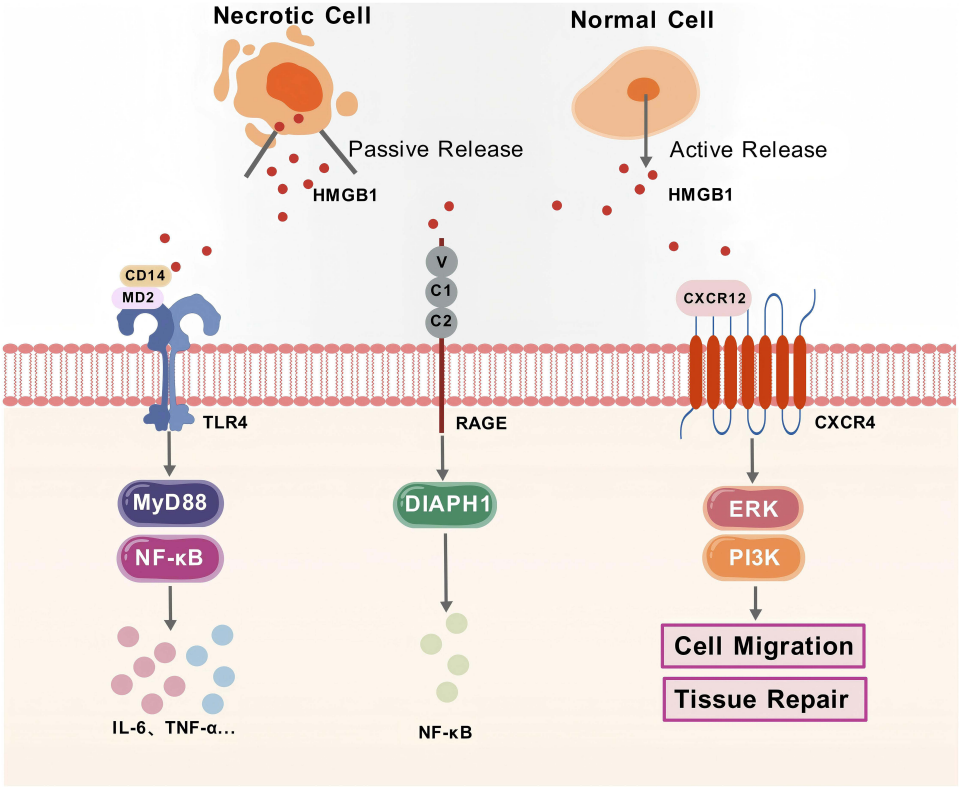

Figure 1 Receptors and co-receptors/partners of HMGB1 and their functions.

(MX)-adducted abasic sites.[36] Additionally, in vitro experiments with (CAG)20-containing substrates reveal that HMGB1 promotes CAG repeat expansion. This effect is mediated through the stimulation of APE1's incision activity, generating more single-strand break intermediates during the BER process.[36] These findings underscore HMGB1's dual role as both a facilitator of repair and a potential contributor to genomic instability in repetitive DNA contexts. Moreover, HMGB1 interacts with chromatin remodeling factors to enhance lesion accessibility and post-repair chromatin restoration, further linking its structural and enzymatic functions to genome integrity.[37]

HMGB1 and Telomere Attrition

HMGB1 regulates telomere stability by specifically recognizing G-quadruplex structures in telomeric regions through its DNA-binding domains (A-box and B-box).[38] Knockout of HMGB1 significantly increases telomeric DNA damage foci (γ-H2AX foci),[39] suggesting a potential role for HMGB1 in telomere maintenance. Furthermore, HMGB1 facilitates the recruitment of telomere-protective protein complexes, such as TRF2, to telomeric regions,[40] thereby preventing telomere fusion and chromosomal abnormalities. During cellular senescence, HMGB1 translocates from the nucleus to the cytoplasm, reducing its nuclear levels and impairing its protective effects on telomeric G-quadruplex structures.[41] In human fibroblast models, loss of intracellular HMGB1 strongly correlates with telomere shortening and upregulation of senescence markers (eg, p21 and SA-β-gal).[42] Extracellular HMGB1 exacerbates telomeric oxidative damage by promoting ROS generation via RAGE/TLR4 signaling, creating a feedback loop between senescence and inflammation.[42,43] Given HMGB1's dual roles in telomere maintenance—nuclear protection and extracellular pro-aging signaling—therapeutic strategies must be carefully targeted. Inhibition of extracellular HMGB1 (eg, using anti-HMGB1 neutralizing antibodies) effectively mitigates telomere damage-associated senescence, while enhancing nuclear HMGB1 function (eg, through small-molecule agonists) may delay telomere shortening.

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HMGB1 and Epigenetic Alterations

HMGB1 plays a central role in modulating epigenetic processes, particularly through its dynamic interaction with chromatin structure and immune regulation. As a chromatin-binding protein, HMGB1 facilitates chromatin relaxation and transcriptional activation by interacting with nucleosomes, thereby enhancing the accessibility of transcription factors in the nucleus.[44] Pharmacological inhibition of DNA methyltransferases (DNMTi), such as decitabine, induces the translocation of HMGB1 from the nucleus to the cytoplasm, followed by its release into the extracellular space.[45] Epigenetic modifiers further influence HMGB1-mediated immune modulation by altering histone acetylation and DNA methylation patterns. Histone deacetylase inhibitors (HDACi), such as vorinostat and panobinostat, induce chromatin hyperacetylation, disrupting HMGB1-chromatin interactions and promoting its release. HMGB1 has also emerged as a key player in neuropsychiatric disorders, where it interacts with epigenetic mechanisms. Predominantly expressed in microglia, HMGB1 is implicated in inflammation-driven pathogenesis.[46,47]

Preclinical evidence indicates that HMGB1 expression is regulated by DNA methylation, histone deacetylases (HDAC4/5), and microRNA-129 (miR-129).[48] Chronic stress activates hippocampal microglia, leading to depression-like behaviors in rats. Such stress elevates HMGB1 expression in hippocampal microglia, and exogenous HMGB1 infusion into the hippocampus has been shown to induce depression.[49] This stress-induced HMGB1 overexpression can be attenuated by minocycline or imipramine, both known suppressors of microglial activation. Moreover, DNA hypomethylation of the HMGB1 promoter has been linked to increased HMGB1 expression in cardiac progenitor cells under hypoxic conditions, indicating context-dependent epigenetic regulation.[50] Pharmacological inhibitors further modulate HMGB1 activity, offering potential therapeutic avenues to reverse aberrant histone acetylation patterns. Collectively, these findings link HMGB1's role in neuropathology to epigenetic dysregulation, involving changes in DNA methylation, histone modifications, and interactions with specific microRNAs (eg, HMGB1 regulation by miR-129), though evidence for HMGB1–miRNA interplay remains limited.

HMGB1 and Disabled Macroautophagy

HMGB1 is a critical mediator of autophagy in various diseases, such as diabetic retinopathy (DR), where it orchestrates pathological progression through the modulation of the autophagy-lysosomal pathway.[51] Hyperglycemia-induced upregulation of HMGB1 exacerbates DR by activating cathepsin B (CTSB)-dependent lysosomal membrane permeabilization (LMP), compromising lysosomal integrity, and impairing autophagic flux. This disruption leads to the abnormal accumulation of SQSTM1/p62. Lysosomal dysfunction triggers inflammation in retinal pigment epithelial (RPE) cells, with elevated secretion of IL-1β, IL-6, and VEGF,[52] while simultaneously inducing mitochondrial dysfunction and apoptosis through excessive ROS production.[53] The HMGB1-CTSB-LMP axis disrupts lysosomal stability under high-glucose conditions, characterized by excessive CTSB release, impaired lysosomal acidification, and reduced cathepsin activity. These changes hinder the fusion of autophagosomes with lysosomes and impede substrate degradation. Additionally, the cytosolic leakage of lysosomal contents activates mitochondrial apoptotic pathways and NLRP3 inflammasome signaling, creating a self-perpetuating cycle of cellular damage. Notably, pharmacological inhibition of HMGB1 restores lysosomal membrane integrity by downregulating CTSB,[54,55] enhances lysosomal acidification and enzymatic activity, and alleviates RAGE/ROS-mediated inflammatory cascades, ultimately mitigating mitochondrial injury and slowing DR progression.[52,56]

HMGB1 and Mitochondrial Dysfunction

Mitochondrial dysfunction is one of the aging hallmarks.[57] HMGB1 has been shown to translocate to mitochondria, where it mediates mitochondrial fission, leading to mitochondrial DNA (mtDNA) leakage into the cytoplasm. This, in turn, activates the cGAS-STING pathway and creates an extracellular inflammatory microenvironment, which is associated with necrotic apoptosis and accelerates peripheral cellular senescence.[58] HMGB1 induces mitochondrial dysfunction, characterized by increased mitochondrial superoxide release, decreased mitochondrial membrane potential, reduced mtDNA content, and impaired ATP generation. Both mitochondrial DNA mutations and oxidative stress contribute to aging, which is a major risk factor for neurodegenerative diseases. Consequently, mitochondrial dysfunction

is closely linked to the pathogenesis of Parkinson's disease (PD), including mtDNA mutations, electron transport chain damage, and alterations in mitochondrial dynamics and morphology. For instance, rotenone treatment has been reported to cause mitochondrial deformation and crest swelling in human neuroblastoma cells. HMGB1 overexpression exacerbates these effects, while inhibition of HMGB1 via siRNA-HMGB1 partially reduces these mitochondrial changes.[59,60] Emerging evidence highlights the therapeutic potential of HMGB1 inhibition in restoring mitochondrial homeostasis by modulating inflammatory and oxidative stress pathways.[61] Notably, in a cerebral ischemia/reperfusion injury model, pharmacological inhibition of HMGB1 or downregulation of miR-320 significantly restored mitochondrial function, as evidenced by reduced mitochondrial ROS accumulation, replenished endogenous antioxidants (eg, MnSOD and GSH), diminished lipid peroxidation markers (eg, 8-isoprostane), and improved ATP synthesis. Mechanistically, HMGB1 blockade disrupts the HMGB1/NF-κB signaling axis, suppressing the expression of pro-inflammatory cytokines (TNF-α, IL-1β) and adhesion molecules (ICAM-1, VCAM-1), thereby mitigating the synergistic damage caused by inflammation and oxidative stress on mitochondrial integrity. Furthermore, HMGB1 inhibitors indirectly attenuate miR-320-mediated regulation of HMGB1 overexpression, enhancing mitochondrial functional preservation. These findings underscore the potential of targeting HMGB1 as a therapeutic strategy to mitigate mitochondrial destabilization in pathological conditions.[62]

HMGB1 and Cellular Senescence

HMGB1, involved in DNA organization and repair, plays a critical role in regulating cellular senescence through its Box A domain. For example, Secretomes from HMGB1 Box A-over-expressing adipose-derived stem cells (BoxA-SC) effectively reverse PM2.5-induced cellular senescence by inducing the expression of stem cell markers such as OCT4, NANOG, and SOX2.[63] Mechanistically, BoxA-SC attenuates senescence-associated β-galactosidase (SA-β-gal) activity, downregulates cell cycle inhibitors p21 and p16, and suppresses the release of SASP factors, including interleukin-1α (IL-1α), C-X-C motif chemokine ligand 1 (CXCL1), and interleukin-7 (IL-7). These effects are attributed to BoxA-mediated stabilization of genomic microenvironments and activation of stem cell regenerative capacity, which counteract oxidative stress-driven senescence pathways. Collectively, these findings provide a mechanistic basis for secretome-based anti-aging therapies targeting age-related degenerative disorders.[64] Additionally, HMGB1 has been implicated in mediating tau oligomer (TauO)-induced cellular senescence. Its extracellular release activates the p38-MAPK and NF-κB signaling pathways, driving the SASP and promoting astrocytic senescence and paracrine senescence in tauopathies, such as Alzheimer's disease (AD) and frontotemporal dementia (FTD).[65] Notably, Galkwad et al[66] demonstrated that TauO exposure triggers the nucleo-cytoplasmic translocation and release of HMGB1 in astrocytes, significantly elevating the expression of senescence markers, including p16INK4A and SA-β-gal. Pharmacological inhibition of HMGB1 release using ethyl pyruvate (EP) and glycyrrhizic acid (GA) significantly reduced cellular senescence phenotypes in vitro, as evidenced by decreased DNA damage markers (γH2AX foci) and inflammatory cytokines (IL-6/TNF-α).[67] Additionally, these inhibitors ameliorated TauO burden, neurofibrillary tangle (NFT) deposition, and senescent cell accumulation in the brains of hTau transgenic mice, accompanied by improved cognitive performance. Therefore, targeting the HMGB1-SASP axis may be a promising therapeutic strategy for mitigating tau pathology progression in neurodegenerative disorders.

HMGB1 and Altered Intercellular Communication

HMGB1 plays an important role in modulating intercellular communication under pathological conditions. Extracellular HMGB1 binds to receptors such as Toll-like receptors (TLRs) and RAGE, activating downstream signaling pathways like NF-κB and the NLRP3 inflammasome.[68] This cascade promotes the secretion of pro-inflammatory cytokines (eg, IL-1β, TNF-α) and chemokines, amplifying neuroinflammation and disrupting cellular homeostasis. In the SOD1G93A mouse model of amyotrophic lateral sclerosis (ALS), upregulated HMGB1 during the symptomatic stage correlates with NLRP3 inflammasome activation, microgliosis, and astrocyte dysfunction, exacerbating motor neuron degeneration. HMGB1 also synergizes with microRNA-155, a pro-inflammatory regulator, to sustain neurotoxic glial phenotypes[69] and impair phagocytic clearance by reducing MFG-E8 expression.[70] Collectively, HMGB1 mediates pathological

intercellular communication, bridging cellular damage with systemic inflammatory responses and representing a promising therapeutic target for diseases characterized by dysregulated inflammation.

HMGB1 and Chronic Inflammation

HMGB1 is a well-characterized DAMP that can mediate inflammatory and immune responses. Age-related increases in circulating HMGB1 concentrations may contribute to the pathogenesis of chronic low-grade inflammation, obesity, and subclinical cardiovascular disease.[71] HMGB1 is central to obesity-associated chronic inflammation. Adipose tissue serves as a major source of HMGB1, with expression levels being twice as high in obese individuals compared to those with normal weight.[72] Mechanistically, HMGB1 released through adipocyte necrosis, can activate local immune cells and then lead to a self-amplifying positive feedback loop, enhancing inflammatory signaling. A longitudinal cohort study of young adults revealed that HMGB1 bound to Toll-like receptors (TLR2/4) and RAGE[73] would activate key inflammatory pathways such as NF-κB and MAPK. This interaction triggers a cascade of pro-inflammatory cytokine release (eg, TNF-α, IL-6), perpetuating chronic inflammation and immune dysregulation. Cancer, often the end stage of chronic inflammation, involves HMGB1 as an inflammatory amplifier in the tumor microenvironment. HMGB1 activates dendritic cells (DCs) via the TLR4/p38-MAPK pathway, upregulating co-stimulatory molecules (CD80/CD86) and maturation markers (CD83), while promoting the secretion of pro-inflammatory cytokines (IL-6, IL-12, IL-23).[74,75] In lung cancer models, HMGB1 upregulates CXCR3/CCR5 chemokine receptors on DCs, enhancing their tumor-directed migration. Furthermore, HMGB1-driven IL-23 secretion promotes Th17 polarization, while HMGB1-mediated DC-derived TSLP signaling amplifies regulatory T cell (Treg) activation, collectively fostering an immunosuppressive microenvironment.[76]

HMGB1 and Stem Cell Exhaustion

HMGB1 impairs stem cell function through three interconnected mechanisms: promoting a pro-inflammatory microenvironment, disrupting oxidative stress regulation, and inducing pyroptosis. In mesenchymal stem cells (MSCs), HMGB1 activates the TLR4/p38-MAPK-NLRP3 inflammasome axis, driving the release of IL-1β, IL-6, and TNF-α, which creates a chronic inflammatory environment that inhibits MSC survival and function.[77] Simultaneously, HMGB1 downregulates S-lactoylglutathione metabolism, depleting intracellular glutathione (GSH) levels and exacerbating oxidative stress-induced mitochondrial dysfunction. Additionally, HMGB1 upregulates the NLRP3/Caspase-1/GSDMD-N pathway, triggering microglial pyroptosis and DAMPs, establishing a self-amplifying cycle that accelerates MSC functional decline.[78] In a cecal ligation and puncture (CLP) model, MSC-derived exosomes (MSCs-exo) combined with antibiotic therapy reduced hippocampal HMGB1 expression by 60%, suppressed NLRP3/Caspase-1/GSDMD-N levels, reversed pyroptosis, and improved cognitive function.[79] Dual-luciferase reporter assays further confirmed that MSC-exo-delivered miR-140-3p binds to the 3'UTR of HMGB1 mRNA, reducing HMGB1 protein levels. These findings demonstrate that MSC-exo-mediated miR-140-3p delivery alleviates microglial pyroptosis, restores S-lactoylglutathione metabolism, and rescues cognitive deficits in CLP mice, highlighting HMGB1 inhibition as a promising therapeutic strategy for sepsis-associated encephalopathy.

HMGB1 and Dysbiosis

Gut microbiota composition progressively diverges with aging and is associated with microbial metabolites involved in immunomodulation, inflammation, and senescence. Clinical data have shown elevated HMGB1 levels in older cohorts, suggesting an interplay between dysbiosis and HMGB1 in the pathogenesis of nonalcoholic fatty liver disease (NAFLD).[80] In preclinical models, gut microbiota imbalance was linked to intestinal barrier damage and upregulated HMGB1 expression, and further analyses indicated that HMGB1 can be transported from the gut to the liver via exosomes, thereby promoting lipid accumulation, inflammation, and disease progression.[81,82] Consistently, pharmacological inhibition of HMGB1 release (eg, glycyrrhizic acid) alleviated hepatic steatosis and downregulated pro-inflammatory cytokines.

Furthermore, the association between HMGB1 and aging was supported by the finding that serum HMGB1 levels of older healthy adults are increased by 16% than those of younger ones.[83] Elevated HMGB1 levels were negatively correlated with muscle strength ($r = -0.410$) and daily physical activity ($r = -0.483$). Age-related gut dysbiosis compromises intestinal barrier integrity, resulting in HMGB1 release and concomitant increases in serum zonulin (a biomarker of intestinal permeability) in older adults. Both factors significantly correlate with inflammatory cytokine

levels and frailty indices. These findings suggest a possible role of HMGB1 in age-related gut pathology, potentially through effects on intestinal permeability and inflammation, which may in turn influence "gut-liver axis" dysfunction during aging. However, these associations remain correlative and require further validation. Preclinical studies showed that probiotic treatments (eg, Bifidobacterium longum and the multi-species formulation VSL#3®) reduce HMGB1 levels and improve intestinal barrier integrity, thereby interrupting the HMGB1–inflammation–gut leakage cycle.[83,84]

HMGB1 and Extracellular Matrix Changes

In osteoarthritis (OA), suppression of Nrf2 leads to HMGB1 upregulation, which subsequently activates NF-κB signaling through RAGE. This activation increases the expression of pro-inflammatory cytokines (eg, IL-6, TNF-α) and ECM-degrading enzymes such as MMP13 and ADAMTS-5, thereby accelerating the breakdown of cartilage components including type II collagen and aggrecan.[85,86] Experimental studies further show that enhancing Nrf2 or silencing HMGB1 can reverse IL-1β–induced ECM degradation and chondrocyte apoptosis, whereas recombinant HMGB1 counteracts the protective effects of Nrf2 activation.[80] Immunohistochemical analyses of osteoarthritic cartilage demonstrated significantly elevated HMGB1 levels, which correlated with apoptosis markers (eg, BAX and cleaved caspase-3) and inflammatory cytokine expression.[87] Collectively, these findings suggest that HMGB1 contributes to ECM metabolic imbalance and cartilage degeneration through the Nrf2/HMGB1/NF-κB axis, and may represent a potential therapeutic target in OA. A detailed summary of the related mechanisms, effects, and therapeutic implications is provided in Table 1. Figures 2 and 3 illustrate the key interactions between HMGB1 and the 14 hallmarks of aging.

Table 1 Summary of HMGB1's Involvement Across the 14 Hallmarks of Aging

Hallmark of Aging	HMGB1 Mechanism Involved	Direction of Effect (Pro-Aging ↑/Anti-Aging ↓)	Preclinical Evidence	Therapeutic Implication
Genomic Instability	Regulates BER; modulates APE1 and FEN1 activity	↑	√	Target HMGB1-APE1 axis
Telomere Attrition	Stabilizes G-quadruplex; recruits TRF2; oxidative damage via RAGE	↑	√	Enhance nuclear HMGB1 / inhibit extracellular
Epigenetic Alterations	Alters DNA methylation; histone acetylation; miRNA interactions (limited evidence)	↑	√	HDAC/DNMT inhibitors; miRNA targeting
Loss of Proteostasis	Not well defined	?	×	Underexplored
Impaired Macroautophagy	Disrupts lysosomal membrane via CTSB; impairs autophagic flux	↑	√	HMGB1 inhibition restores autophagy
Deregulated Nutrient Sensing	Minimal data available	?	×	Research gap
Mitochondrial Dysfunction	Induces fission; activates cGAS-STING; ROS accumulation	↑	√	Antioxidants; HMGB1 inhibitors
Cellular Senescence	Promotes SASP via NF-κB; p16/p21 upregulation	↑	√	Box A peptides; EP/GA
Stem Cell Exhaustion	TLR4/NLRP3-mediated pyroptosis and inflammation	↑	√	miR-140-3p; MSC-exosomes
Altered Intercellular Communication	Activates NF-κB, inflammasome via TLR4/RAGE	↑	√	Anti-HMGB1 antibodies
Chronic Inflammation	Canonical DAMP; activates TLR4/RAGE → cytokine storm	↑	√	Ethyl pyruvate; glycyrrhizic acid
Dysbiosis	Exosomal transport from gut to liver; epithelial leakage	↑	√	Probiotics (VSL#3, Bifidobacterium)
ECM Remodeling	Upregulates MMP13/ADAMTS-5 via NF-κB; cartilage degradation	↑	√	Target Nrf2/HMGB1 axis
Psychosocial Isolation	Not covered in current literature	?	×	Potential future direction

Note: ↑ indicates pro-aging effect; ↓ indicates anti-aging effect; √ denotes available preclinical evidence; × indicates lack of evidence; ? Denotes unclear or underexplored mechanism.

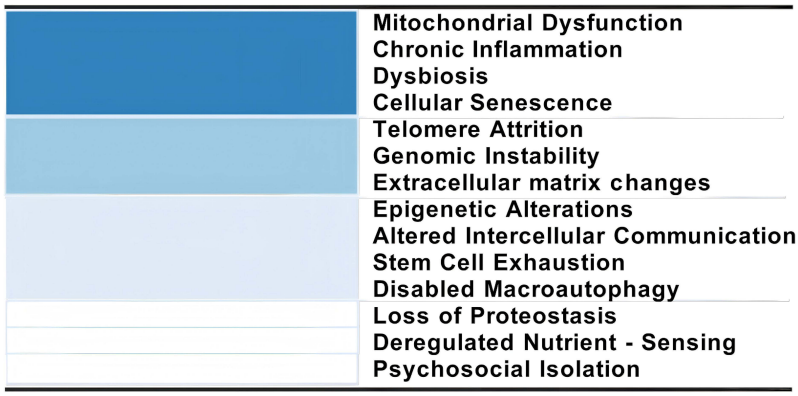

Figure 2 The relationship strength between HMGB1 and the hallmarks of aging. This figure summarizes the reported associations between HMGB1 and the 14 recognized hallmarks of aging based on literature reviews. The intensity of the color indicates the relative strength of the reported association: darker blue denotes a stronger relationship, while blank areas indicate no currently reported connection in the literature.

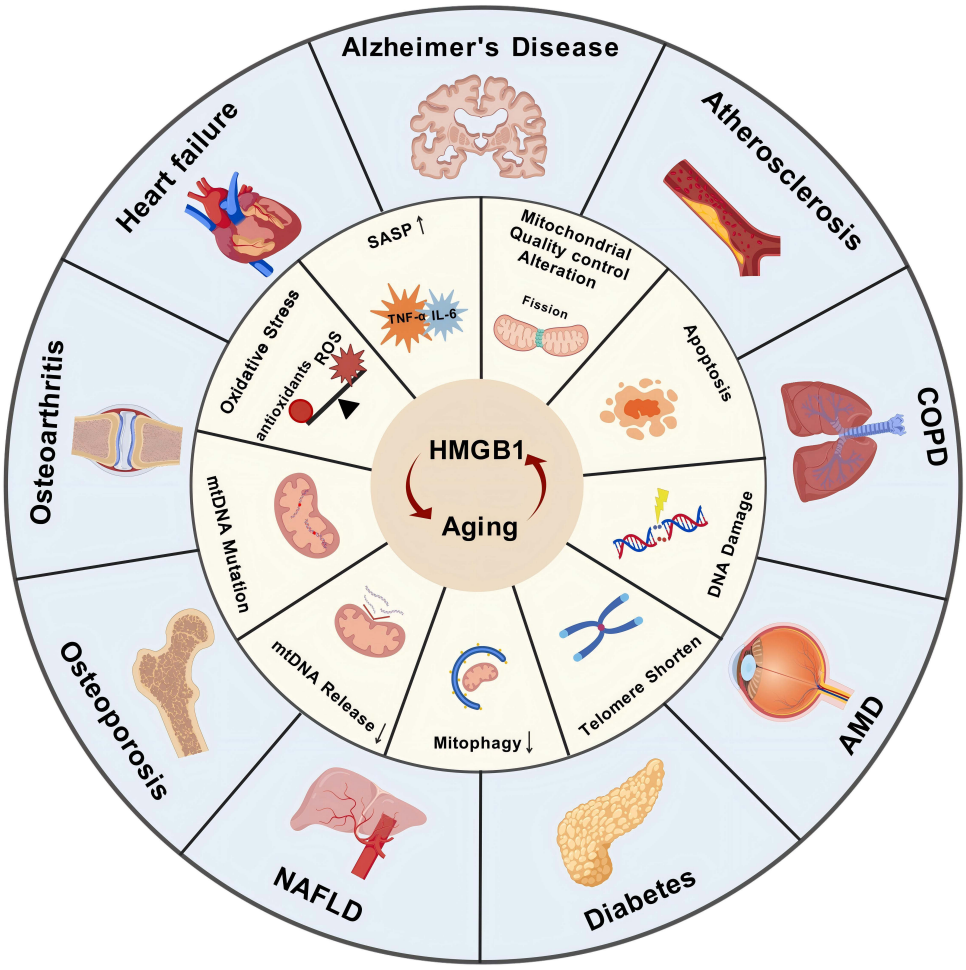

Figure 3 Pre-clinical data supporting the relationship between diseases and hallmarks of aging and available clinical evidence about the potential impact of HMGB1 on the hallmarks of aging.
Note: ↑ represents an increase; ↓ represents a decrease.

Discussion and Future Perspectives

Aging is a complex biological process characterized by the progressive decline of cellular and systemic homeostasis, ultimately resulting in functional impairment and increased vulnerability to age-related diseases. The fourteen recognized

aging hallmarks — form an interdependent network. These hallmarks synergistically contribute to cellular damage accumulation and drive the progression of aging-associated pathologies.

Recent evidence indicates that HMGB1 plays a multifaceted regulatory role across these hallmarks through both nuclear and extranuclear mechanisms. This review systematically delineates the mechanistic links of HMGB1 to the eleven aging hallmarks of the fourteen. As a result, the targeted modulation of HMGB1 translocation between the nucleus and cytoplasm has emerged as a promising therapeutic strategy for decelerating aging processes and mitigating age-related diseases.

Despite encouraging preclinical findings, several challenges hinder the clinical translation of HMGB1-targeted therapies. A key issue is reconciling its protective nuclear functions in DNA repair with its pro-inflammatory extracellular activities. Current approaches—including small-molecule inhibitors (eg, ethyl pyruvate, glycyrrhizin), neutralizing antibodies (eg, 2G7), and epigenetic modulators—have shown promise but require rigorous clinical validation. Small molecules are accessible yet prone to off-target effects, antibodies offer specificity but face delivery and immunogenicity barriers, and epigenetic modulators provide reversibility but raise concerns regarding specificity and long-term safety. While evidence largely derives from preclinical models, agents such as glycyrrhizin and HMGB1-binding peptides have shown efficacy in inflammatory diseases, offering proof-of-concept for clinical feasibility. These advances underscore the need for longitudinal human studies and early-phase clinical trials to evaluate HMGB1-targeted strategies in aging contexts.

Nonetheless, increasing attention has been directed toward the therapeutic potential of HMGB1 in human diseases. For example, HMGB1 inhibitors such as glycyrrhizin and specific binding peptides (eg, cIY8) have demonstrated efficacy in alleviating inflammation and pruritus in atopic dermatitis models, with the possibility of topical application in patients.[88] Similarly, studies have highlighted the involvement of HMGB1 in inflammatory skin disorders, further supporting its relevance as a therapeutic target.[89] Although these investigations are disease-specific rather than aging-focused, they provide proof-of-concept that pharmacological modulation of HMGB1 is clinically feasible.

Importantly, potential biomarkers related to HMGB1 activity—such as its nuclear-to-cytoplasmic translocation, circulating HMGB1 release, and downstream SASP factors (eg, IL-6, IL-8, MMPs, and PAI-1)[90]—may serve as clinically relevant indicators for monitoring HMGB1 dynamics during aging or therapeutic intervention.

Future studies should extend these insights to aging contexts. In particular, longitudinal human studies are urgently needed to clarify how HMGB1 dynamics correlate with aging phenotypes, frailty indices, and age-related diseases at the population level. Moreover, early-phase clinical trials evaluating HMGB1-targeted interventions in relevant age-associated conditions could provide critical translational evidence. By bridging preclinical findings with human research, these efforts will be essential for determining whether HMGB1-targeted strategies can be safely and effectively leveraged to delay aging and mitigate its pathological consequences.

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Disclosure

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References

1. Tosato M, Zamboni V, Ferrini A, Cesari M. The aging process and potential interventions to extend life expectancy. *Clin Interv Aging*. 2007;2(3):401–412.

2. Shek N, Choy A-M, Lang CC, et al. Accelerated elastin degradation by age-disease interaction: a common feature in age-related diseases. *Npj Aging*. 2024;10(1):15. doi:10.1038/s41514-024-00143-7
3. Laffon B, Bonassi S, Costa S, Valdiglesias V. Genomic instability as a main driving factor of unsuccessful ageing: potential for translating the use of micronuclei into clinical practice. *Mutation Res Rev* 2021;787:108359. doi:10.1016/j.mrrev.2020.108359
4. Kroemer G, Maier AB, Cuervo AM, et al. From geroscience to precision geromedicine: understanding and managing aging. *Cell*. 2025;188 (8):2043–2062. doi:10.1016/j.cell.2025.03.011
5. Turgeon MO, Perry NJS, Poulogiannis G. DNA damage, repair, and cancer metabolism. *Front Oncol*. 2018;8:15. doi:10.3389/fonc.2018.00015
6. Ohndorf UM, Rould MA, He Q, Pabo CO, Lippard SJ. Basis for recognition of cisplatin-modified DNA by high-mobility-group proteins. *Nature*. 1999;399(6737):708–712. doi:10.1038/21460
7. Li J, Kokkola R, Tabibzadeh S, et al. Structural basis for the proinflammatory cytokine activity of high mobility group box 1. *Mol Med*. 2003;9 (1–2):37–45. doi:10.1007/BF03402105
8. Ugrinova I, Zlateva S, Pashev IG, Pasheva EA. Native HMGB1 protein inhibits repair of cisplatin-damaged nucleosomes in vitro. *Int J Biochem Cell Biol*. 2009;41(7):1556–1562. doi:10.1016/j.biocel.2009.01.010
9. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell*. 2023;186(2):243–278. doi:10.1016/j.cell.2022.11.001
10. Petropoulos M, Champeris TS, Taraviras S, Lygerou Z. Replication licensing aberrations, replication stress, and genomic instability. *Trends Biochem Sci*. 2019;44(9):752–764. doi:10.1016/j.tibs.2019.03.011
11. Madabhushi R, Pan L, Tsai L-H. DNA damage and its links to neurodegeneration. *Neuron*. 2014;83(2):266–282. doi:10.1016/j.neuron.2014.06.034
12. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L. Physical activity and telomere length: impact of aging and potential mechanisms of action. *Oncotarget*. 2017;8(27):45008–45019. doi:10.18632/oncotarget.16726
13. La Torre A, Lo Vecchio F, Greco A. Epigenetic mechanisms of aging and aging-associated diseases. *Cells*. 2023;12(8):1163. doi:10.3390/cells12081163
14. Labbadia J, Morimoto RI. The biology of proteostasis in aging and disease. *Annu Rev Biochem*. 2015;84(1):435–464. doi:10.1146/annurev-biochem-060614-033955
15. Guo J, Huang X, Dou L, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. *Signal Transduct Target Ther*. 2022;7(1):391. doi:10.1038/s41392-022-01251-0
16. Lu YX, Regan JC, Eßer J, et al. A TORC1-histone axis regulates chromatin organisation and non-canonical induction of autophagy to ameliorate ageing. *Elife*. 2021;10:e62233.
17. Lapierre LR, Kumsta C, Sandri M, Ballabio A, Hansen M. Transcriptional and epigenetic regulation of autophagy in aging. *Autophagy*. 2015;11 (6):867–880. doi:10.1080/15548627.2015.1034410
18. Wu Q, Tian A-L, Li B, et al. IGF1 receptor inhibition amplifies the effects of cancer drugs by autophagy and immune-dependent mechanisms. *J Immunother Cancer*. 2021;9(6):e002722. doi:10.1136/jitc-2021-002722
19. Efeyan A, Comb WC, Sabatini DM. Nutrient-sensing mechanisms and pathways. *Nature*. 2015;517(7534):302–310.
20. Suomalainen A, Nunnari J. Mitochondria at the crossroads of health and disease. *Cell*. 2024;187(11):2601–2627. doi:10.1016/j.cell.2024.04.037
21. López-Otín C, Kroemer G. Hallmarks of health. *Cell*. 2021;184(7):1929–1939. doi:10.1016/j.cell.2021.03.033
22. Zhang L, Pitcher LE, Yousefzadeh MJ, Niedernhofer LJ, Robbins PD, Zhu Y. Cellular senescence: a key therapeutic target in aging and diseases. *J Clin Invest*. 2022;132(15):e158450. doi:10.1172/JCI158450
23. Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A. Cellular senescence: aging, cancer, and injury. *Physiol Rev*. 2019;99 (2):1047–1078. doi:10.1152/physrev.00020.2018
24. Blanpain C, Fuchs E. Epidermal homeostasis: a balancing act of stem cells in the skin. *Nat Rev Mol Cell Biol*. 2009;10(3):207–217. doi:10.1038/nrm2636
25. Mittelbrunn M, Sánchez MF. Intercellular communication: diverse structures for exchange of genetic information. *Nat Rev Mol Cell Biol*. 2012;13 (5):328–335. doi:10.1038/nrm3335
26. Bhatt V, Tiwari AK. Sirtuins, a key regulator of ageing and age-related neurodegenerative diseases. *Int J Neurosci*. 2023;133(10):1167–1192. doi:10.1080/00207454.2022.2057849
27. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol a Biol Sci Med Sci*. 2014;69(Suppl 1):S4–S9. doi:10.1093/gerona/glu057
28. Shen PP, Zhang LB, Jiang XW, Yu BY, Zhang JA. Targeting HMGB1 and its interaction with receptors: challenges and future directions. *J Med Chem*. 2024;67(24):21671–21694. doi:10.1021/acs.jmedchem.4c01912
29. Claesson MJ, Jeffery IB, Conde S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature*. 2012;488 (7410):178–184. doi:10.1038/nature11319
30. Cani PD, Van HM, Lefort C, et al. Microbial regulation of organismal energy homeostasis. *Nat Metab*. 2019;1(1):34–46. doi:10.1038/s42255-018-0017-4
31. Mavrogonatou E, Papadopoulou A, Pratsinis H, Kletsas D. Senescence-associated alterations in the extracellular matrix: deciphering their role in the regulation of cellular function. *Am J Physiol Cell Physiol*. 2023;325(3):C633–C647. doi:10.1152/ajpcell.00178.2023
32. Uribarri J, Cai W, Peppa M, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. *J Gerontol Biol Sci Med Sci*. 2007;62(4):427–433. doi:10.1093/gerona/62.4.427
33. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–1217. doi:10.1016/j.cell.2013.05.039
34. López-Otín C, Kroemer G. The missing hallmark of health: psychosocial adaptation. *Cell Stress*. 2024;8:21–50. doi:10.15698/cst2024.03.294
35. Prasad R, Liu Y, Deterding LJ, et al. HMGB1 is a cofactor in mammalian base excision repair. *Mol Cell*. 2007;27(5):829–841. doi:10.1016/j.molcel.2007.06.029
36. Liu Y, Prasad R, Wilson SH. HMGB1: roles in base excision repair and related function. *Biochim Biophys Acta*. 2010;1799(1–2):119–130. doi:10.1016/j.bbagrm.2009.11.008
37. Bonaldi T. The DNA chaperone HMGB1 facilitates ACF/CHRAC-dependent nucleosome sliding. *EMBO J*. 2002;21(24):6865–6873. doi:10.1093/emboj/cdf692

38. Amato J, Cerofolini L, Brancaccio D, et al. Insights into telomeric G-quadruplex DNA recognition by HMGB1 protein. *Nucleic Acids Res*. 2019;47(18):9950–9966. doi:10.1093/nar/gkz727
39. Polanská E, Dobšáková Z, Dvořáčková M, Fajkus J, Štros M. HMGB1 gene knockout in mouse embryonic fibroblasts results in reduced telomerase activity and telomere dysfunction. *Chromosoma*. 2012;121(4):419–431. doi:10.1007/s00412-012-0373-x
40. Ke S, Zhou F, Yang H, et al. Downregulation of high mobility group box 1 modulates telomere homeostasis and increases the radiosensitivity of human breast cancer cells. *Int J Oncol*. 2015;46(3):1051–1058. doi:10.3892/ijo.2014.2793
41. Sofiadis K, Josipovic N, Nikolic M, et al. HMGB1 coordinates SASP-related chromatin folding and RNA homeostasis on the path to senescence. *Mol Syst Biol*. 2021;17(6):e9760. doi:10.15252/msb.20209760
42. Lee -J-J, Park IH, Rhee WJ, Kim HS, Shin J-S. HMGB1 modulates the balance between senescence and apoptosis in response to genotoxic stress. *FASEB J*. 2019;33(10):10942–10953. doi:10.1096/fj.201900288R
43. Lu J, Yue Y, Xiong S. Extracellular HMGB1 augments macrophage inflammation by facilitating the endosomal accumulation of ALD-DNA via TLR2/4-mediated endocytosis. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(10):166184. doi:10.1016/j.bbadis.2021.166184
44. Yang H, Wang H, Chavan SS, Andersson U. High mobility group box protein 1 (HMGB1): the prototypical endogenous danger molecule. *Mol Med*. 2015;21(Suppl S1):S6–S12. doi:10.2119/molmed.2015.00087
45. Esteller M. Epigenetic gene silencing in cancer: the DNA hypermethylome. *Hum Mol Genet*. 2007;16(R1):R50–R59. doi:10.1093/hmg/ddm018
46. Marks PA, Richon VM, Breslow R, Rifkind RA. Histone deacetylase inhibitors as new cancer drugs. *Curr Opin Oncol*. 2001;13(6):477–483. doi:10.1097/00001622-200111000-00010
47. Shan W, Xu L, Qiu Z, et al. Increased high-mobility group box 1 levels are associated with depression after acute ischemic stroke. *Neurol Neurol Sci*. 2022;43(5):3131–3137.
48. Yang Y, Huang JQ, Zhang X, Shen LF. MiR-129-2 functions as a tumor suppressor in glioma cells by targeting HMGB1 and is down-regulated by DNA methylation. *Mol Cell Biochem*. 2015;404(1–2):229–239. doi:10.1007/s11010-015-2382-6
49. Franklin TC, Wohleb ES, Zhang Y, Fogaça M, Hare B, Duman RS. Persistent increase in microglial RAGE contributes to chronic stress-induced priming of depressive-like behavior. *Biol Psychiatry*. 2018;83(1):50–60. doi:10.1016/j.biopsych.2017.06.034
50. Rohde K, Rønningen T, Poulsen LC, Keller M, Blüher M, Böttcher Y. Role of the DNA repair genes H2AX and HMGB1 in human fat distribution and lipid profiles. *BMJ Open Diabetes Res Care*. 2020;8(1):e000831. doi:10.1136/bmjdrc-2019-000831
51. Tang DL, Kang R, Livesey KM, et al. Endogenous HMGB1 regulates autophagy. *J Cell Biol*. 2010;190(5):881–892. doi:10.1083/jcb.200911078
52. Feng L, Liang L, Zhang S, Yang J, Yue Y, Zhang X. HMGB1 downregulation in retinal pigment epithelial cells protects against diabetic retinopathy through the autophagy-lysosome pathway. *Autophagy*. 2022;18(2):320–339. doi:10.1080/15548627.2021.1926655
53. Rubsam A, Parikh S, Fort PE. Role of inflammation in diabetic retinopathy. *Int J Mol Sci*. 2018;19(4):942. doi:10.3390/ijms19040942
54. Morinaga Y, Yanagihara K, Nakamura S, et al. Legionella pneumophila induces cathepsin B-dependent necrotic cell death with releasing high mobility group box1 in macrophages. *Respir Res*. 2010;11(1):158. doi:10.1186/1465-9921-11-158
55. Duncan JA, Gao X, Huang MT-H, et al. Neisseria gonorrhoeae activates the proteinase cathepsin B to mediate the signaling activities of the NLRP3 and ASC-containing inflammasome. *J Immunol*. 2009;182(10):6460–6469. doi:10.4049/jimmunol.0802696
56. Zhang JX, Wang XL, Vikash V, et al. ROS and ROS-mediated cellular signaling. *Oxid Med Cell Longev*. 2016;2016(1):4350965. doi:10.1155/2016/4350965
57. Ruggieri E, Domenico ED, Locatelli AG, et al. HMGB1, an evolving pleiotropic protein critical for cellular and tissue homeostasis: role in aging and age-related diseases. *Ageing Res Rev*. 2024;102:102550. doi:10.1016/j.arr.2024.102550
58. Zhao YP, Zhang JY, Lu HH, et al. Cardiopulmonary bypass-derived plasma exosomal HMGB1 contributes to alveolar epithelial cell necroptosis via mtDNA/CGAS/STING pathway. *Shock*. 2022;58(6):534–541. doi:10.1097/SHK.0000000000002006
59. Angelopoulou E, Piperi C, Papavassiliou AG. High-mobility group box 1 in Parkinson's disease: from pathogenesis to therapeutic approaches. *J Neurochem*. 2018;146(3):211–218. doi:10.1111/jnc.14450
60. Goyal A, Agrawal A, Dubey N, Verma A. High mobility group box 1 protein: a plausible therapeutic molecular target in Parkinson's disease. *Curr Pharm Biotechnol*. 2024;25(8):937–943. doi:10.2174/1389201025666230905092218
61. Liang S, Cao W, Zhuang Y, Zhang D, Du S, Shi H. Suppression of microRNA-320 induces cerebral protection against ischemia/reperfusion injury by targeting HMGB1/NF-kappaB axis. *Physiol Res*. 2024;73(1):127–138. doi:10.33549/physiolres.935081
62. Jover-Mengual T, Hwang JY, Byun HR, et al. The role of NF-κB triggered inflammation in cerebral ischemia. *Front Cell Neurosci*. 2021;15:633610. doi:10.3389/fncel.2021.633610
63. Ei ZZ, Mutirangura A, Chanvorachote P. Secretome from HMGB1 box A-over-expressing adipose-derived stem cells shows potential for skin rejuvenation by senescence reversal in PM2.5-induced senescence cells via stem cell induction. *Vivo*. 2025;39(2):766–777. doi:10.21873/invivo.13881
64. Ei ZZ, Mutirangura A, Arunmanee W, Chanvorachote P. The role of box A of HMGB1 in enhancing stem cell properties of human mesenchymal cells: a novel approach for the pursuit of anti-aging therapy. *Vivo*. 2023;37(5):2006–2017. doi:10.21873/invivo.13298
65. Salminen A, Kauppinen A, Kaarniranta K. Emerging role of NF-κB signaling in the induction of senescence-associated secretory phenotype (SASP). *Cell Signal*. 2012;24(4):835–845. doi:10.1016/j.cellsig.2011.12.006
66. Gaikwad S, Puangmalai N, Bittar A, et al. Tau oligomer induced HMGB1 release contributes to cellular senescence and neuropathology linked to Alzheimer's disease and frontotemporal dementia. *Cell Rep*. 2021;36(3):109419. doi:10.1016/j.celrep.2021.109419
67. Pellegrini L, Xue J, Larson D, et al. HMGB1 targeting by ethyl pyruvate suppresses malignant phenotype of human mesothelioma. *Oncotarget*. 2017;8(14):22649–22661. doi:10.18632/oncotarget.15152
68. Johann S, Heitzer M, Kanagaratnam M, et al. NLRP3 inflammasome is expressed by astrocytes in the SOD1 mouse model of ALS and in human sporadic ALS patients. *Glia*. 2015;63(12):2260–2273. doi:10.1002/glia.22891
69. Butovsky O, Jedrychowski MP, Cialic R, et al. Targeting mi R −155 restores abnormal microglia and attenuates disease in SOD 1 mice. *Ann Neurol*. 2015;77(1):1085. doi:10.1002/ana.24304
70. Hanayama R, Tanaka M, Miwa K, Shinohara A, Iwamatsu A, Nagata S. Identification of a factor that links apoptotic cells to phagocytes. *Nature*. 2002;417(6885):182–187. doi:10.1038/417182a
71. Chen L, Zhu H, Su S, et al. High-mobility group box-1 is associated with obesity, inflammation, and subclinical cardiovascular risk among young adults: a longitudinal cohort study. *Arterioscler Thromb Vasc Biol*. 2020;40(11):2776–2784. doi:10.1161/ATVBAHA.120.314599

72. Gunasekaran MK, Viranaicken W, Girard A-C, et al. Inflammation triggers high mobility group box 1 (HMGB1) secretion in adipose tissue, a potential link to obesity. *Cytokine*. 2013;64(1):103–111. doi:10.1016/j.cyto.2013.07.017
73. Fehrenbach H, Weiskirchen R, Kasper M, Gressner AM. Up-regulated expression of the receptor for advanced glycation end products in cultured rat hepatic stellate cells during transdifferentiation to myofibroblasts. *Hepatology*. 2001;34(5):943–952. doi:10.1053/jhep.2001.28788
74. Xue J, Ge H, Lin Z, et al. The role of dendritic cells regulated by HMGB1/TLR4 signalling pathway in myocardial ischaemia reperfusion injury. *J Cell Mol Med*. 2019;23(4):2849–2862. doi:10.1111/jcmm.14192
75. Zhang F, Huang G, Hu B, et al. Anti-HMGB1 neutralizing antibody ameliorates neutrophilic airway inflammation by suppressing dendritic cell-mediated Th17 polarization. *Mediators Inflamm*. 2014;2014:257930. doi:10.1155/2014/257930
76. Pandey S, Singh S, Anang V, Bhatt AN, Natarajan K, Dwarakanath BS. Pattern recognition receptors in cancer progression and metastasis. *Cancer Growth and Metastasis*. 2015;8:25–34. doi:10.4137/CGM.S24314
77. Kader M, El Andaloussi A, Vorhaour J, et al. Interferon type i regulates inflammasome activation and high mobility group box 1 translocation in hepatocytes during ehrlichia -induced acute liver injury. *Hepatol Commun*. 2021;5(1):33–51. doi:10.1002/hep4.1608
78. Xi S, Wang Y, Wu C, Peng W, Zhu Y, Hu W. Intestinal epithelial cell exosome launches IL-1β-mediated neuron injury in sepsis-associated encephalopathy. *Front Cell Infect Microbiol*. 2022;11:783049. doi:10.3389/fcimb.2021.783049
79. Ma Y, She X, Liu Y, Qin X. MSC-derived exosomal miR-140-3p improves cognitive dysfunction in sepsis-associated encephalopathy by HMGB1 and S-lactoylglutathione metabolism. *Commun Biol*. 2024;7(1):562. doi:10.1038/s42003-024-06236-z
80. Chen Y, Sun H, Bai Y, Zhi F. Gut dysbiosis-derived exosomes trigger hepatic steatosis by transiting HMGB1 from intestinal to liver in mice. *Biochem Biophys Res Commun*. 2019;509(3):767–772. doi:10.1016/j.bbrc.2018.12.180
81. Sobhonslidsuk A, Chanprasertyothin S, Pongrujikorn T, et al. The association of gut microbiota with nonalcoholic steatohepatitis in thais. *Biomed Res Int*. 2018;2018:9340316. doi:10.1155/2018/9340316
82. Marra F, Svegliati-Baroni G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. *J Hepatol*. 2018;68(2):280–295. doi:10.1016/j.jhep.2017.11.014
83. Chen X, Fu Y, Wang L, Qian W, Zheng F, Hou X. Bifidobacterium longum and VSL#3® amelioration of TNBS-induced colitis associated with reduced HMGB1 and epithelial barrier impairment. *Dev Comp Immunol*. 2019;92:77–86. doi:10.1016/j.dci.2018.09.006
84. Zhang H-L, Yu L-X, Yang W, et al. Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. *J Hepatol*. 2012;57(4):803–812. doi:10.1016/j.jhep.2012.06.011
85. Zheng L, Zhang Z, Sheng P, Mobasheri A. The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis. *Ageing Res Rev*. 2021;66:101249. doi:10.1016/j.arr.2020.101249
86. Hosseinzadeh A, Kamrava SK, Joghataei MT, et al. Apoptosis signaling pathways in osteoarthritis and possible protective role of melatonin. *J Pineal Res*. 2016;61(4):411–425. doi:10.1111/jpi.12362
87. Heinola T, Kouri V-P, Clarijs P, et al. High mobility group box-1 (HMGB-1) in osteoarthritic cartilage. *Clin Exp Rheumatol*. 2010;28(4):511–518.
88. Zhou L, Yuan X, Hu Y, et al. Blockade of HMGB1 reduces inflammation and pruritus in atopic dermatitis by inhibiting skin fibroblasts activation. *Int Arch Allergy Immunol*. 2024;185(2):170–181. doi:10.1159/000534568
89. Satoh TK. The role of HMGB1 in inflammatory skin diseases. *J Dermatol Sci*. 2022;107(2):58–64. doi:10.1016/j.jdermsci.2022.07.005
90. Wang AS, Dreesen O. Biomarkers of cellular senescence and skin aging. *Front Gene*. 2018;9:247. doi:10.3389/fgene.2018.00247