Gene name: **HMGB1** **Previous HGNC Symbols for HMGB1 Gene:** HMG1

External Ids for HMGB1 Gene: HGNC: 4983 NCBI Gene: 3146 Ensembl: ENSG00000189403
OMIM®: 163905 UniProtKB/Swiss-Prot: P09429

NCBI Gene Summary: This gene encodes a protein that belongs to the High Mobility Group-box superfamily. The encoded non-histone, nuclear DNA-binding protein regulates transcription, and is involved in organization of DNA. This protein plays a role in several cellular processes, including inflammation, cell differentiation and tumor cell migration. Multiple pseudogenes of this gene have been identified. Alternative splicing results in multiple transcript variants that encode the same protein.
GeneCards Summary: HMGB1 (High Mobility Group Box 1) is a Protein Coding gene. Diseases associated with HMGB1 include Brachyphalangy, Polydactyly, And Tibial Aplasia/Hypoplasia and Adams-Oliver Syndrome 1. Among its related pathways are Toll Like Receptor 7/8 (TLR7/8) Cascade and Diseases of Immune System. Gene Ontology (GO) annotations related to this gene include *RNA binding* and *chromatin binding*. An important paralog of this gene is HMGB1P1.
UniProtKB/Swiss-Prot Summary: Multifunctional redox sensitive protein with various roles in different cellular compartments. In the nucleus is one of the major chromatin-associated non-histone proteins and acts as a DNA chaperone involved in replication, transcription, chromatin remodeling, V(D)J recombination, DNA repair and genome stability (PubMed:33147444). Proposed to be an universal biosensor for nucleic acids. Promotes host inflammatory response to sterile and infectious signals and is involved in the coordination and integration of innate and adaptive immune responses. In the cytoplasm functions as a sensor and/or chaperone for immunogenic nucleic acids implicating the activation of TLR9-mediated immune responses, and mediates autophagy. Acts as a danger-associated molecular pattern (DAMP) molecule that amplifies immune responses during tissue injury (PubMed:27362237). Released to the extracellular environment can bind DNA, nucleosomes, IL-1 beta, CXCL12, AGER isoform 2/sRAGE, lipopolysaccharide (LPS) and lipoteichoic acid (LTA), and activates cells through engagement of multiple surface receptors (PubMed:34743181). In the extracellular compartment fully reduced HMGB1 (released by necrosis) acts as a chemokine, disulfide HMGB1 (actively secreted) as a cytokine, and sulfonyl HMGB1 (released from apoptotic cells) promotes immunological tolerance (PubMed:23446148, 23519706, 23994764, 25048472). Has proangiogdenic activity (By similarity). May be involved in platelet activation (By similarity). Binds to phosphatidylserine and phosphatidylethanolamide (By similarity). Bound to RAGE mediates signaling for neuronal outgrowth (By similarity). May play a role in accumulation of expanded polyglutamine (polyQ) proteins such as huntingtin (HTT) or TBP (PubMed:23303669, 25549101). (HMGB1_HUMAN,P09429)
Nuclear functions are attributed to fully reduced HGMB1. Associates with chromatin and binds DNA with a preference to non-canonical DNA structures such as single-stranded DNA, DNA-containing cruciforms or bent structures, supercoiled DNA and ZDNA. Can bent DNA and enhance DNA flexibility by looping thus providing a mechanism to promote activities on various gene promoters by enhancing transcription factor binding and/or bringing distant regulatory sequences into close proximity (PubMed:20123072). May have an enhancing role in nucleotide excision repair (NER) (By similarity). However, effects in NER using in vitro systems have been reported conflictingly (PubMed:19360789, 19446504). May be involved in mismatch repair (MMR) and base excision repair (BER) pathways (PubMed:15014079, 16143102, 17803946). May be involved in double strand break repair such as non-homologous end joining (NHEJ) (By similarity). Involved in V(D)J recombination by acting as a cofactor of the RAG complex: acts by stimulating cleavage and RAG protein binding at the 23 bp spacer of conserved recombination signal sequences (RSS) (By similarity). In vitro can displace histone H1 from highly bent DNA (By similarity). Can restructure the canonical nucleosome leading to relaxation of structural constraints for transcription factor-binding (By

similarity). Enhances binding of sterol regulatory element-binding proteins (SREBPs) such as SREBF1 to their cognate DNA sequences and increases their transcriptional activities (By similarity). Facilitates binding of TP53 to DNA (PubMed:23063560). Proposed to be involved in mitochondrial quality control and autophagy in a transcription-dependent fashion implicating HSPB1; however, this function has been questioned (By similarity). Can modulate the activity of the telomerase complex and may be involved in telomere maintenance (By similarity). (HMGB1_HUMAN,P09429)
In the cytoplasm proposed to dissociate the BECN1:BCL2 complex via competitive interaction with BECN1 leading to autophagy activation (PubMed:20819940). Involved in oxidative stress-mediated autophagy (PubMed:21395369). Can protect BECN1 and ATG5 from calpain-mediated cleavage and thus proposed to control their proautophagic and proapoptotic functions and to regulate the extent and severity of inflammation-associated cellular injury (By similarity). In myeloid cells has a protective role against endotoxemia and bacterial infection by promoting autophagy (By similarity). Involved in endosomal translocation and activation of TLR9 in response to CpG-DNA in macrophages (By similarity). (HMGB1_HUMAN,P09429)
In the extracellular compartment (following either active secretion or passive release) involved in regulation of the inflammatory response. Fully reduced HGMB1 (which subsequently gets oxidized after release) in association with CXCL12 mediates the recruitment of inflammatory cells during the initial phase of tissue injury; the CXCL12:HMGB1 complex triggers CXCR4 homodimerization (PubMed:22370717). Induces the migration of monocyte-derived immature dendritic cells and seems to regulate adhesive and migratory functions of neutrophils implicating AGER/RAGE and ITGAM (By similarity). Can bind to various types of DNA and RNA including microbial unmethylated CpG-DNA to enhance the innate immune response to nucleic acids. Proposed to act in promiscuous DNA/RNA sensing which cooperates with subsequent discriminative sensing by specific pattern recognition receptors (By similarity). Promotes extracellular DNA-induced AIM2 inflammasome activation implicating AGER/RAGE (PubMed:24971542). Disulfide HMGB1 binds to transmembrane receptors, such as AGER/RAGE, TLR2, TLR4 and probably TREM1, thus activating their signal transduction pathways. Mediates the release of cytokines/chemokines such as TNF, IL-1, IL-6, IL-8, CCL2, CCL3, CCL4 and CXCL10 (PubMed:12765338, 18354232, 19264983, 20547845, 24474694). Promotes secretion of interferon-gamma by macrophage-stimulated natural killer (NK) cells in concert with other cytokines like IL-2 or IL-12 (PubMed:15607795). TLR4 is proposed to be the primary receptor promoting macrophage activation and signaling through TLR4 seems to implicate LY96/MD-2 (PubMed:20547845). In bacterial LPS- or LTA-mediated inflammatory responses binds to the endotoxins and transfers them to CD14 for signaling to the respective TLR4:LY96 and TLR2 complexes (PubMed:18354232, 21660935, 25660311). Contributes to tumor proliferation by association with ACER/RAGE (By similarity). Can bind to IL1-beta and signals through the IL1R1:IL1RAP receptor complex (PubMed:18250463). Binding to class A CpG activates cytokine production in plasmacytoid dendritic cells implicating TLR9, MYD88 and AGER/RAGE and can activate autoreactive B cells. Via HMGB1-containing chromatin immune complexes may also promote B cell responses to endogenous TLR9 ligands through a B-cell receptor (BCR)-dependent and ACER/RAGE-independent mechanism (By similarity). Inhibits phagocytosis of apoptotic cells by macrophages; the function is dependent on poly-ADP-ribosylation and involves binding to phosphatidylserine on the cell surface of apoptotic cells (By similarity). In adaptive immunity may be involved in enhancing immunity through activation of effector T cells and suppression of regulatory T (TReg) cells (PubMed:15944249, 22473704). In contrast, without implicating effector or regulatory T-cells, required for tumor infiltration and activation of T-cells expressing the lymphotoxin LTA:LTB heterotrimer thus promoting tumor malignant progression (By similarity). Also reported to limit proliferation of T-cells (By similarity). Released HMGB1:nucleosome complexes formed during apoptosis can signal through TLR2 to induce cytokine production (PubMed:19064698). Involved in induction of immunological

tolerance by apoptotic cells; its pro-inflammatory activities when released by apoptotic cells are neutralized by reactive oxygen species (ROS)-dependent oxidation specifically on Cys-106 (PubMed:18631454). During macrophage activation by activated lymphocyte-derived self apoptotic DNA (ALD-DNA) promotes recruitment of ALD-DNA to endosomes (By similarity). (HMGB1_HUMAN,P09429)
Cellular localization: mainly in the endoplasmic reticulum, nucleus, extracellular and plasma membrane.

Full Name: *High Mobility Group Box 1*
Protein Type: Non-histone nuclear DNA-binding protein
Key Role: Acts as both a nuclear architectural protein and an extracellular danger signal (DAMP) during inflammation and injury.

🔬 Biological Function of HMGB1

- Inside the nucleus:
  - Binds DNA without sequence specificity.
  - Helps in chromatin organization, DNA repair, and transcriptional regulation.
- Outside the cell:
  - When released during cell death (necrosis) or actively secreted by immune cells, HMGB1 functions as a DAMP (damage-associated molecular pattern).
  - It alerts the immune system to tissue damage or infection.

🛠️ Main Actions of HMGB1 extracellularly:

- Binds pattern recognition receptors like:
  - RAGE (Receptor for Advanced Glycation End Products)
  - TLR2
  - TLR4
- Triggers:
  - NF-κB activation → leading to cytokine production (TNF-α, IL-6, IL-1β).
  - Release of other proinflammatory mediators.
  - Recruitment of immune cells to sites of damage or infection.
- NETs are networks of DNA, histones, and antimicrobial proteins expelled by activated neutrophils to trap and kill pathogens.HMGB1 is:
  - Released during NET formation.
  - Can be physically embedded inside NETs.
  - Further promotes inflammation by acting as a DAMP (danger signal).

🦠 Role of HMGB1 in Sepsis

- One of the most critical late mediators of sepsis.
- Unlike early mediators (such as, TNF-α, IL-1β) that peak quickly, HMGB1 is released later (typically 8–24 hours after infection onset).
- Drives sustained inflammation, vascular leakage, hypotension, and multi-organ failure.
- Excessive NET formation (and HMGB1 release) leads to:Vascular injury, Thrombosis (NETs act as a scaffold for clotting factors), Organ failure

- High HMGB1 and NET markers (like citrullinated histones) are strong predictors of poor outcomes in sepsis.

🔴 Importantly:

- HMGB1 can perpetuate inflammation even when the initial infection is controlled.
- High HMGB1 levels contribute to persistent immune activation and poor recovery.

📈 Clinical Relevance in Sepsis

Diagnostic Role:

- Elevated HMGB1 levels in plasma/serum are detected in sepsis patients.
- It can be measured as part of DAMP panels alongside other markers like S100A8/S100A9.

Prognostic Role:

- Higher HMGB1 concentrations correlate with:
    - Severity of organ dysfunction (like, SOFA score).
    - Development of septic shock.
    - Increased mortality rates.
- Persistent elevation of HMGB1 even after antibiotic treatment suggests ongoing inflammatory risk.

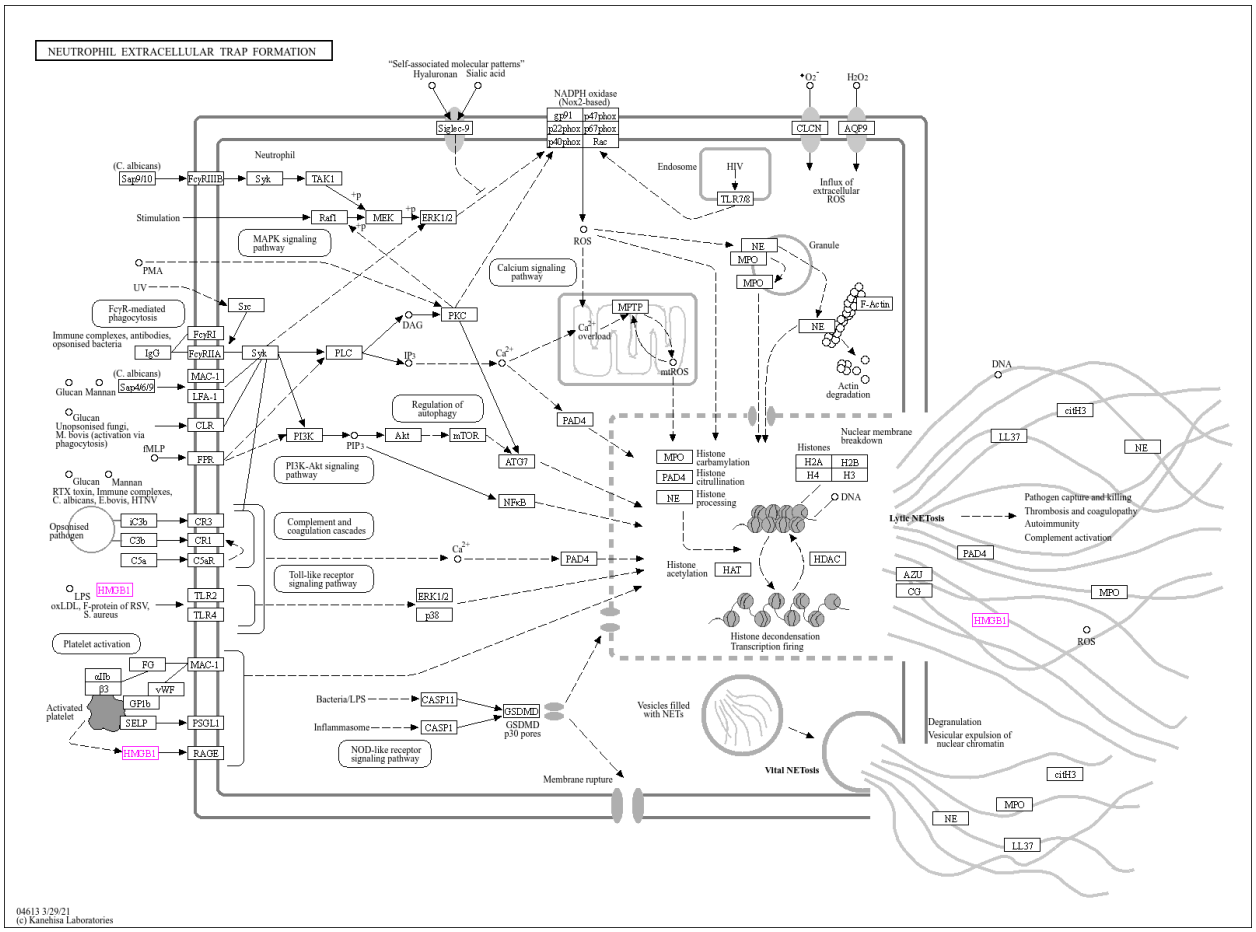
Therapeutic Target:

- HMGB1 inhibitors (like, neutralizing antibodies, glycyrrhizin, ethyl pyruvate) have shown:
    - Reduced inflammation
    - Improved survival in animal models of sepsis

🧪 Supporting Literature

Doi: 10.1038/s41401-021-00676-7
Doi: 10.1111/j.1365-2796.2003.01302.x.
Doi: 10.1007/s00134-008-1032-9
Doi: 10.1080/00365540310016286
Doi: 10.1084/jem.20052203

KEGG:



Enrichr-KG