BIBLIOGRAPHY REVIEW

DECEMBER 2018

HMGB1:

what it is and how it could play a role in malignant pleural mesothelioma

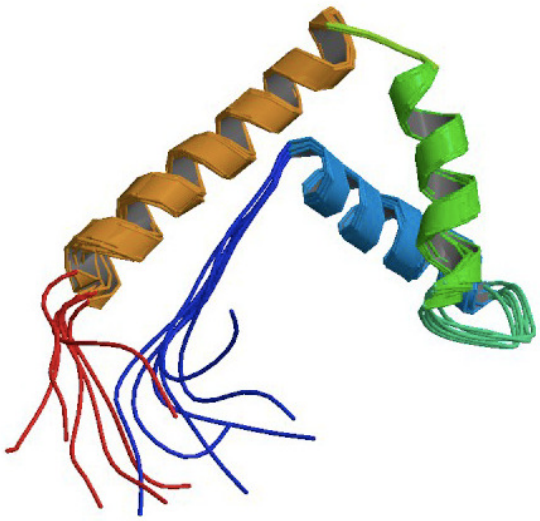
DEFINITION

HMGB1 is an acronym that stands for High Mobility Group Box 1. It is a protein that belongs to the high mobility group family, in other words, high electrophoretic mobility proteins. ("Electrophoretic mobility" can be defined as a measurement of the ability of a chemical substance to move when subjected to an electric field, and usually depends on various parameters such as the charge, size, conformation characteristics, the voltage applied to the field and the concentration of the electrophoretic medium).

This protein is also known as amphoterin or HMG1, and is a non-histone scaffold protein of chromatin.

HMGB1 also belongs to a subfamily of proteins that contain a domain involved in DNA binding, namely HMG-box.

Below is a three-dimensional image of the structure of this protein.

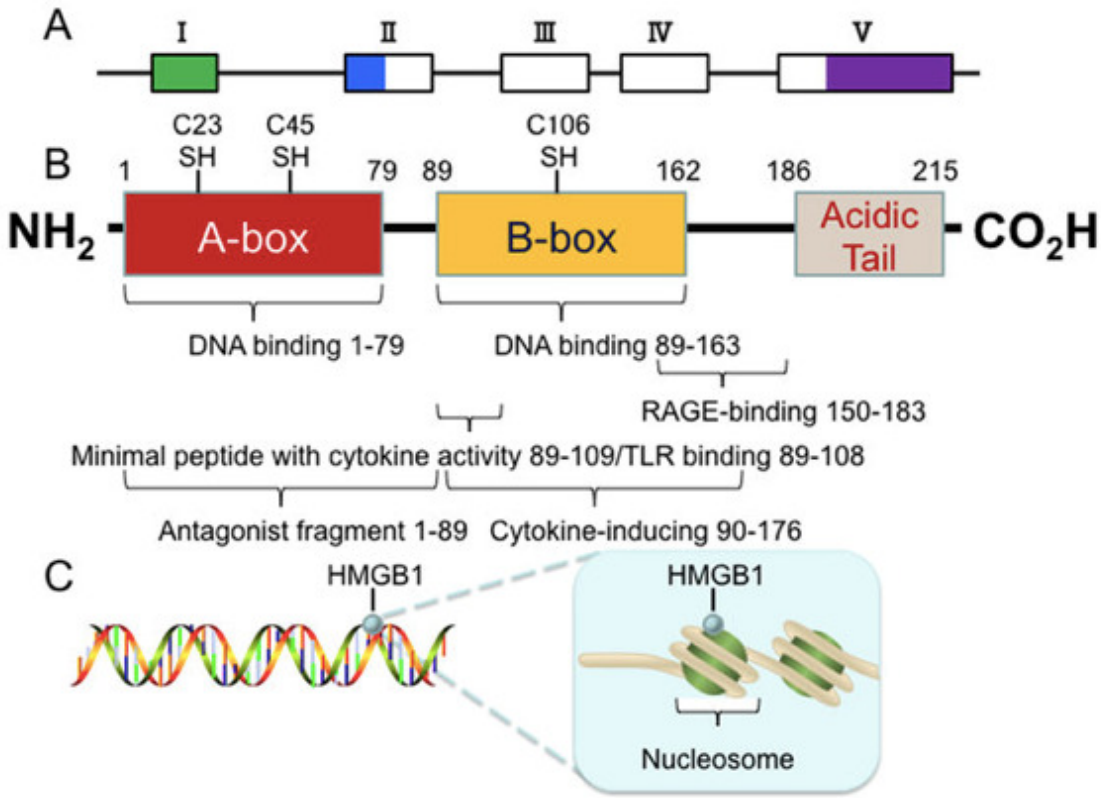


(from PDB: Protein Data Bank. https://www.rcsb.org/structure/1aab)

The HMGB1 gene is located on the long arm of chromasome 13 13q12. The figure below shows the 5 exons of the HMGB1 gene in the form of small parallelepipeds (hollow for translated regions and solid for non-translated regions).

Part (B) of the figure below shows the 215 amino acid residues and is composed of three domains: A box, B box and an acidic C-terminal tail. There are three cysteine residues at positions 23, 45 and 106, which regulate HMGB1 function in response to oxidative stress.

Part C of the figure shows HMGB1, which is loosely and transiently associated with nucleosomes. HMGB1 is important for spatial segregation and nuclear homeostatis.



(from He SJ, et al. Oncotarget. 2017)

In general, HMGB1 is ubiquitously expressed (only 10 times less than core histones). However, HMGB1 expression and subcellular localization varies depending on cell types and tissues and are developmentally regulated to cues from the environment.

Tissue	HMGB1 level	Subcellular location	Tumor	HMGB1 level	Subcellular location	Reference
Liver	Low	C	Hepatocellular carcinoma	High	N, C	[130]
Stomach	Low	nd	Gastric carcinoma	High	N	[131]
Colon	Low	nd	Colorectal carcinoma	High	N,C N	[132]
Pancreas	Low	nd	Pancreatic carcinoma	High	N, C	[133]
Breast	Low	nd	Breast cancer	High	N, C	[134]
Cervix	Low	nd	Cervical carcinoma	High	N, C	[135]
Brain	Undetectable in most cells in adult mouse brain, present during development	C	Glioma	High	C, N	[136]
Thymus	High in young rats, low in old rats	N, C	Thymic epithelial tumors	High	N, C	[137]
Lymphoid tissues	Low	N, C	Non-Hodgkin lymphoma	High	N	[138]

N: nuclear localization; C: cytoplasmic localization; nd: not determined.

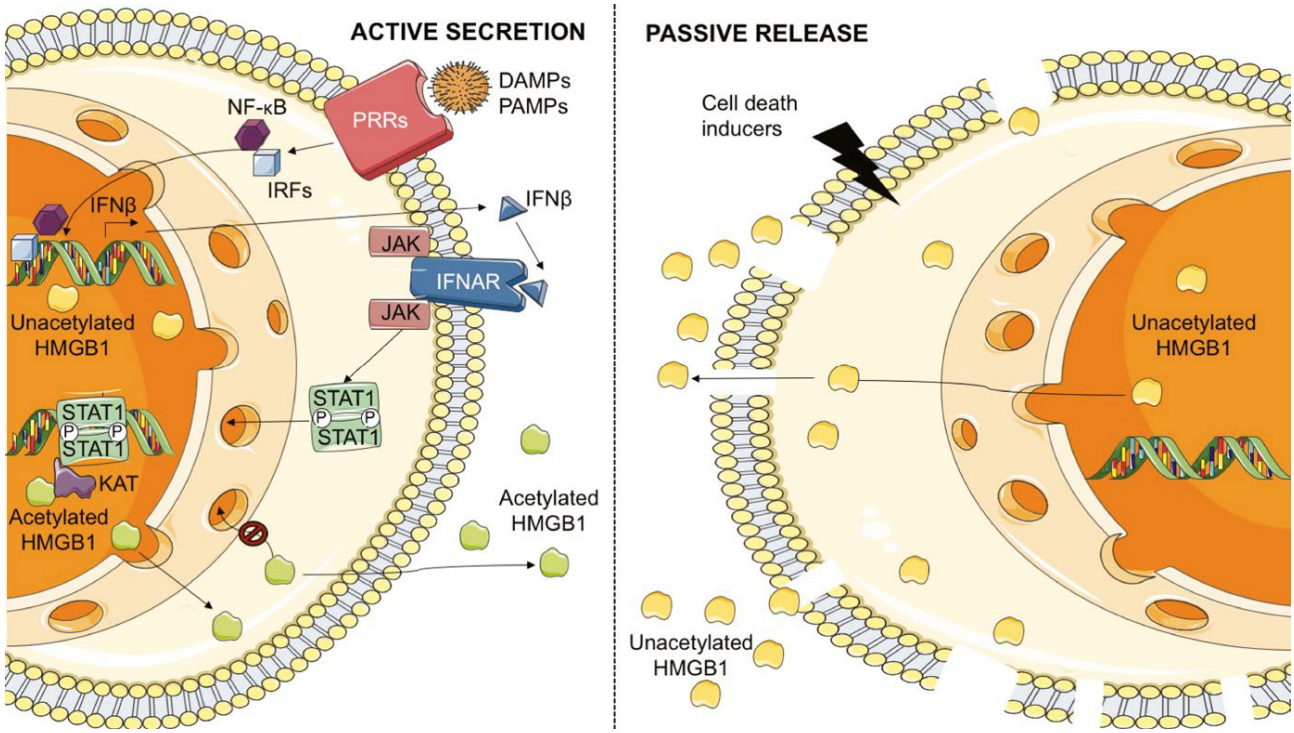
(from He SJ, et al. Oncotarget. 2017)

MAIN FUNCTIONS

HMGB1 is found in large quantities within the nucleus of all eukaryotic cells and its main role is to remodel chromatin.

It has also recently been discovered that this protein is an important mediator in the inflammation process, especially in the case of cellular necrosis. As such, HMGB plays an important role in triggering inflammation but it also appears to be involved in innate and adaptive responses and in repairing tissue damage.

Cells undergoing stress actively secrete HMGB1, which is relocated from the nucelus to the cytoplasm and then to secretory lysosomes or directly to the extracellular space.



(from Bianchi ME, et al. Immunol Rev. 2017)

The HMGB1 protein can be passively released from dead cells, as shown on the right in the figure. In other cases, it is actively secreted as a result of cellular stress, as shown on the left.

Under normal conditions, this protein is located in the nucleus in a reduced and unacetylated form. Following tissue damage, this unmodified protein is released from dead cells and subsequently converted into the disulfide-HMGB1 form by spontaneous oxidation, or through reactive oxygen species (ROS), which are produced in abundance by inflammatory cells.

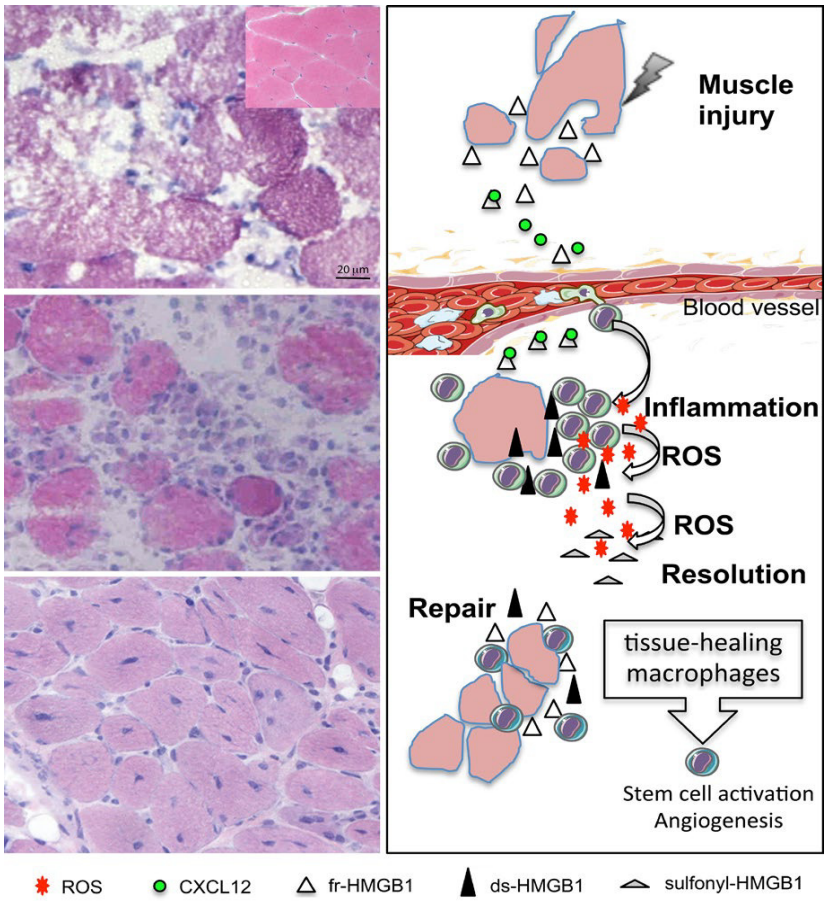
Leukocytes can also secrete HMGB1, which is first released into the cytoplasm and subsequently acetylated or phosphorylated, and then passes into the extracellular space after being transformed. This often occurs after it has been loaded into secretory lysosomes or through a little-known mechanism into non-hematopoietic cells.

Secreted HMGB1 can be distinguished from passively released HMGB1 (in yellow), due to the acetylated state, shown in green in the figure. The secreted form is also oxidized.

The figure at left shows the pathway of LPS- and interferon-induced HMGB1 secretions after a bacterial or viral infection.

Immune cells are first recruited to the damaged tissue site and are then activitated after arriving at the site.

The HMGB1 protein supports tissue repair by coordinating the switch of macrophages to a tissue-healing phenotype, activation and profileration of stem cells, and neoangiogenesis. Unfortunately, this protein similarly helps repair tissue of all damaged cells, including tumor cells.



(from Bianchi ME, et al. Immunol Rev. 2017)

The figure above shows the role of HMGB in tissue repair.

As shown, this protein plays an important role during muscle injury.

HMGB1 is released from damaged or necrotic muscle cells. Under these conditions, this protein can also promote the recruitment of immune system cells such as leukocytes by forming heterocomplexes with CXCL12. Inflammation occurs when the leukocytes arrive at the damaged tissue site. HMGB1 is then oxidized to disulfide through free oxygen radicals, which are formed after infiltration by the leukocytes. HMGB1 also activates the leukocytes to promote the release of a series of pro-inflammatory cytokines and chemokines, but loses its ability to form heterocomplexes with CXCL12.

After resolving the inflammatory state, the tissue-healing phenotype macrophages release HMGB1, which can activate stem cells and promote angiogenesis as well as coordinate muscle injury repair.

HMGB1 AND CANCER

The HMGB1 protein appears to play an important role in cancer progression.

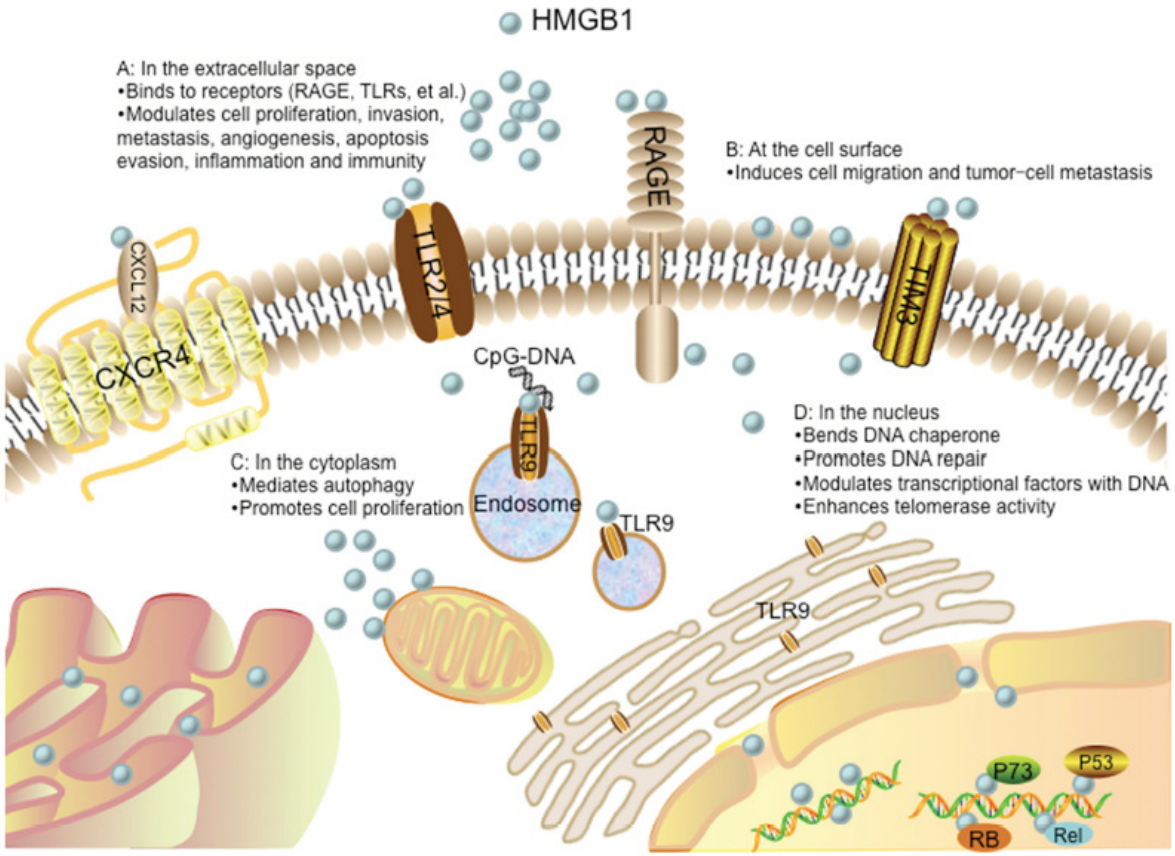
The figure below shows how HMGB1 can interact biologically to promote carcinogenesis.

In the extracellular space, as shown in part A, HMGB1 signals through receptors such as RAGE, TLRs, TIM3 and CXCR4, driving cell proliferation, invasion and angiogenesis, metastasis, apoptosis evasion, inflammation and immunity. The interaction between HMGB1 and CXCR4 is dependent on CXCL12. TLR9 is initially localized on the endoplasmic reticulum (ER) and then redistributes to endosomes upon stimulation with CpG-DNA via an HMGB1-dependent pathway.

In part B, HMGB1 is present at the cell surface and promotes cell migration and tumor-cell metastasis.

In the cytoplasm, as shown in part C of the figure, HMGB1 regulates autophagy and promotes cell proliferation.

In the nucleus, as shown in part D, HMGB1 acts as a DNA chaperone participating in DNA repair and transcription. HMGB1 can also interact with transcription factors such as p53, p73 and RB and enhance their activities. Nuclear HMGB1 enhances telomerase activity and modulates telomere homeostatis.



(from He SJ, et al. Oncotarget. 2017)

HMGB1 AND MALIGNANT PLEURAL MESOTHELIOMA

HMGB1 is highly involved in tumor biology.

HMGB1 appears to be associated with mesothelioma. In this neoplasm, asbestos causes inflammation of the mesothelium but the biomolecular pathways underlying this inflammatory-neoplastic process are not completely known.

However, it was recently discovered that asbestos induces the death of mesothelial cells by necrosis, with the resulting release of HMGB1 into the extracellular space and recall of inflammatory cells.

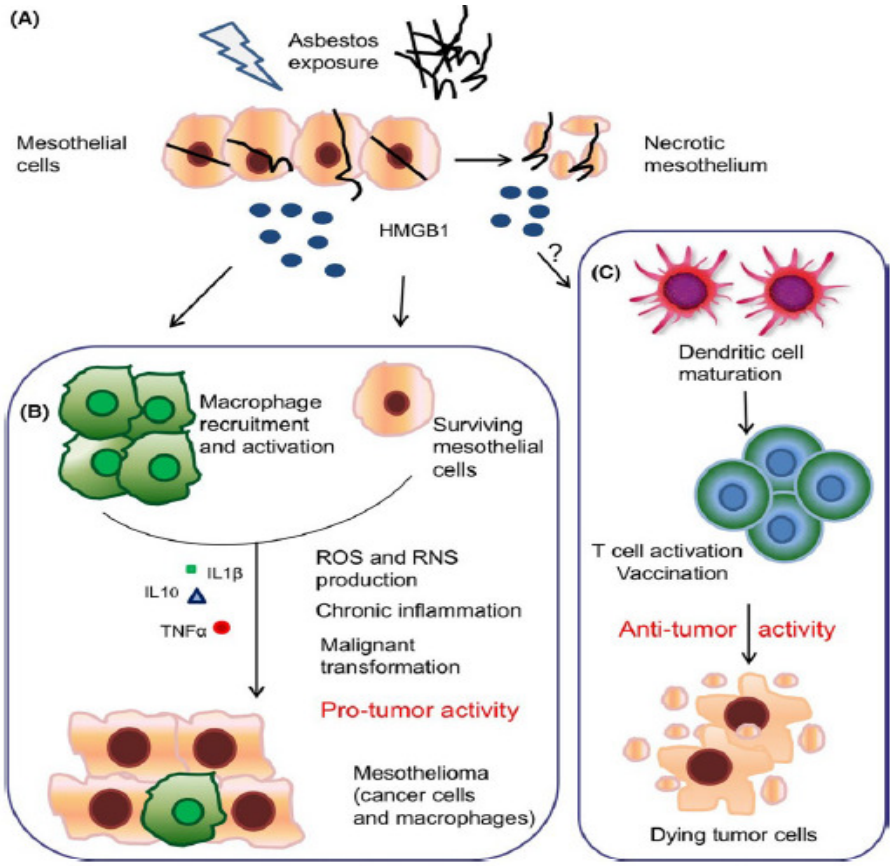
The persistence of the asbestos fibers is one of the main causes of the perpetuation of inflammation in the pleura and often the lungs of subjects who have been exposed to this carcinogen and then develop MPM. High levels of HMGB1 have been seen in the blood of subjects exposed to asbestos as well as those with MPM, demonstrating that this protein could be involved in these carcinogenesis and inflammation processes. Here too, it is not fully understood how persistent inflammation can induce carcinogenesis but some studies suggest that macrophages play a role in cell survival, demonstrated by the fact that macrophages have been found in abundance in neoplastic tissue.

The figure below shows the pro- or anti-tumoral activity of HMGB1.

In part A, mesothelial cells are damaged by exposure to asbestos and induce programmed necrotic cell death, resulting in the release of HMGB1.

Part B shows the pro-tumoral activity of HMGB1, which bends TLR4 and produces a state of chronic inflammation leading to malignant transformation. Macrophages are present in the mesothelial tissue and HMGB1 is constitutively secreted by the mesothelioma cells.

Part C shows the anti-tumoral characteristics of this protein. The question mark shown in the figure means that the mechanisms involving HMGB1 and the pathogenesis of mesothelioma have never beeen fully investigated. However, the activity of this protein against various tumors has been widely documented. HMGB1 is secreted by the cells and probably involved in the mechanisms that lead to the responses of B- and T-cells to immunological memory.



(from Bianchi ME, et al. Immunol Rev. 2017)

CONCLUSIONS

Further research into this protein will lead to a greater understanding of the pathogenesis of cancer.

Many researchers are specifically trying to determine the actual rol of HMGB1 in MPM to better define the carcinogenesis of this disease.

Future research also aims to design therapeutic approaches that may involve this protein or pathways activated by it.

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