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HMGB1 protein as a novel target for cancer

Alok Tripathi, Kriti Shrinet, Arvind Kumar*

School of Biotechnology, Institute of Science, Banaras Hindu University, Varanasi, 221005, Uttar Pradesh, India

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ABSTRACT

Highly conserved nuclear protein High Mobility Group Box1 (HMGB1) present in mammals has functionality as an immuno-modulator in the form of cytokine molecule, as a nuclear factor to regulate these molecules and DNA structural determination. It has proximal homologous DNA binding domains Box-A, Box-B and distal C-terminal domain. Reduced form exists in basic condition has chemotaxis activity, while form with disulphide bond reduced at 106th cysteine showed cytokine activity. The oxidized form is devoid of both activities. HMGB1 binds and bends dsDNA and also activates genes for secretion of inflammatory cytokines such as IL-1β, TNF-α, IL-6 and IL-18. It can interact with transcription factors Rel/NF-κB and p53 responsible for up-regulating oncogenes. Oxidative stressed injured tissues actively secrete HMGB1 outside cells to necrotize other nearby tissues passively in cytosol. Acetylation of HMGB1 weakens its binding with DNA, and promotes its migration to different tissues leading to secretion of inflammatory-cytokines. HMGB1 expression has been found very important in the genesis and promotion of different cancer by promoting metastasis. In current article, we emphasized on condition based structural variability of HMGB1, mechanism of release, physiological functions and its functionality as a biomarker for cancer to be targeted to curb cancer genesis and progression.

1. Introduction

HMGB protein family contains three sub-types of proteins HMGB1, HMGB2 and HMGB3. HMGB1 protein was discovered in 1973 as DNA binding nuclear protein in calf thymus [1]. All sub-types of HMGB share common structure and abbreviated name is used due to its higher electrophoretic mobility on polyacrylamide gel expressed from the gene with three different boxes. Clinically HMGB1 plays decisive role in various types of diseases such as autoimmune, infectious, and inflammatory such as cancer (Fig. 1) [2–4]. Initially, HMGB1 was considered as a nuclear protein involved in transcription level regulation of various genes but nowadays researchers have proved its secondary role as cytokine which could trigger the expression of inflammation and infection related genes [5]. Secretory HMGB1 protein molecules have an ability to bind with Toll like receptors (TLRs) present on immune cells and with RAGE (Receptor for advanced glycation end products) expressed on cancer cells [5]. HMGB1 has been reported to work as damage associated molecular pattern (DAMP) as well as in the progression of inflammatory and autoimmune diseases [6,7]. To explicate the sundry role of HMGB1, in current review, we would be elaborating the various structural forms to be targeted by drugs to mitigate the genesis of inflammatory diseases particularly different types of cancers and its different clinical and biological aspects.

2. Structural variability of HMGB1 protein

HMGB1 protein has been known as highly conserved protein and made up of 215 amino acids (AAs). Structurally HMGB1 protein has two proximal homologous DNA binding domains Box-A and Box-B, which are basic in nature due to their positive charges. Third negative C-terminal domain was known to be acidic in nature due to presence of aspartate and glutamate AA residues [8]. Box-A (1st to 79th) and Box-B (89th to 163rd) have approximately equal number of AAs while C-tail (186th to 215th) comparatively smaller with less number of AAs (Fig. 2a).

2.1. Structure in reduced state

The reduced form is generated by the reduction of the basic AA cysteine present at 23rd, 45th and 106th position (Fig. 2b). Reduced cysteine renders chemo-attractant activity to HMGB1 [9]. Observations from *in vitro* and *in vivo* experimental results proved that reduced form of HMGB1 protein has an ability to recruit leukocyte without involvement of traditional cytokines/chemokines (*e.g.* IL-1β, IL-6, IL-8 *etc.*). Reduced form of HMGB1 has an ability to maintains the structural integrity against terminal oxidation by reactive-oxygen species (ROS) [10]. Reduced state also favours the promotion and regeneration of

* Corresponding author at: School of Biotechnology; Institute of Science; Banaras Hindu University, Varanasi, U.P., 221005, India.
E-mail addresses: k_arvindk@rediffmail.com, arvindkumararvind8@gmail.com (A. Kumar).

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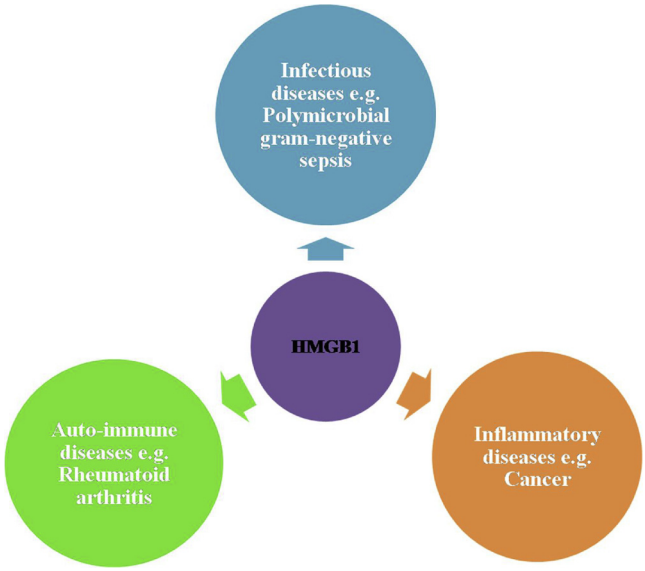

Fig. 1. Clinical importance of HMGB1 protein.

damaged tissues [11]. Chemo-attractant activity of reduced HMGB1 was due to complex formation with CXCL12 for signalling *via* the CXCR4 receptor. Reduced form of HMGB1 protein might be responsible for increased phagocytic activity of phagocytic cells as well as increased autophagic activity by neighbour cancerous cells [12].

2.2. Structure in oxidized state

Oxidized form of HMGB1 with neither chemotaxis activity nor cytokine inducing activity has been reported to predominantly present in highly acidic HMGB1. The sulphur of HMGB1 cysteine present at 23rd, 45th and 106th position of peptide got oxidized in acidic environment (Fig. 2c). Immunogenic function of HMGB1 protein can be blocked by oxidation of cysteine residue at 106th position [13]. Intra-molecular interactions between anterior A–B box and posterior C-terminal acidic tail were responsible for conformational equilibrium between the open and closed form of HMGB1. The association of any substance to HMGB1 weakens intra-molecular interactions between box-A, box-B & tail-C and thus increases the chance of oxidation of protein by exposing the thiol group of cysteine at 23rd and 45th position [14].

2.3. Structure with disulphide bond

Only disulphide bond containing Box-A (between 23rd and 45th) was devoid of any cytokine inducing activity. However, HMGB1 protein with disulphide bond between 23rd and 45th cysteine residues and unpaired cysteine residue at 106th position has cytokine like activity (Fig. 2d) [9]. It was found that formation of disulphide bond between 23rd and 45th cysteine residue in non-reducing condition is linked with the increment in electrophoretic mobility. It's due to better compact folding of the polypeptide chain of HMGB1 resulting in decrease of molecular weight upto 26 kDa from 28 kDa [10]. Terminal oxidation of cysteine to sulfonate by ROS resulted in the loss of pro-inflammatory activity of HMGB1. HMGB1 with intramolecular disulphide bond between cysteine at 23rd and 45th position activates NF-κB inflammatory pathway and also promotes the production of different pro-inflammatory cytokines such as IL-6, IL-8 and TNF-α [10]. Researchers experimentally proved that disulfide-HMGB1 was present in the injured muscles but not in healthy muscle. This prompted the establishment hypothesis that disulfide-HMGB1 could be considered as a marker for damaged tissues [10]. The half-life of reduced HMGB1 is about seventeen min (17 min) in serum. The conversion of reduced form to disulfide reduced form is responsible for the recruitment of leukocytes and release of pro-inflammatory cytokines at the site of injury. However, majority of extracellular HMGB1 could not get recruited at the inflammation site or site of injury due to its short half-life in reduced form [14].

3. Mechanism of release of HMGB1 protein

There are two nuclear localizing sequences (NLSs) present in HMGB1, one in Box-A and other in Box-B. Both NLSs have lysine AA residues. Hyper-acetylation of these lysine residues enables translocation of HMGB1 from nucleus to cytoplasm [8]. The shuttling of HMGB1 protein from nucleus to cytoplasm was determined by the overall acetylation (Fig. 3) state [15]. There are two possible mechanisms for the release of nuclear HMGB1 protein by the immune cells, active secretion or passive secretion.

3.1. Active secretion of HMGB1

HMGB1 was actively secreted by inflammatory cells like macrophages or monocytes and NK-cells during the tissue injury and oxidative stress [16]. However, different exogenous stimuli such as products of microbial origin like CpG-DNA, endotoxin, mycobacterial infection, lysophosphatidylcholine and different endogenous stimuli of host origin such as TNF-α, IFN-α, IFN-β, IFN-γ, hydrogen peroxide, nitric oxide, peroxynitrite have ability to induce the secretion of HMGB1 [17–20]. UV-B, ATP and hyperglycaemic condition could be precursor for the secretion of HMGB1 [21–23]. The active secretion was initiated by exportin-1 mediated nuclear export and completed with secretory lysosome mediated exocytosis. Active release of HMGB1 from macrophage or monocytes requires a pro-inflammatory stimulus that was responsible for the acetylation of HMGB1 and leading to accumulation in cytoplasm. Active secretion of HMGB1 could not be possible either by Endoplasmic reticulum or Golgi complex secretory pathway due to absence of leader peptide sequence. The two different phenomenon are involved in the active secretion of HMGB1 protein either by nuclear receptor Chromosome-Region Maintenance-1 (CRM-1) mediated or by post-translational HMGB1 modification mediated.

3.1.1. Role of nuclear receptor chromosome-region Maintenance-1 (CRM-1)

CRM-1 (also known as exportin1), a primary nuclear transport receptor that belongs to importin-β super family and plays a crucial role in the export of leucine rich nuclear export sequence (NES) proteins [24]. In response to inflammatory stimulus, CRM-1 interacts with HMGB1 to promote the export of protein from nucleus to cytoplasm. Leptomycin-B, a nuclear export inhibitor inhibits the CRM-1 by preventing the interaction with HMGB1 protein [25]. This proves that the interaction of HMGB1 with CRM-1 protein is essential for the export of nuclear protein to cytoplasm. Hsp72 protein has been reported to play protective role by inhibiting the release of HMGB1 during the inflammation mediated oxidative stress. This is because up-regulated Hsp72 has capability to inhibit the interaction between HMGB1 and CRM-1 in LPS induced macrophages [25].

3.1.2. Post-translational modification of HMGB1

Different types of extensive post-translational modifications such as methylation, reversible acetylation, phosphorylation, ADP-ribosylation and glycosylation were exhibited by HMGB1 protein [26]. Among these various types of posttranslational modification, acetylation took place at lysine AA residues of NLS of HMGB1 protein. The acetylation was done by PCAF (P300/CBP-associated factor), CBP (CREB-binding protein), and p300 (Histone acetyltransferase p300) and responsible for cytoplasmic secretion of HMGB1 from immune cells macrophages and monocytes [27]. Recent reports suggested that acetylation and nuclear shuttling of HMGB1 could be promoted by JAK/STAT1 signalling pathway [17]. This known acetylated site of HMGB1-NLS, could be

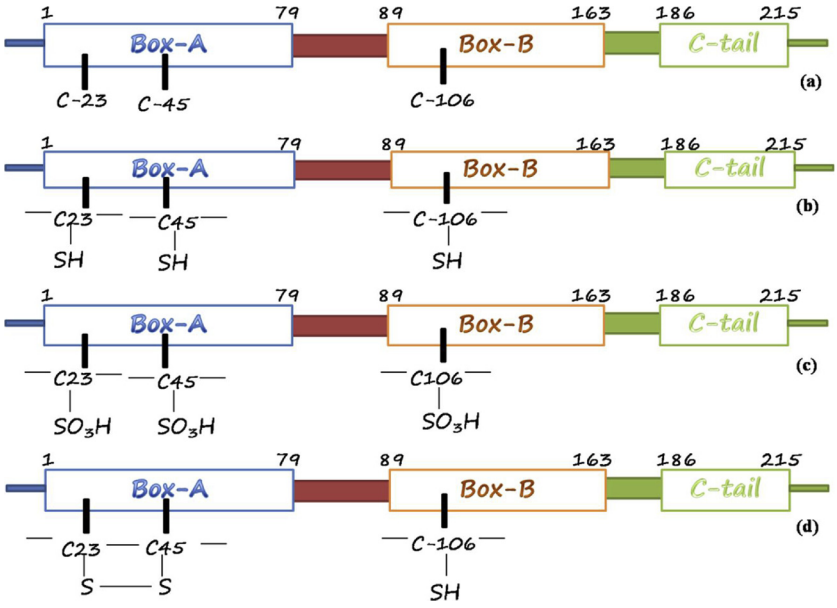

Fig. 2. (a) General structural arrangement of HMGB1 protein; **(b)** Structural arrangement of HMGB1 protein in reduced state; **(c)** Structural arrangement of HMGB1 protein in oxidized state; **(d)** Representation of disulphide bond formed structure of HMGB1.

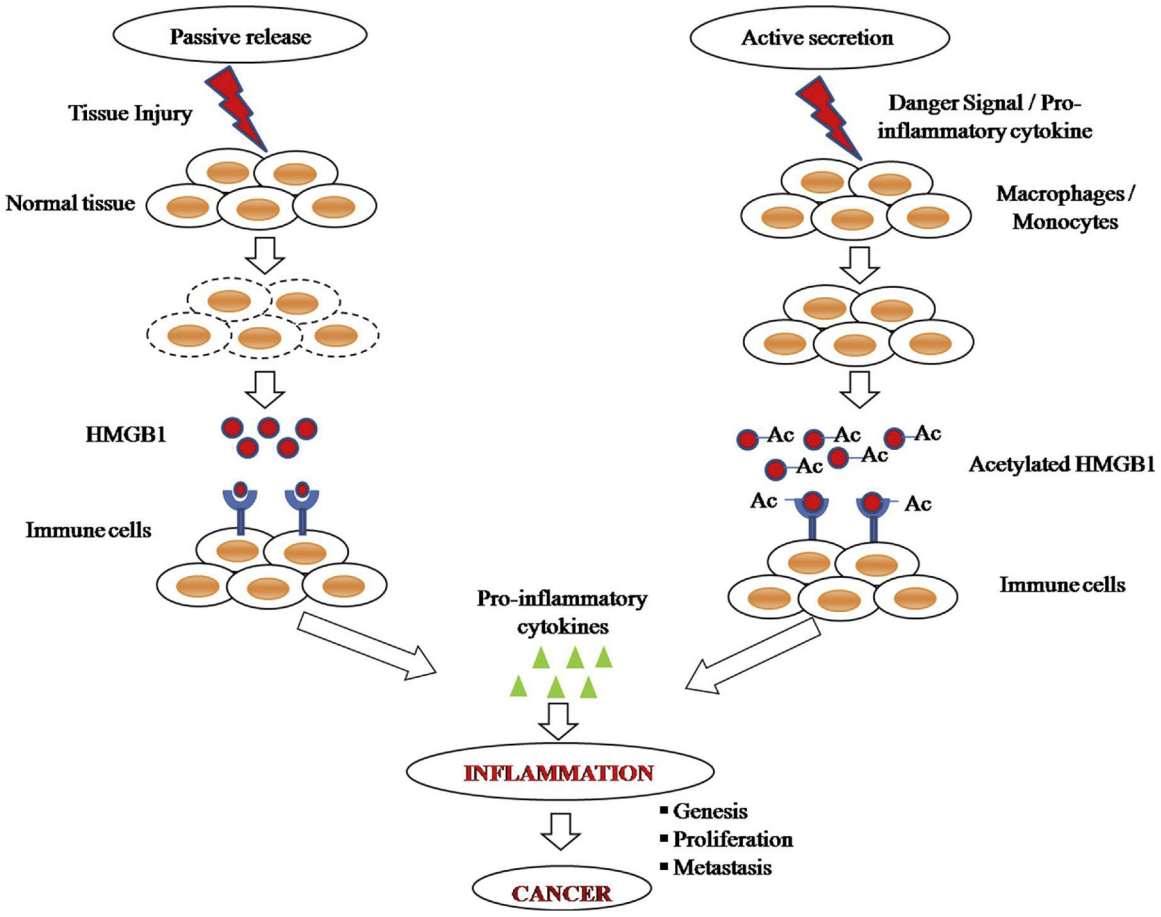

Fig. 3. Schematic diagrammatic representation of active secretion and passive release mechanism of HMGB1 protein.

used as a potent clinical biomarker of inflammation as it's shown in acetaminophen induced hepatotoxicity and pyroptosis. The sensitivity of idiosyncratic drugs (such as Ketoconazole, Trovafloxacin, Diclofenac, Troglitazone) in heptocytes injury induced was augmented by an inflammatory milieu created during inflammation or contamination and the condition was promoted by the pro-inflammatory cytokines primarily by TNF [28]. Inflammation was characterized by the release of intracellular content of cells into the extracellular space by osmotic lysis promoted by pro-inflammatory cytokines [29,30]. Overall, it could be postulated that secretion of acetylated HMGB1 occurred during the

pyroptosis condition and its extracellular release triggered the secretion of different cytokines in TLR4 and RAGE dependent manner [30,31]. Protein kinase-C was found to be responsible for the phosphorylation of HMGB1 which was released by calcium dependent mechanism [18].

3.2. Passive release of HMGB1

Extracellular HMGB1 was one of the main endogenous damage-associated molecular pattern molecules that trigger the array of inflammatory responses [7]. Extent of acetylation was the key factor responsible for the release and binding of HMGB1 with dsDNA. There were marked molecular differences between active or passive secretion of HMGB1. In necrotic cells, the extents of hyper-acetylation weaken the binding of HMGB1 to DNA and thus facilitated the release of HMGB1 from nucleus in passive manner. While in apoptotic cells intracellular maintenance of hypo-acetylated HMGB1 was due to its strong binding with dsDNA thus limited release into nearby environment, hence responsible for causing insignificant inflammation in the neighbouring tissue after apoptosis [13]. However, passively released HMGB1 in extracellular milieu could be considered as necrotic cell death marker with inflammation and immuno-modulatory effects.

4. Physiological functions of HMGB1 protein

The functions of HMGB1 could be divided on the basis of its localization and modifications. It may represent intracellular as well as extracellular functions. Different physiological functions of the HMGB1 protein are as follows.

4.1. Nuclear function of HMGB1

Inside nucleus, the HMGB1 binds with dsDNA in non-sequence specific manner to act like chaperon [32]. It facilitates different processes like transcriptional assembly, DNA base excision repair and recombination [33,34]. As TF, HMGB1 mediate regulation of cell-cycle and expression of genes. However, cells devoid of HMGB1 showed altered gene expression that is involved in cell-cycle regulation. Different cells passing through cell-cycle stages have different fate of utilization of nuclear HMGB1 as experimentally proved in HMGB1+/+ and HMGB1-/- cells [35]. Mammalian HMGB1 maintains stability of genome [36] and has intrinsic property to change the DNA structures, increasing its importance in different biological processes such as transcription, regulation of chromatin structure, DNA damage repair and recombination [3,37]. Loss of activity in HMGB1 has been found to increase the frequency of DNA damage in response to DNA damaging factors like radiation, carcinogens, chemotherapy and oxidative stress. HMGB1 can bind directly to bulky DNA lesions formed by environmental carcinogens, chemotherapeutic agents, and consequently promote DNA repair pathways. All four major repair pathways namely mismatch repair, base excision repair, nucleotide excision repair and double strand break repair *via* non-homologous end-joining were directly regulated by HMGB1 protein [38].

4.2. Cytosolic function of HMGB1

HMGB1 has also been reported to express in cytosol and into the extracellular space [39]. Extracellular HMGB1 showed immune responses either alone or by forming complex with other molecules [5]. The extracellular released HMGB1 has pathological symptoms such as cellular necrosis, liver injury, lung injury and different inflammatory processes [2]. Cytoplasmic HMGB1 expression has role in the autophagy regulation in cancerous cells. The expression level of cytoplasmic HMGB1-Beclin1 complex was found up-regulated in radio-resistant oral squamous cell carcinoma (oral SSC) in compare to non-irradiated oral SSC. However, the expression level of total HMGB1 inside cells remained constant, categorically proved the role of HMGB1-Beclin1 complex as the primary autophagy regulator in the oral SSC [40]. Cytosolic HMGB1 accumulation was favoured by acetylation and phosphorylation by preventing the re-localization of HMGB1 into the nucleus. Extracellular released HMGB1 has also been reported to promote inflammation, cell migration, proliferation, tumour growth and metastasis processes [41]. All types of cancer (Fig. 2) genesis steps like cell growth, migration, invasion and metastasis were induced by extracellular HMGB1 upon binding to membrane receptors like RAGE and TLRs [5].

4.3. HMGB1 as a cytokine / chemokine

HMGB1 induced secretion of different pro-inflammatory cytokines like IL-1β, TNF-α, IL-6, and IL-8 in the culture medium of human monocytes and neutrophils, act as an immuno-stimulator to pass signals to fresh immune cells further to secrete fresh pro-inflammatory cytokines [42]. The secreted pro-inflammatory cytokines IL-1β, TNF-α and LPS [42] consequently promoted the secretion of same and other inflammatory cytokines from other nearby located fresh immune cells and other cells to cause chronic inflammation [43]. The antigen presenting dendritic immune cells get matured by HMGB1 with enhanced antigen presentation ability. Apart from promoting cytokines secretion, secreted HMGB1 also acted as chemo-attractant cytokines that as chemokines and supported in up-regulated expression of vascular adhesion molecules consequently impaired the barrier function of epithelia. HMGB1 protein has been observed to reduce the phagocytosis by binding to phospahatidyl serine amino acid molecule exposed on the surface of neutrophil and other phagocytic cells [44].

4.4. HMGB1 as nucleosome stabilizer and transcription factor (TF)

HMGB1 has different cellular functions such as stability of nucleosomes, bending of DNA and acting as TF and interacting with other TFs to help them in binding with promoter consensus sequence [37]. DNA binding ability of HMGB1 has been primarily due to the Box-A, while ability of DNA bending was associated with Box-B. Binding and bending of DNA normally promoted by HMGB1 with the formation of nucleoprotein complex [32]. HMGB1 protein by interacting to other transcription factors on promoter modulates the expression of cytokine genes and thus promotes genesis and progression of cancer. For an example HMGB1 modulated TFs were reported from the family of Rel/NF-κB and p53 [45,46]. The Rel/NF-κB family TFs have role in the regulation of cancer *via* activation of signals that lead to division, differentiation and apoptosis. The p53 protein worked as a tumour suppressor and have important role in the regulation of cell cycle. Box-A and C-terminal domain of HMGB1 interacts with the N-terminal amino acids (363–376 residues) of p53, to regulate the cells [46]. As earlier discussed, both HMGB1 and p53 works as transcription factor in mutual cooperation to regulate the transition of autophagy to apoptosis, induced by the polychlorinated biphenyl quinone [47]. Optimal DNA structure for p53 binding has been found due to bending/binding property of HMGB1.

4.5. Can Tumour cell death induced by HMGB1 protein?

Recent development in HMGB1 research pointed out that endogenous HMGB1 has important role in the cellular energy metabolism which depends either on increased or decreased expression of HMGB1 protein. It has been observed that HMGB1 knock-out mice unable to survive due to lack of ability to utilize stored glycogen of hepatocytes [48]. On the other hand polymyositis patient unable to survive when there is increased level of HMGB1 protein in the myoplasm [49]. Increased level of secretory HMGB1 has ability to block the glucose dependent aerobic respiration by inhibiting enzyme M2 which is an isoform of piyruvate kinase. The inhibition causes metabolic shift from aerobic to anaerobic respiration for energy production by choosing

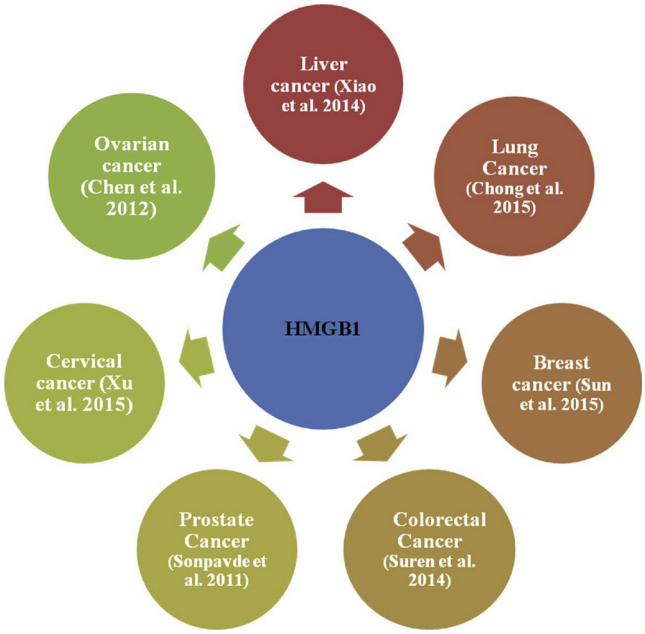

Fig. 4. HMGB1 in different types of cancer.

alternative energy production method of glutaminolysis [50]. Blocking the energy production by the inhibition of glutaminolysis in HMGB1 activated tumour cells could provide a therapeutic strategy for prevention and cure of cancer. Such metabolic dependent death of cancer cell could be triggered by HMGB1. It has been reported that HMGB1 boost innate immune defence by targeting glutaminolysis [50]. Thus tumour cell death induced by HMGB1 was found totally different that is by formation of giant mitochondria [51], which differ from the known classical pathway of cell death such as, necrosis, autophagy and apoptosis.

5. Role of HMGB1 protein in genesis and promotion of cancers

Currently HMGB1 expression has been found very important in the genesis and promotion of different inflammatory diseases including different types of cancers. Extracellular HMGB1 promoted cell migration and metastasis, thus established and proved its important role in the development and progression of cancers [41]. Role of HMGB1 in the genesis of different cancers has been reported so far in liver, lung, breast, colorectal, prostrate, cervical, and ovarian cancer by different research groups all over the world (Fig. 4). Role of HMGB1 in genesis and promotion of different types of cancer has been described below in details.

5.1. HMGB1 protein and liver cancer

Hepatocellular carcinoma (HCC) has been considered as one of the most common destructive tumours worldwide showing high mortality rate among different malignant tumours [52]. Several studies have shown that there were strong relationships between serum HMGB1 and pathological symptoms of liver cancer [53]. HMGB1 could be used as marker for the estimation and prognosis of tumour stages in HCC [41]. Induction of HMGB1 was found to be a decisive step in liver injury as induced HMGB1 participated in LPS/Gal N-induced mouse liver failure [53–55]. The HMGB1 along with ATP and surface-exposed calreticulin was one of the three main damage associated molecular pattern (DAMP) produced by cancer cells [56]. Seven mi-RNAs *i.e.* miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192, and miR-505 obtained from microarray analysis were differentially expressed in the serum of HCC patient in comparison to control revealing the involvement of mi-RNA in liver cancer [57]. The ability of proliferation, migration and invasion of HCC cells was suppressed and enhanced with the disruption of endogenous HMGB1 using small interfering RNAs [58]. As a mediator of delayed endotoxin lethality and injury, HMGB1 could be therapeutic target for lethal systemic inflammatory diseases [59].

5.2. HMGB1 protein and lung cancer

Lung cancer has been considered as one of the most lethal type among different types of cancer worldwide, due to lack of diagnosis at early stage [60]. Non–small cell lung cancer (NSCLC) was characterized as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma that accounts between 80–85% of all lung cancers [61]. Mutation profiling was used to differentiate between lung adenocarcinomas and squamous cell carcinomas [62]. In lung cancer, HMGB1 has up-regulated the expression of two key cancer regulating proteins MMP-2 and MMP-9 *via* Myd88-dependent pathway [63]. The mi-RNAs may exert their functions by base-pairing with 3′-untranslated region (3′-UTR) of target mRNAs and could be used as a biomarker for onset of malignancy [64]. Expression of miR-325-3p contributed the cell proliferation and invasion *via* targeting HMGB1 in NSCLC [65]. Overall, miR-325-3p demonstrated the functional effect on NSCLC cell lines in HMGB1 dependent manner and thus miR-325-3p could be a potential prognostic marker for NSCLC [65]. The expression of MMP-9 has *in-vitro*metastatic ability and was found significantly higher in HMGB1 over-expressed human NSCLC [63]. The activation state of phosphoinositide 3-kinase (PI3K) was supported by the over expression of HMGB1 and provided evidence for the involvement of HMGB1 in cancer progression, invasion, and metastasis [63,66,67]. Moreover, many investigation suggested that, HMGB1 gene polymorphisms have correlation with the risk factor in the lung cancer genesis. It was found that out of four single nucleotide polymorphisms, rs1045411 HMGB1 polymorphism primarily reduced the risk of development of lung cancer [68].

5.3. HMGB1 protein and breast cancer

Breast cancer has been considered as one of the foremost cause of cancer mediated death worldwide in females [69]. The genes BRCA1/2, CA15.3, and CA27.29 were already used in the diagnosis of breast cancer but the parameters were not enough for early detection [70]. Finding revealed that HMGB1 could be able to promote growth of breast cancer cells *in-vitro*. The mammary carcinoma for DAMP expression showed elevated HMGB1 compared to normal mammary epithelium. Myd88 inhibitory peptide analysis changed the HMGB1 expression level in cancerous cells which was mediated in a Myd88 dependent manner. The inhibition of Myd88 function lowered the HMGB1 gene expression [71]. Higher expression of α-Smooth Muscle Actin (ASMA), a cancer-associated fibroblasts and lower expression of cytoplasmic HMGB1combindly depict poor prognosis of breast cancer. However, both combinedly illustrated metastatic relapse most trust worthily [72]. The HMGB1 levels in cancerous tissue could be correlated with lymphatic metastasis but were not associated with the age of patient and tumour size [73]. The recent report showed that invasion and migration of breast cancer cells can be suppressed by miR-200c which was regulated *via* expression level of HMGB1. The miR-200c and HMGB1 may prove to be useful biomarkers to detect the progression of breast cancer and could be targeted by gene therapy technique for cure [74].

5.4. HMGB1 protein and colorectal cancer

Colorectal cancer has been reported as the fourth leading cause of cancer-related death worldwide. Over 1.3 million new colorectal cancer cases were diagnosed globally, with a mortality rate of nearly 700,000 in the year 2012 [75]. Generally, colorectal cancer developed as a result

of neoplastic progression from adenomas into adenocarcinomas. This transformation could be triggered by both genetic and epigenetic factors and take decades in complete transformation, thus providing opportunity for early detection [76]. Expression of HMGB1 and its role as a prognostic factor in colorectal carcinoma was focused by different researchers [77]. Over-expression of HMGB1 showed an important role in migration of cells, tumour progression and metastasis in colorectal cancer, thus could be consider as a significant predictive factor [78,79]. However, HMGB1 gene silencing approach found to slow down the growth of colorectal tumours, decreased invasion, slow migration and also found to inhibit the development of xenograft tumour in nude mice [80]. Thus it corroborates the idea that HMGB1 may be a prognostic factor and could be affecting the expression of other genes having role in cell growth, apoptosis, invasion and metastasis.

5.5. HMGB1 protein and prostate cancer

The continuous increase in the emergence and death related to prostate cancer showed that approximately 1.7 million new cases and 499,000 new deaths could be recorded by near 2030 [75]. The research groups working on the prostate cancer reported that HMGB1 had a pivotal role in prostate cancer progression and development [81]. Further, study demonstrated that HMGB1 derived peptides could be tested as an adjuvant for enhancing the efficacy of prostate cancer vaccines and new type of vaccine development [82]. Drug untreated primary prostate cancer tissue showed significantly higher HMGB1 mRNA expression than the normal non-cancerous prostate tissues.

5.6. HMGB1 protein and cervical cancer

Cervical cancer that occurs in women has become the primary cause of cancer-related deaths among women in developing nations due to late diagnosis. The researchers have found up-regulated gene expression of HMGB1 in most of the cervical cancer [83]. Increased expression level of HMGB1 has a major role in SCC progression and could be used as a marker for predicting the prognosis of SCC patients [84]. However, level of HMGB1 protein and serum SCC-Ag content were found higher in the cancer patient than the non-cancerous. The research reports using micro RNA were highly encouraging and could be used in future for treatment of cervical cancer which has been reported resistance to most of the cancer drugs. The micro RNA called miR-142 down regulated the expression of HMGB1 and also enhanced the cell apoptosis in cervical cancer cells thus could be used in future to treat the cervical cancer [85].

5.7. HMGB1 protein and ovarian cancer

Expression of HMGB1 protein was found over-expressed in ovarian cancer but the expression was linked with poor clinico-pathologic explanation [86]. Like many other cancer HMGB1 up-regulated expression was correlated with genesis, growth and metastasis of ovarian cancer [87]. The gene knockout strategy for HMGB1 was found to suppress cell proliferation by cell-cycle arrest at G1/G0 phase and decreased expression of cyclin-D1 and PCNA [86].

6. Conclusion

Primarily HMGB1 was believed to be as a DNA binding nuclear protein involved in nucleosome stability and playing strong role in transcriptional regulation but researches occurred in recent time proved that it has diverse biological role in clinico-pathological aspect, apart from nucleosome stability. It can play an important role as a cytokine which involved in triggering the genesis of inflammation and inflammation related diseases including cancer by up-regulating the expression of other inflammatory cytokines. HMGB1 could be either actively secreted by inflammatory cells like macrophages and NK-cells during the tissue injury and oxidative stress or can be passively released from necrotized tissues in the outside environment activating other normal immune cells to secrete different types of inflammatory cytokines to create microenvironment for the genesis and promotion of cancer [88,89]. As a transcription factor HMGB1 binds to the promoter region either alone or with help of the other transcription factors already bound or vice-versa to the DNA thus regulating the expression of respective genes [37].

Even in hypoxia condition solid tumours keep on growing and cancerous cells remain alive and proliferating became an unique features of the tumours. Most probably this is due to many features but hypoxia induces HIF-1 (Hypoxia inducible factor-1) expression, which promotes the translocation of HMGB1 from nucleus to the cytoplasm [90,91] is one of most prominent reason. Binding of HMGB1 with TLR2, TLR4 and TLR5 receptors activates Myd88 molecule which finally responsible for the activation of inflammatory transcription factor NF-kB by phosphorylation and ubiquitin mediated degradation of IkB [Yamamoto and Gaynor, 2004]. After damage of cells released HMGB1 binds to the cell's DNA and this HMGB1- DNA complex subsequently activates TLR9 signaling pathway which leads to cancer genesis [92]. In another report, binding of HMGB1 to the RAGE receptor activates Ras-oncogene that leads to activation of MAP kinase mediated NF-kB inflammatory pathway [93,94]. Moreover, activated NF-kB promotes the expression of different downstream pro-inflammatory cytokines such as IL-1β, IL-6, IL-18 and TNF-α, which is responsible for inflammation and cancer genesis [88,89,95,96]. Up-regulated endogenous inflammatory cytokines IL-1β, IL-6, IL-18 and TNF-α further activates macrophage and dendritic cells for the secretion of HMGB1 into extracellular milieu [97,98]. Also, over-expressed NF-κB promotes the expression of COX-2 and COX-2 finally causes necrotic cell death, which is responsible for release of HMGB1. Descendent gene involved in Cox-2 mediated signaling pathway are PGE2, iNOS, NO, and ONOO− [90] (Fig.5).

Recent findings by different research groups reported in different journals showed that increased level of HMGB1 could block aerobic respiration by inhibiting isoform of enzyme leading a metabolic shift from aerobic to anaerobic respiration choosing alternative energy production pathway of glutaminolysis [50]. Blocking or inhibition of glutaminolysis alternate pathway of energy production in HMGB1 dependent tumour cells could be an alternative therapeutic strategy for prevention and cure of cancer.

Overall research outputs with different research results have proved that there is well-built correlation between up-regulated HMGB1 expression and pathological symptoms of cancers. Moreover, HMGB1could be used as a marker protein for the prognosis of tumour stages in different cancer and should be targeted to stop expression thus preventing and curing the cancer. Research on the use of different drugs and micro RNA to control the expression of HMGB1 is under progress and many groups are working actively. Some of the groups have got success in showing the down regulation of HMGB1 in response to drugs and micro RNA, however, the effectiveness to treat cervical and other cancer has yet to be clinically authenticated for human use.

Transparency document

The Transparency document associated with this article can be found in the online version.

Conflict of interest

The authors declare no conflict of interest.

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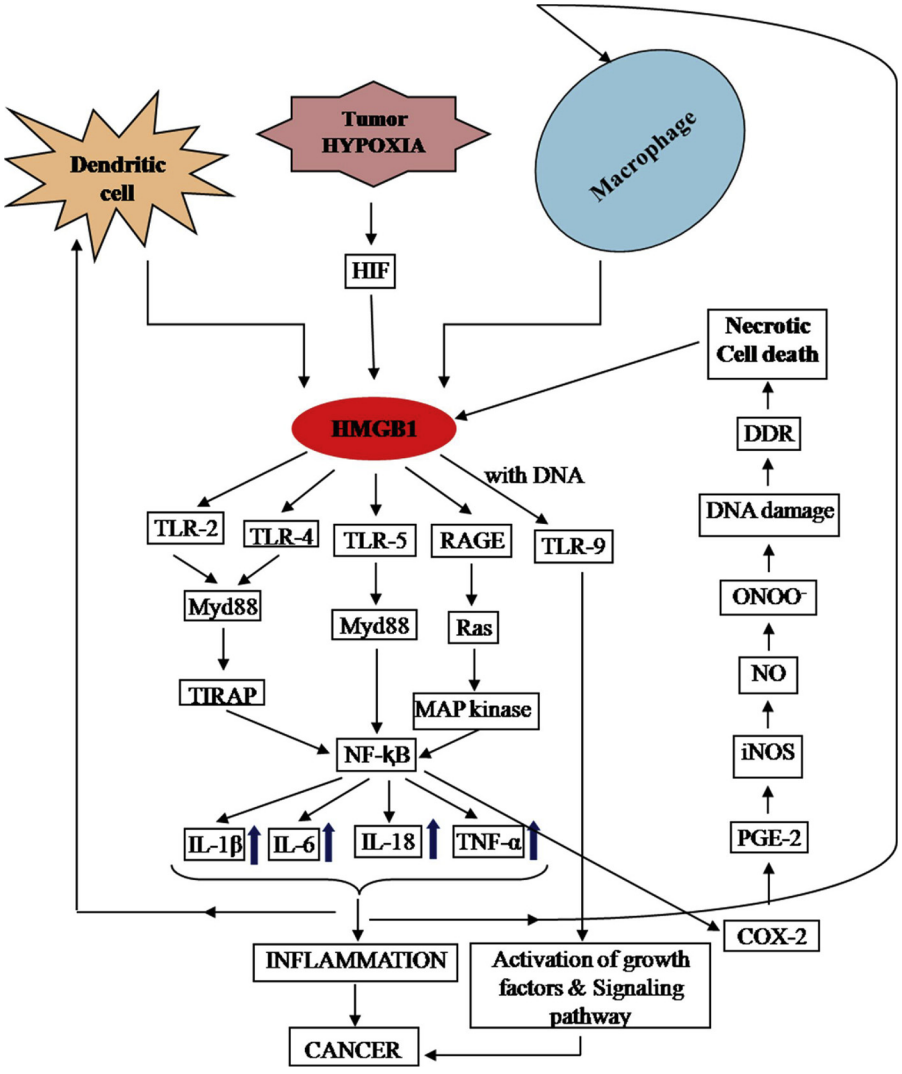

Fig. 5. Mechanism for crosstalk between tumor hypoxia, DNA damage and inflammation in the genesis of cancer.

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