

Paradoxical role of high mobility group box 1 in glioma: a suppressor or a promoter?

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Abstract

Gliomas represent 60% of primary intracranial brain tumors and 80% of all malignant types, with highest morbidity and mortality worldwide. Although glioma has been extensively studied, the molecular mechanisms underlying its pathology remain poorly understood. Clarification of the molecular mechanisms involved in their development and/or treatment resistance is highly required. High mobility group box 1 protein (HMGB1) is a nuclear protein that can also act as an extracellular trigger of inflammation, proliferation and migration, through receptor for advanced glycation end products and toll like receptors in a number of cancers including gliomas. It is known that excessive release of HMGB1 in cancer leads to unlimited replicative potential, ability to develop blood vessels (angiogenesis), evasion of programmed cell death (apoptosis), self-sufficiency in growth signals, insensitivity to inhibitors of growth, inflammation, tissue invasion and metastasis. In this review we explore the mechanisms by which HMGB1 regulates apoptosis and autophagy in glioma. We also looked at how HMGB1 mediates glioma regression and promotes angiogenesis as well as possible signaling pathways with an attempt to provide potential therapeutic targets for the treatment of glioma.

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Introduction

Gliomas are primary brain tumors that originates from nerve stromal cells including glial cells, ependymal cells, choroid plexus epithelial cells, and nerve parenchymal cells and noted for their high morbidity, high recurrence, high case-fatality rate (overall 5-year survival of only 13%), low cure rate and accounts for about 60% of all intracranial primary brain tumors.^{1,2} Gliomas are malignant tumors with multigene abnormality and their pathogenesis propose to be as a result of activation of proto-oncogene's high-expression and/or deletion as well as inactivation of cancer suppressor gene causing abnormalities in cell signaling conduction path, change in cell cycles, extension of life cycle, defect of apoptosis etc. which leads to ferocious cell proliferation and malignant transformation.^{3,4} High mobility group box 1 protein (HMGB1) was discovered forty years ago in calf thymus and named according to its electrophoretic mobility in polyacrylamide gels.⁵ HMGB1 has been detected in immature cells and a variety of solid tumors. Many researchers have found HMGB1 to be highly expressed in many malignancies including lung cancer, breast cancer, head and neck squamous cell carcinoma, colon cancer, nasopharyngeal carcinoma,⁶⁻⁸ and have associated it with their occurrence, invasion, and metastasis. It is still unclear the specific mechanisms governing the biological activities of HMGB1 and gliomas and very few researches have explored the role of HMGB1 in the development of glioma cells. Current studies in molecular biology of tumors are exploring the mechanisms of gliomas occurrence, progress and therapy, such as targeted therapy, which could be a new and effective treatment method. Our review focuses on the mechanisms by which HMGB1 regulates apoptosis and autophagy in glioma. We also looked at how HMGB1 mediates glioma regression and promotes angiogenesis as well as possible signaling pathways with an attempt to provide potential therapeutic targets for the treatment of gliomas.

Structure

Human HMGB1 is an alarmin encoded by a single gene that is located in chromosome 13q12. It contain four introns and five exons, encoding a 215-aminoacid protein, with a molecular weight of about 30 KD and highly conserved, with an amino acid sequence homology of over 98% between human and rodents.^{9,10} HMGB1 protein is divided into three domains: two positively charged DNA-binding motifs (boxes A, B) and a C-terminal acidic tail. While the two motifs contains 80-90 amino acid residues and are strongly alkaline, the carboxyl terminus also known as acidic terminal is rich in aspartic and glutamic acids and negatively charged.¹¹

Function

HMGB1 binds to DNA with specific structures and affect the structural state of their target sequence and thus participate in the key life activities including the division, differentiation, and maturation of cells, DNA repair, DNA recombination, regulation by steroid hormones, and regulation of gene transcription^{12,13} hence HMGB1 is a DNA binding protein in the nucleus. Outside the cells, HMGB1 acts as typical injury-related molecule when released by necrotic cells or activated immune cells and by interacting with cytokines, chemokines, and growth factors, it regulates various activities of cells.⁵ Excessive secretion of HMGB1 can suppress apoptosis and thus cause the occurrence and development of tumors hence it is an anti-apoptotic protein.¹⁴ HMGB1 is also associated with the activation of the matrix metalloproteinases, plasminogen system and the migration of adherent cells.¹⁵ Therefore HMGB1 is a multifunctional protein.

HMGB1 acts as a pro-tumor protein in the extracellular compartment due to its cytokine, chemokine and growth factor activity. It is now clear that certain amino acids in the B box domain are vital for the protein's pro-inflammatory cytokine function, particularly the cysteine amino acid in the position 106 (C106) in the B box domain that is a requisite for HMGB1 to bind to toll like receptor-4 (TLR-4) activating macrophages.^{16,17} HMGB1 activates dendritic cell via the reduced form of C106. HMGB1 has no post-translational modifications in its completely reduced state. The reduced form is usually the main form in nucleus and cytoplasm in basal conditions and interacts with numerous receptors, such as CXCR4, to promote cell migration. HMGB1 inflammatory ability is prohibited when cysteines are oxidized to sulfonic acids, implying that the function of HMGB1 can be modified via the cysteine redox modifications.^{16,18} HMGB1 is oxidized in the cytoplasm after reactive oxygen species (ROS production).^{16,19} It is well known that the extracellular environment is mainly oxidative during inflammatory processes. The oxidation of HMGB1 acts as a physiological negative feedback that restricts the pro-inflammatory activity of HMGB1 preventing excessive inflammatory damage.^{16,18} After oxidation, sulfonyl HMGB1 has no activity for cell migration or cytokine induction.^{16,19} Oxidative stress appears to be a central regulator of HMGB1's translocation, release and activity in inflammation and cell death although this mechanism is not yet clear.^{16,20} Calcium- or ROS-dependent mechanisms have been confirmed to induce HMGB1 release.^{13,16}

HMGB1 regulates apoptosis in glioma

Zhao and Chen demonstrated that HMGB1 is eminently released under normal conditions and authenticate potential activity of cancer suppressor gene. They indicated that the percentage of apoptotic cells relatively elevated after the exogenous *HMGB1* gene is transferred into the CD133 glioma cells with an originally low release, which means that HMGB1 is on the upstream of the regulatory pathway and its stimulation or over-release can promote apoptosis of glioma cells.²¹

Studies have shown that necrotic cells can release HMGB1 into the extracellular environment,²² and necrosis is a characteristic feature of malignant gliomas. It is well noted that consistent secretion of HMGB1 enhances the growth and progress of gliomas leading to continues necrosis of the lesions. This was supported by Jing and colleagues who explored the role of *HMGB1* gene in the

U251 and U-87MG cells and also concluded that the up-regulated HMGB1 plays a key role in the development of gliomas.²³ Further study has demonstrated that the degree of secretion of HMGB1 in different pathological grade of gliomas and noted a profound difference between them. The central role of HMGB1 in necrosis and malignancy in glioma is due to an autocrine factor which promotes the growth and migration of tumor cells.²⁴

Other authors are of the view that HMGB1 that is released into the extracellular environment may cause surrounding tumor cells to undergo constant proliferation and induce the regeneration of small blood vessels, thus promoting tumor growth. HMGB1 may cause tumorigenesis by disordered gene secretion, resulting in glial cells obtaining a tumor phenotype and resistance to apoptosis.²⁵ Research has further indicated that the necrotic tumor cells which secrete HMGB1 accelerates tumor development and infiltration into the surrounding brain tissue hence presents a stronger resistance, which makes it difficult to attain whole resection leading to poor prognosis.²⁶ Also, growth and migration cells in gliomas *in vitro* were suppressed when HMGB1 was inhibited.²³

HMGB1 induces autophagy in glioma

Studies have shown that HMGB1 promotes Beclin-1-PI3K-III complex formation by binding with Beclin-1 potentially through the methyl ethyl ketone (MEK) or extracellular signal-regulated kinase [ERK] (MEK/ERK) 1/2 pathway.^{27,28} Mizushima and associates stated that the phosphatidylinositide 3-kinases (PI3K) family consists of three classes: I, II, and III. They explained that, the PI3K-III activity is required for autophagic activation, while PI3K-I has a negative effect on autophagy.²⁹ He and Klionsky also demonstrated that Beclin1 mobilize PI3K-III to form the Beclin-1-PI3KIII complex, consequently bringing about autophagosome nucleation.³⁰ Banzhou and colleagues showed that HMGB1 modulated autophagy by triggering the MEK/ERK1/2 pathway, while the genetic suppression of PI3K-III deprived the HMGB1-induced phosphorylation of the MEK-ERK1/2 pathway and inhibited autophagic stimulation. They proposed that MEK/ERK1/2 signaling functions as a downstream signal of PI3K-III in HMGB1-induced autophagy. They also confirmed that stimulation of the MEK/ERK1/2 signaling pathway was linked with HMGB1-mediated formation of the Beclin-1-PI3K-III complex.²⁷

Thorburn and associates have indicated that autophagy can regulate the pattern of dying cells by modulating the selective secretion of HMGB1, and therefore selectively controlling an influential pattern of dying cells that is usually associated with necrosis.³¹ They indicated that epidermal growth factor receptor-targeted diphtheria toxin (DT-EGF) activates autophagy more cogently in the glioblastoma cell lines. They further argue that autophagy that is induced by DT-EGF in U87MG cells inhibits caspase activation and hence did not activate apoptosis. They demonstrated that tumor cells that are dying with increased autophagy selectively secreted the nuclear HMGB1 protein, but do so without displaying other characteristics of necrosis such as lipopolysaccharide (LDH) secretion or loss of membrane integrity such that propidium iodide can stain DNA.³¹ They concluded that autophagy can activate the amount of death in response to a specific stimulus and the characteristics associated with the dying cells and that the overall biological effect of autophagy manipulation during treatment with targeted anticancer drugs like DT-EGF that kill tumor cells may depend on both aspects.³¹

HMGB1 mediates glioma regression

HMGB1 secreted from dying tumor cells might be liable for activating toll like receptor-2 (TLR-2) on dendritic cell (DC) *in vivo* and resultant T cell-dependent tumor regression (Figure 1). Curtin *et al.* establish that treatment of brain tumors with an adenoviral vector-thymidine kinase (Ad-TK) + ganciclovir (GCV) [Ad-TK (+GCV)] and adenoviruses expressing Flt3L (Ad-Flt3L) injected directly into the brain tumor microenvironment induce a systemic adaptive antiglioma immune response. They indicated that this treatment is stringently relying on the stimulation of TLR signaling on bone marrow DCs that infiltrate the tumor. They further stated that dying glioma cells secreted HMGB1 in response to infection and killing with Ad-TK (+GCV); HMGB1 in turn induced TLR-2-dependent nuclear factor-kappaB (NF- κ B) signaling and DC stimulation (Figure 1). They again confirmed that glioma-derived HMGB1 secreted from dying cells is necessary for the clonal expansion of CD8+ T cells specific for glioma antigens including the Trp₂₁₈₀₋₁₈₈ peptide (H-2Kb), and that the effects of HMGB1 are mediated through TLR-2 signaling on tumor-infiltrating DCs.³²

Initial studies demonstrated that glioma-derived HMGB1 as the endogenous TLR-2 ligand, whose signaling is essential to evoke systemic adaptive immune-mediated glioblastoma (GBM) regression and long-term immunological memory in an intracranial glioma model.³³ Curtin *et al.* concluded that tumor-derived HMGB1 evokes endogenous TLR-2 signaling and initiates a CD8+ T cell dependent anti-GBM immune response. Hence they proposed that endogenous TLR2 ligands would also be released from isogenic glioma cells (GL261 cells) treated with Ad-TK + GCV. HMGB1-mediated TLR-2 signaling links the effects of Flt3L on the recruitment of immune cells to the brain tumor microenvironment to their capacity to induce a systemic antitumor immune response. Therefore endogenous TLR-2 ligands could play a part in tumor regression.³²

HMGB1 promotes angiogenesis in glioma

Glioma-associated stromal cells like astrocytes, endothelial cells, mesenchymal cells and infiltrating inflammatory cells play a crucial function in tumorigenesis, angiogenesis, invasion and immune evasion.³⁴ Piao *et al.* demonstrated that, in the midst of

these cells, infiltrating microglia (MG) and macrophages (MP), (known as tumor-associated macrophages or TAMs) have recently gained attention due to their participation in glioma leakage from anti-angiogenic agents.³⁵ Sorci and colleagues proposed that as a pattern identifying receptor, receptor for advanced glycation end products (RAGE) binds to HMGB1 that arise from damaged cells and trigger the immune system.³⁶

Kierdorf and associates indicated that the enthrallment of RAGE by its ligands elucidate in the stimulation of multiple downstream signaling pathways which sooner or later lead to the induction of NF- κ B, ERK1/2, p38 and signal transducer and activator of transcription (STAT3) and subsequent regulation of cytokines, chemokines, adhesion molecules, and pathways that modulate cell proliferation, survival, differentiation, migration, phagocytosis and autophagy³⁷ (Figure 2). Also the activation of RAGE in TAMs, modifications in the manifestation of RAGE ligands may have differently wedged tumor angiogenesis in reaction to RAGE ablation in each model. van Beijnum *et al.* demonstrated that the K-Luc model released high levels of HMGB1 and S100A9, which intensify tumor invasion, migration and angiogenesis.³⁸ Advanced levels of HMGB1 secreted by K-Luc gliomas may have subdue the physiological state of RAGE signaling for angiogenesis in this model. Possibly suppression of HMGB1 production in this model could be a more effective anti-angiogenic strategy than inhibiting RAGE signaling.³⁴

HMGB1 signaling pathways in gliomas

HMGB1 is secreted by inflammatory cells and passively released from necrotic cells and actively functions as an extracellular signaling molecule during processes such as cell differentiation, tumor cell proliferation, inflammation, cell migration and tumor metastasis.^{39,40} Although the mechanism by which HMGB1 is involved in tumorigenesis is unclear, it is believed that activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, which occurs through HMGB1 binding with high affinity to several receptors, including the receptor for advanced glycation end products (RAGE), toll-like receptors TLR-2, TLR-4 and TLR-9 are some of the mechanisms (Figure 1). These interactions trigger the activation of key signaling pathways involved in the regulation of cell differentiation, growth, motility and apoptosis. While some researchers have indi-

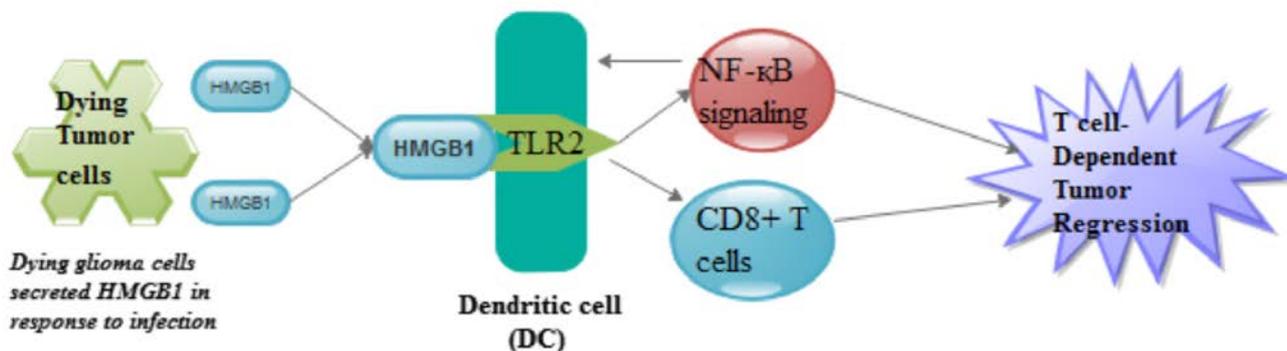


Figure 1. HMGB1 secreted from dying tumor cells in response to infection might be liable for activating TLR2 on dendritic cell (DC) *in vivo* and resultant T cell-dependent tumor regression.

cated that HMGB1 can over activate STAT by activating the JAK/STAT pathway and activated STAT, particularly STAT3, inhibits tumor cell apoptosis hence accelerates the cell cycle and thus leads to tumorigenesis.⁴¹⁻⁴³ Others are of the view that HMGB1-RAGE interactions activate mitogen-activated protein kinase and protein kinase B signaling pathways, resulting in extracellular matrix degradation, tumor invasion and metastasis, leading to tumor development⁴⁴ (Figure 2). Rosaria and colleagues noted an increase in ERK phosphorylation in their study with HMGB1 and glioblastoma cells and indicated that HMGB1-induced ERK activation and cell proliferation was effectively inhibited by PD98059 and the selective inhibitor of the mitogen-activated protein kinase (MEK) and that the functional blockade of RAGE by means of neutralizing anti-RAGE antibody strikingly prevented both the ERK phosphorylation and cell proliferation elicited by exogenous HMGB1.⁴⁵ Studies have shown that HMGB1 when released into the extracellular environment unites with its high affinity receptor RAGE and upregulates RAGE expression.⁴⁶

It is well known that the activated form of Ras-related C3 botulinum toxin substrate 1 (Rac1), a member of the Rho-family of small GTPases, stimulates cell migration and, as recent studies have revealed that it plays a major role in glioma invasion.⁴⁷ These findings show that RAGE binding induces Rac1 activation and concomitantly promotes cell migration, and thus support the view of RAGE as the major receptor mediating HMGB1-dependent migration^{48,49} (Figure 2). HMGB1 up-regulates the expression of MMP-9, which belongs to matrix metalloproteinases (MMPs) involved in the initiation, invasion, and metastasis of many kinds of cancers as well as glioma and gastric cancer cells which may explain its association with invasion and metastasis of glioma tumor^{23,50} (Figure 1). Yu and colleagues indicated that the hyper methylation of the CpG island upstream of miR-129-2 led to the down-regulation of miR-129-2 in glioma patients and that the demethylation of miR-129-2 by 5-aza-2'-deoxycytidine (5-Aza-dC) treatment increased miR-129-2 expression in glioma cells and resulted in significant inhibitory effects on cell cycle, migration, and invasion. The concluded that, the methylation status of miR-129-2 may be employed as a potential biomarker in glioma.⁵¹

Therapeutic potentials of HMGB1 in gliomas

HMGB1 has been proposed as a novel target for cancer therapy,⁵² and further studies have shown that the validated involvement of miR-129-1/HMGB1 link in glioma cells may provide potential to use miR-129-2 and HMGB1 as therapeutic targets for glioma. Reintroducing expression of miR-129-2 in glioma cells suppresses cell growth, migration, and invasion and promotes cell apoptosis, which may provide a novel therapeutic strategy for treatment of glioma.^{51,53}

Although no specific research data have been published concerning HMGB1 expression and functional role (and those of RAGE) in human astrocytomas, the most frequent and deadly primary intracranial tumors in adults. These tumors can show different stages of malignancy, and most low-grade tumors subsequently progress.^{45,54} The characteristics of high-grade tumors (including anaplastic astrocytomas and glioblastomas) are excessive proliferation, infiltrative growth, increased angiogenesis and resistance to apoptosis, which limit the success of current therapeutic approaches. Malignant gliomas also show areas of necrosis, which is a significant prognostic factor and allows the categorization of a tumor as glioblastoma.^{45,54}

HMGB1 is also closely associated with tumor drug resistance. A previous study found that HMGB1 induces autophagy, causing the cells to become resistant to chemotherapy drugs. Release of HMGB1 from dying tumor cells has been postulated to direct the immunologic response to dying cells, which determines the clinical outcome of anticancer therapies.^{32,55,56} Marianela and colleagues demonstrated that HMGB1 release from dying tumor cells is crucial for the efficacy of Ad-TK+GCV+Ad-Flt3L in GBM-bearing rats and its blockade completely abolishes the efficacy of the therapy. HMGB1 did not seem to play a critical role in the induction of anti-GBM immunologic memory induced by the combined therapy.⁵⁷ Further, the efficacy of the combined treatment is mediated by the release of the endogenous ligand HMGB1, which we have previously shown signals *via* TLR-2 receptors on tumor-infiltrating dendritic cells.³²

HMGB1 as an endogenous TLR-2 agonist that is secreted from

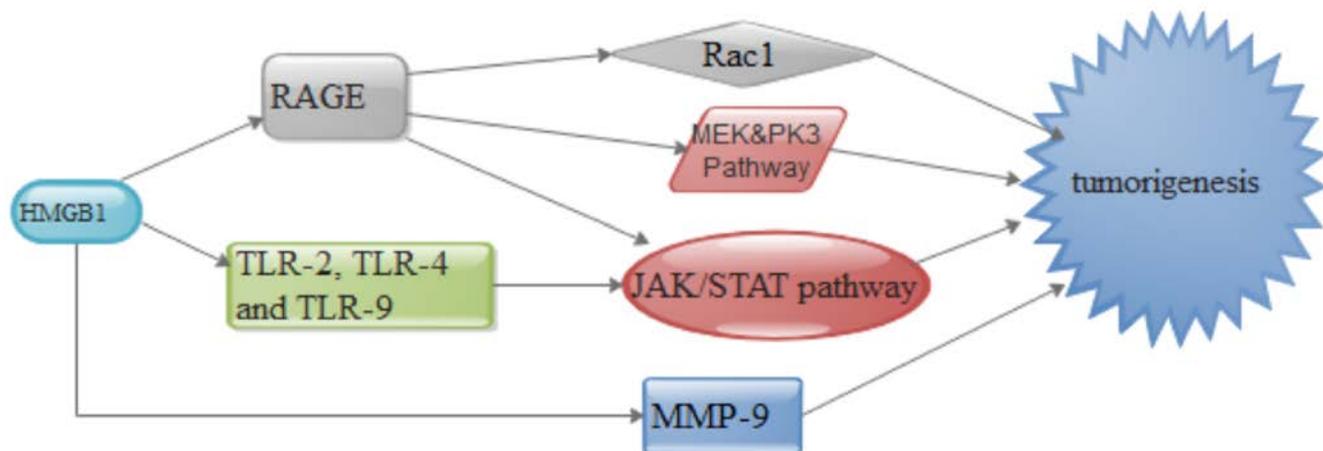


Figure 2. HMGB1 binding with high affinity to several receptors, including the receptor for advanced glycation end products (RAGE), Toll-like receptors TLR-2, TLR-4 and TLR-9 which activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway leading to tumorigenesis. HMGB1-RAGE interactions activate mitogen-activated protein kinase and protein kinase B signaling pathways leading to tumor development. RAGE binding induces Rac1 activation and concomitantly promotes tumorigenesis. HMGB1 up-regulates the expression of MMP-9 leading to tumorigenesis.

dying tumor cells, both *in vitro* and *in vivo* in reacts to several tumor cell killing conceptualization, *i.e.*, adenoviral vector (Ad-TK (+GCV), radiation, and temozolomide. Ad-Flt3L + Ad-TK has been proven to have potential therapeutic value in the treatment of other solid tumors, and implying that the same molecular mechanism described initially could also be liable for the elimination of metastatic brain tumors.³²

Glycyrrhizin, directly binds to and suppress HMGB1,⁵ has been proven to block proliferation, migration, and angiogenesis in several tumors.⁵⁸ Glycyrrhizin totally blocked TLR-2-dependent NF- κ B stimulation by supernatants from dying meaning that HMGB1 release from GL261 cells stimulates TLR-2 signaling. Blocking HMGB1 action *in vivo* using glycyrrhizin or specific anti-HMGB1 neutralizing antibodies, suppressed Flt3L/TK-induced brain tumor regression.³² Glycyrrhizin does not cause the secretion of HMGB1 from apoptotic chromatin, meaning that it will not produce paradoxical pro-inflammatory responses to apoptotic cells.⁵⁹

Conclusions

Glioma-associated stromal cells like astrocytes, endothelial cells, mesenchymal cells and infiltrating inflammatory cells play a crucial function in tumorigenesis, angiogenesis, invasion and immune evasion. HMGB1 is on the upstream of the regulatory pathway and its stimulation or over-release can promote apoptosis of glioma cells. Autophagy can regulate the pattern of dying cells by modulating the selective secretion of HMGB1, and thus selectively controlling an influential pattern of dying cells that is usually associated with necrosis. HMGB1 secreted from dying tumor cells might be liable for activating TLR-2 on dendritic cell (DC) *in vivo* and resultant T cell-dependent tumor regression. Furthermore, HMGB1 may be an important prognostic marker. Therefore, treatments targeting HMGB1 are expected to become a novel therapeutic approach towards the treatment of patients with glioma.

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