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The Dual Role of HMGB1 in Pancreatic Cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of exocrine pancreatic cancer with a 9% five-year survival rate. High mobility group box 1 (HMGB1) is a nuclear protein that can act as a DNA chaperone in the sustainment of chromosome structure and function. When released into the extracellular space, HMGB1 becomes the most well-characterized damage-associated molecular pattern (DAMP) to trigger immune responses. Recent evidence indicates that intracellular HMGB1 is a novel tumor suppressor in PDAC, which is connected to its role in the prevention of oxidative stress, genomic instability, and histone release. However, since extracellular HMGB1 is a DAMP and pro-inflammatory cytokine, cancer cells can also exploit it to survive through the receptor for advanced glycation endproducts (RAGE) in the pancreatic tumor microenvironment. Interestingly, targeting the HMGB1-RAGE pathway has become a new anticancer therapy strategy for PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common histological type of pancreatic cancer, accounting for more than 90% of cases. Pancreatic cancer is the third leading cause of cancer-related death, with a five-year survival rate of just 9% in the United States according to the American Cancer Society (1). In 2018, about 55,440 and 44,330 people will be diagnosed or die with pancreatic cancer in the United States, respectively (1). Indeed, rates are rising faster than any other cancer and the disease is anticipated to become the second leading cause of cancer-related death around 2020 in the United States. Age, smoking, being overweight, pancreatitis, and diabetes are the major known risk factors for pancreatic cancer. Compared to other tumor types, PDAC has different biological features that make it so deadly. The location of the pancreas is deep in the abdominal cavity and pancreatic cancer is seldom detected early or show early noticeable symptoms. In turn, 80% of PDAC patients are diagnosed with advanced metastatic disease, and surgical removal of the tumor is possible in less than 20% of patients with PDAC. In addition, chemotherapy or radiation is commonly used before or after surgery in the treatment of metastatic PDAC (2). Improving knowledge of histology and the genetics of pancreatic tumorigeneses is essential for designing new anticancer approaches to treat this deadly disease (3, 4).

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Chromatin, a mass of genetic material composed of proteins, DNA, and RNA, is found inside the nucleus of eukaryotic cells. In 1973, “high mobility group (HMG)” proteins, which can recognize and bind different DNA structures, were first isolated from the chromatin of calf thymus (5). Currently, the HMG family is divided into three superfamilies, namely HMGB (e.g., HMGB1, HMGB2, HMGB3, and HMGB4), HMGA (e.g., HMGA1 and HMGA2), and HMGN (e.g., HMGN1 and HMGN2) according to the characteristic sequence motif (6). Among them, high mobility group box 1 (HMGB1, also termed amphoterin) is a well-characterized non-histone nuclear protein that can be released by various cells under stresses. Dysfunction of HMGB1 signaling contributes to each hallmark of cancer (7, 8). In this review, we outline the basic function of HMGB1 inside and outside of cells and highlight the multifaceted role of HMGB1 in pancreatic tumorigenesis and therapy.

Nuclear HMGB1

HMGB1 was extremely conserved during evolution and contains two HMG boxes that bind and bend DNA. Nuclear HMGB1 is an essential chromosomal architectural factor and implicated in a number of nuclear events such as nucleosome stability and sliding (9). Nucleosome is a basic unit of DNA packaging in eukaryotes, consisting of a segment of DNA wound in sequence around a histone octamer core (histones H2A, H2B, H3, and H4). HMGB1 is required for the assembly of chromatin *in vitro* (10). HMGB1 can bind to linker histones (H1 and H5) to relax nucleosome, which leads to more accessibility of chromatin at the distorted site. Moreover, loss of HMGB1 decreases the number of nucleosomes by 20–30%, increases histone release, and causes telomere shortening, which in turn affects genome chromatinization (10). HMGB1 has powerful functions in DNA binding, with structure specificity, but not sequence specificity (11). HMGB1 not only binds to normal DNA, but also to distorted and damaged DNA such as H-DNA (12), four-way DNA junctions (13–15), and oxidative-damaged DNA (16). As a DNA chaperone, HMGB1 can bend and change DNA structure and morphology by unwinding (17), looping (18), or compacting DNA (17). This DNA chaperone activity of HMGB1 contributes to V(D)J recombination, gene transcription, DNA replication, DNA repair, and gene transfer. Consequently, loss of HMGB1 increases DNA damage and decreases DNA repair efficiency in response to oxidative stress and injury (19).

Cytosolic HMGB1

It is well known that most of HMGB1 is found in the nucleus, whereas little HMGB1 has been observed in the cytoplasm under normal conditions. In contrast, HMGB1 translocates from the nucleus to the cytosol and then releases into the extracellular space under various stresses, especially inflammatory stimuli and oxidative stress (20). Although the function of cytosolic HMGB1 remains largely unknown, it plays a potential role in promoting autophagy (21). Autophagy is a lysosomal-dependent degradation pathway that removes unused proteins or damaged organelles. Disruption of autophagic pathways is implicated in multiple human diseases including neurodegenerative diseases, cancer, and inflammatory diseases. Cytosolic HMGB1 promotes autophagy through directly binding to BECN1 (also termed ATG6), a core component of the class III phosphatidylinositol 3-kinase complexes

(21). HMGB1 is a redox protein and contains three conserved redox-sensitive cysteine residues: C23 and C45 can form an intramolecular disulfide bond, whereas C106 affects HMGB1 localization. Mutation of cysteine 106 (C106) increases cytosolic HMGB1 and subsequent interaction between HMGB1 and BECN1 in the induction of autophagy (21). Nuclear and extracellular HMGB1 also promotes autophagy, which will be discussed later. In addition, cytosolic HMGB1 is involved in the regulation of an unconventional secretory pathway in the lysosome through binding to annexin A2, myosin-9, and Rab10 (22). It remains unclear whether HMGB1-dependent autophagy is required for HMGB1-mediated protein secretion.

Extracellular HMGB1

In 1999, Dr. Haichao Wang's lab reported that HMGB1 is secreted into the extracellular space by activated macrophages and functions as a late lethal mediator in pathogen infection (23). In addition to its active secretion by immune cells, HMGB1 can be passively released by dead, dying, or injured cells as a DAMP in sterile inflammation (24). Indeed, HMGB1 release is observed in various types of cell death including necrosis, necroptosis, apoptosis, ferroptosis, pyroptosis, and autophagic cell death (25). Although the release mechanism may change depending on the cell death type, oxidative stress plays a central role in the coordination of cell death and HMGB1 release (26). Once released, extracellular HMGB1 can trigger an inflammatory and immune response through both receptor-dependent and -independent manners. A number of receptors have been identified to mediate extracellular HMGB1 activity *in vitro* or *in vivo*. In particular, Toll like receptor (TLR) and the receptor for advanced glycation endproducts (RAGE) play a major role in the control of HMGB1 activity in immune cells such as macrophages (27), monocytes (28), neutrophils (29, 30), eosinophils, astrocytes (31), fibroblasts (32–34), keratinocytes (35), dendritic cells (36), natural killer cells, and T cells. Exogenous HMGB1 promotes cell migration, invasion, and proliferation through activation of several signaling pathways such as the mitogen-activated protein kinase pathway, the NF-κB pathway, and the PI3K/AKT/mTOR pathway (25). Apart from direct receptor interaction, HMGB1 may form heterocomplexes with other immune co-activators such as IL-1, CXCL12, DNA, nucleosome, or lipopolysaccharide that generate synergistic responses in inflammation and immunity (37).

HMGB1 and acute pancreatitis

As a basic pathological process of various diseases, inflammation contributes to progressive pancreatic disease ranging from pancreatitis to pancreatic cancer. Acute pancreatitis (AP) is an inflammatory process of the pancreatic gland that exhibits a broad clinical spectrum and its severity may vary from mild and edematous to a serious, necrotizing disease with high morbidity and mortality (38). In its most severe forms, AP involves remote organ systems. In fact, systemic inflammatory response syndrome (SIRS) is one of the major pathobiological processes underlying severe AP. It is widely accepted that the premature activation of digestive enzymes (trypsin, elastase, and lipase) within pancreatic acinar cells is a critical initiating event that leads to organelle injury and autodigestion of the pancreas (39). However, AP is also an inflammatory disorder involving a complex cascade of immunological events, including inflammatory mediator production, which affects not

only the pathogenesis but also the course of the disease. Some of these inflammatory mediators are initially released by pancreatic acinar cells and result in the recruitment and activation of neutrophils, monocytes, and macrophages (40–43), which lead to further acinar cell injury. When released, these mediators gain access to the systemic circulation and play a central role in the progression of SIRS and multisystem organ failure (44). However, the exact molecular mechanisms linking the progression of local pancreatic damage to systemic inflammation are still poorly understood.

Serum levels of HMGB1 were significantly elevated in patients with AP and were correlated with the severity of the disease (45). Early blockade or delayed therapeutic delivery (e.g., ethyl pyruvate (46), A box (47) and anti-HMGB1 neutralizing antibody (48)) targeting HMGB1 significantly attenuates the development and associated organ dysfunction in experimental AP. In addition, antioxidant (e.g., pyrrolidine dithiocarbamate (49)) and anticoagulant (e.g., antithrombin III (50) and danaparoid sodium (51)) inhibits HMGB1 release and reduce pancreatic injury in severe AP. These findings indicate that extracellular HMGB1 mediates the inflammatory response and may be an effective therapeutic target of AP. In contrast, intracellular HMGB1 protects against AP (52). Conditional knockout of HMGB1 in the pancreas fails to affect pancreatic development and function (52). However, HMGB1 depletion in the pancreas increases animal death in mice following administration of L-arginine or cerulean (52). Loss of endogenous HMGB1 in the pancreas increases DNA damage and subsequent cell death, nuclear DAMP release (e.g., histone and DNA), and the inflammatory response (52). Moreover, histone and DNA can activate macrophages to release HMGB1, which amplifies the inflammation response in AP (52). These findings may explain increased DNA damage and HMGB1 release in the loss of pancreatic HMGB1.

HMGB1 and pancreatic tumorigenesis

PDAC is characterized by a high frequency (>95%) of activation of *K-Ras* mutations (especially G12D mutation) (53, 54) and progresses from non-invasive pancreatic lesions that include pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs) (55). The ability of mutant *K-Ras* to drive PDAC was not successfully investigated until the generation of mice with a *Cre*-inducible conditional allele (*Pdx1-Cre;K-Ras*$^{G12D/+}$, termed KC mice) targeting the endogenous *K-Ras* locus (56). These KC mice develop lesions that slowly progress further into advanced PDAC and have a median survival of 15 months (56), suggesting that *K-Ras* activation is a tumor-initiating event that requires other elements that accelerate rigorous PDAC progression. We recently developed a novel mouse model combining original *K-Ras*$^{G12D/+}$-driven PDAC models with additional loss of HMGB1 in pancreatic tissue (*Pdx1-Cre;K-Ras*$^{G12D/+}$*;HMGB1*$^{-/-}$, termed KCH mice). Our data demonstrated that intracellular HMGB1 is a novel tumor suppressor of PDAC by sustaining chromosome stability and limiting pro-inflammatory nucleosome release and activity in mice (57).

Epidemiological studies have established a significant correlation between pancreatic cancer and diabetes. People with type 2 diabetes are well known to be at increased risk for pancreatic cancer, and now it seems that the risk extends to those with type 1 diabetes (58). The risk of developing pancreatic cancer was twice as high in subjects with type 1 or

young-onset diabetes as that in people without diabetes (59). Diabetes is either a risk factor or a symptom of pancreatic cancer (58, 60–62). Much is known about these associations, but why pancreatic cancer causes diabetes and how diabetes affects the outcome of pancreatic cancer have yet to be fully determined. Remarkably, 100% of KCH mice also develop type 1 diabetes at five-eight weeks and have an average survival rate of three months (57). Importantly, PDAC patients had reduced pancreatic HMGB1 expression with poor survival outcomes (57). In addition, diabetic human and mouse tissues contain lower levels of HMGB1 expression than their normoglycemic counterparts (63). These findings suggest that loss of HMGB1 expression plays an important pathogenic role in human pancreatic cancer and diabetes.

The emerging role of autophagy in pancreatic cancer and diabetes

Autophagy is an evolutionarily-conserved degradation pathway by which cytoplasmic components, including damaged organelles (e.g., mitochondria or endoplasmic reticulum [ER]) and effete long-lived proteins are digested within the lysosome (64, 65). This dynamic process is primarily controlled by members of the autophagy-related gene (ATG) family and share regulators derived from other trafficking and cell death pathways. The role of autophagy in cancer is complex and is likely dependent on tumor type, stage, genetic context, and tumor microenvironment (66). On one hand, autophagy acts as a tumor suppressor at an early stage by preventing genome instability, limiting oxidative stress, reducing intratumoral necrosis-dependent inflammation, and inhibiting angiogenesis. On the other hand, autophagy acts as a survival mechanism at a late stage that can promote the growth of established tumors and resistance to anticancer treatment by providing substrates for metabolism, removing damaged organelles and proteins, and diminishing apoptosis. Recent studies demonstrated that mice lacking the essential autophagy genes (e.g., ATG5 or ATG7) or mitophagy genes (e.g., PINK1 or PARK2) have accelerated *K-Ras*-driven PanIN formation and reduced animal survival during tumorigenesis (67, 68). In contrast, increased autophagy promotes pancreatic growth at the late stage (69, 70). In addition, increasing evidence supports an active role for autophagy in the pathophysiology of type 1 and type 2 diabetes (71). Increased autophagy is necessary to maintain the mass and function of pancreatic β cells and protects β cells against damage by oxidative stress in diabetic mice (72, 73). Thus, β-cell-specific ATG7-null mice show hypoinsulinemia and hyperglycemia (74). These studies support the idea that autophagy plays an important pathogenic role in the regulation of pancreatic tumor and diabetes development.

HMGB1 as a novel regulator of autophagy

Our studies have demonstrated that HMGB1 has transcription-dependent and transcription-independent pro-autophagic functions. Heat shock protein beta-1 (HSPB1), a regulator of actin cytoskeleton dynamics, is a direct transcriptional target of HMGB1 in autophagy (75). Suppression of HSPB1 and HMGB1 expression inhibits the dynamics of autophagy as well as mitophagy, a form of selective autophagy that removes damaged mitochondria (75). During stress, including starvation, oxidative stress, and chemotherapy, HMGB1 translocates from the nucleus to the cytoplasm and binds to Beclin-1, which initiates autophagosome formation (21). p53 and unc-51-like kinase 1 (ULK1, also called ATG1 in yeast) have

opposing roles in the regulation of HMGB1-Beclin-1 complex formation in cancer cells (76, 77). The ULK1 kinase is an essential component of the core autophagy machinery that regulates autophagosome formation. Once released, reduced HMGB1 triggers autophagy in a RAGE-dependent manner in cancer cells, which promotes tumor cell proliferation (78). In contrast, HMGB1 may not be required for autophagy in some organs such as the liver and heart (79). Thus, understanding HMGB1-dependent and -independent autophagy in more detail will provide insight into the integrated stress response and guide HMGB1-based therapeutic intervention in cancer and other diseases (80).

RAGE as a critical receptor of nuclear danger signal in pancreatic tumorigenesis

RAGE is a transmembrane receptor of the immunoglobulin gene superfamily and a multifunctional receptor within the tumor microenvironment. RAGE expression is associated with inflammation and is implicated in several chronic diseases, including cancer (81, 82). RAGE and its ligands are linked to the development and progression of several cancers by facilitating the maintenance of a chronic inflammatory state (83) and/or by promotion of metastases (84). RAGE is expressed by cancer cells as well as other cells within the tumor microenvironment, including T cells (85), macrophages (86), endothelial cells (87), and fibroblasts (88). We recently provided the first evidence that RAGE plays a unique role in pancreatic tumorigenesis and drug resistance *in vitro* and *in vivo* (89–93). We demonstrated that: 1) RAGE was highly expressed in mouse and human PDAC (90); 2) Targeted genetic ablation of RAGE in mice prevented pancreatic cancer growth in a genetically-modified spontaneous mouse model (*Pdx1-Cre;K-Ras* $^{G12D/+}$*;RAGE*$^{-/-}$, termed KCR mice; B6 background) (90) and a xenograft mouse model (93); 3) RAGE was essential for oncogenic K-Ras-mediated hypoxic signaling in pancreatic cancer development (94); and 4) The mechanism by which this occurs in part involves inflammatory response-associated metabolic changes (90, 93, 95), cell death-promoting limitations in autophagy (91, 92, 96, 97), and a reduction in the accumulation of MDSCs and Tregs (89). In addition, RAGE (but not TLR9) deletion limits pancreatic cancer development in KCH mice (57). These exciting findings indicate that RAGE plays an important role in the pathogenesis of pancreatic cancer.

Conclusions and Perspectives

PDAC is driven by mutant oncogenic *K-Ras* and has a lower overall five-year survival rate. Numerous trials have failed to improve outcomes of this deadliest of all major cancers; potential causes of this failure include a still insufficient understanding of PDAC's key features and imperfect preclinical models for identification of active agents and mechanisms of therapeutic responses and resistance. HMGB1, a highly-conserved chromosomal protein, plays an important role in human diseases, including PDAC. Interestingly, intracellular HMGB1 suppresses whereas extracellular HMGB1 promotes pancreatic tumorigenesis. HMGB1 translocation from the nucleus or deficiency-mediated nucleosome release seem to be key molecular events linking chromosomal instability and the inflammatory response. This process requires activation of RAGE, a DAMP receptor that promotes inflammatory

responses to HMGB1 (93), DNA (98), and histones (99). Importantly, pharmacological inhibition of intracellular HMGB1 loss or release by glycyrrhizin limits *K-Ras*-driven tumorigenesis in mice. Information gleaned from such preclinical studies need to be further studied in the clinic to impact PDAC detection and treatment.

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