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The Role of Receptors for Advanced Glycation End Product in Pancreatic Carcinogenesis

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Abstract

Pancreatic cancer is the fourth-leading cause of cancer deaths worldwide that considered as the malignant tumor with the poorest prognosis and the lowest survival rate. This extremely violent disease is rarely diagnosed at an early level and difficult to treat due to its resistance to radiation therapy and chemotherapy. Here, we show that the receptor for advanced glycation end products (RAGE) and its ligands, advanced glycation end products (AGEs), high-mobility group box 1 (HMGB1) and S100 protein family are required for pancreatic cancer development, angiogenesis and metastasis through up-regulation of some anti-apoptotic molecules as matrix metalloproteinase -9 (MMP-9), kinase insert domain receptor (KDR), vascular endothelial growth factor (VEGF), platelet-derived growth factor-B (PDGF-B), hypoxia-inducible factor 1 (HIF1α), signal transducer and activator of transcription 3 (pSTAT3) and nuclear factor kappa B (NF-κB). In addition to the decrease in reactive oxygen species (ROS) those favouring the cancer cell growth and metastasis. The role of RAGE in pancreatic carcinogenesis needs further studies to investigate the relationship of RAGE with other anti-apoptotic and apoptotic molecules and examine the therapeutic potentials of anti-RAGE drugs for pancreatic cancer.

Keywords: Pancreatic cancer; RAGE; RAGE ligands

Introduction

Pancreatic cancer is a deadly disease, characterized by late diagnosis, early metastasis and chemotherapy resistant [1]. Pancreatic ductal adenocarcinoma (PDA) is a complex disease that arises from the genetic alterations of KRAS, BRCA1, SMAD4, CDKN2A/p16 and TP53 [2]. Activating KRAS mutations and p16 inactivation are genetic abnormalities, most frequently detected in PDA [3]. Oncogenic activation of the KRAS gene occurs in more than 90% of PDA and plays a critical role in PDA malignancy [4]. The mean survival is around six months, and the five years overall survival rate is less than 4% of the patients [5]. PDA is a highly mortal disease. It accounts for only 3% of cancer cases each year but is currently the fourth common cause of cancer mortality [6] due to advanced stage at diagnosis and poor response to current treatment [7]. By 2030, PDA is expected to be the 2nd leading cause of cancer death [8]. The best chance for survival is early detection when the tumor can be treated with surgical aid [9].

RAGE and its ligands

The cell cycle is strictly regulated and controlled by a complex network of cellular signalling pathways [10]. RAGE belongs to the immunoglobulin superfamily of receptors [11] with a molecular weight of about 55-kDa protein, has an extracellular part consisting of a variable (V) immunoglobulin-like domain followed by two constant domains, a single transmembrane domain and a cytosolic tail [12,13]. The N-terminus of the V domain is the ligand-binding site, and the cytosolic tail that necessary for RAGE-induced intracellular signalling [14]. Soluble RAGE (sRAGE) forms lack both the cytosolic and the transmembrane domains [14,15]. sRAGE can be distinguished in circulating blood [16] that can bind with RAGE ligands such as advanced glycation end product (AGE) [12].

RAGE is expressed in a variety of tissues as heart, lung, skeletal muscle and vessel wall. AGE-RAGE interactions inhibit the prostacyclin production by human endothelial cells, which prompt angiogenesis and thrombogenesis [17]. It is generally believed that RAGE-induced pathways are implicated in the development of various diseases [18,19]. RAGE plays a crucial role in numerous diseases including diabetes, inflammation, and cancer [20]. RAGE interacts with diverse ligands, including AGEs and β-amyloid fibrils, S100 protein family (S100B, S100P, S100A4, S100A6, S100A8, S100A9, S100A11, S100A12, and S100A13), high mobility group box-1 (HMGB1), and prions [21,22].

AGEs formed by a non-enzymatic reaction between the ketone and aldehyde groups of sugars and the amino groups of proteins, which called Maillard reaction that, have been concerned in aging and diabetes-related pathological complications [23]. These reactions can be triggered by glucose-6-phosphate, glyceraldehyde-3-phosphate, glyoxal (GO), methylglyoxal (MGO) and 3-deoxyglucosone (3DG) [24]. AGE and RAGE have been associated in cancer development [25]. AGEs binding to RAGE induces signalling pathways of mitogen-activated protein kinases (MAPKs) [26], cdc42/rac and Jak/STAT [22], which modulate the of some genes as the vascular endothelial growth factor (VEGF) [27]. AGE-RAGE activation increases transforming growth factor beta-1 (TGF-β1) levels, with enhanced activity of matrix metalloproteinase 2 (MMP-2); on the other hand, RAGE signalling promotes MMP-9 activity. MMP-2 and -9 induce modifications in collagen IV turnover [28]. AGEs have been shown to induce inflammation and intracellular reactive oxygen species (ROS), which leads to the expression of many atherosclerosis-related genes, including VEGF [29].

HMGB1 protein is a DNA-binding nuclear protein, released actively in response to cytokine stimulation, or passively during cell death [30], and it is present in almost all eukaryotic cells [31]. HMGB1 can activate a series of signalling components, including MAPKs and AKT, which play an important role in tumor growth through binding to RAGE and hastens cell-cycle progression [32]. In vitro studies with pancreatic cancer cells revealed that the targeted knockout or inhibition of HMGB1 and RAGE could increase apoptosis and defeat pancreatic cancer cell growth [33]. This phenomenon has been also noticed with other types of cancer cells [34].

S100 proteins are expressed in vertebrates, and exhibit somewhat cell-specific distribution [35]. S100P is a 95-amino acid member of the S100 family of protein, purified and characterized from placenta [36]. The term "S100" was coined to indicate a group of proteins soluble in a 100% saturated ammonium sulphate solution [37]. The designation "P" was coined to indicate that it was purified firstly from placenta [36]. S100P is a member of the large family of S100 calcium-binding proteins [38]. Expression of S100P was observed to be specific to pancreatic cancer cells [39]. The specificity for cancer cells was further confirmed in micro-dissected pancreatic cancer tissues and isolated primary cultures of cancer cells [40].

RAGE and Cancer

RAGE has been overexpressed in the brain, breast, colon, colorectal, lung, prostate, oral squamous cell, and ovarian cancers, in addition to lymphoma and melanoma [41] this clarifies the direct relationship between RAGE and cancer cell proliferation, survival, migration, and invasion of tumor cells [42]. Targeted knockdown of RAGE in the tumor cell, leads to increased apoptosis. In contrast, overexpression of RAGE is associated with enhanced autophagy and stop apoptosis [33]. The HMGB1-RAGE axis blockage suppressed tumor growth and explores the in vivo role of RAGE during cancer development [43]. RAGE and its ligand, S100P have been shown to mediate tumor growth, drug resistance, and metastasis [44]. RAGE activation has been considered to promote tumor vasculature, tumor growth and invasion [45] by induction of ROS, extracellular signal-regulated protein kinase (ERK1/2), p38MAPKs, phosphoinositol-J kinase, Janus kinase/signal transducer and activator of transcription pathway, nuclear factor kappa B (NF-κB), activator protein-1 (AP-1) and activator of transcription 3 (STAT-3) [22,46,47].

Interaction of full-length RAGE with its ligands, including AGEs, S100 protein family, and HMGB1, triggers the rapid activation of an array of key cell signalling pathways culminating in the activation of the NF-κB pathway [48]. NFκB is a transcription factor for a large group of genes which are involved in several different pathways. For instance, NFκB activates its own inhibitor (IκB) as well as groups of pro-apoptotic and anti-apoptotic genes [49]. Among the latter, NFκB activates transcription of a gene encoding for the inhibitor of apoptosis protein (IAP). This protein, in turn, contributes to downregulate the activity of the caspase cascade [50]. NF-κB is retained inert in the cytoplasm by the inhibitor protein, I-kappaB (IκB) [51]. Following stimulation of the cell by a variety of agents, IκB is degraded, allowing NF-κB to translocate to the nucleus and bind to the promoter regions of its multiple target genes to promote cell survival and proliferation [52].

RAGE and Pancreatic Cancer

RAGE has a crucial role in pancreatic cancer development [53,54]. PDA is a wasteful disease with low survival rates [55]. Loss of RAGE function inhibited the development of PDA in mouse models [3]. The immunohistochemical analysis confirmed the expression of RAGE and its ligands S100P, S100A4, and HMGB-1 in human PDA [56]. RAGE and S100 protein play important roles in the progression of PDA [55]. Indeed, S100 proteins interact with RAGE, which play a role in the degradation of the extracellular matrix facilitating the metastasis of pancreatic cancer [57]. AGE and RAGE are expressed in many tissues and cell types [58].

Induction of S phase

S100P expressed in more than 90% of pancreatic tumors, leading to tumor growth and invasion [59] as in Panc-1 and Mpanc96 cells [60] in which the increased S100P levels increased the growth of tumors in mice with subcutaneous-implanted Panc-1 cells. FACS analysis indicated an over 80% increase in the number of cells in S-phase cells in Panc-1 cells expressing S100P that interact with RAGE promoting Panc-1 cell migration and invasion [61]. This role of RAGE in pancreatic carcinogenesis was evidenced by incubation of wild-type BxPC3 cells with the anti-RAGE antibodies that inhibited the cell growth, migration, and invasion [43].

Induction of angiogenesis and metastasis

S100A4 synergize with VEGF, via the RAGE receptor, in promoting endothelial cell migration by increasing kinase insert domain receptor (KDR) expression and MMP-9 activity [62]. The expression of MMPs correlates with the extracellular matrix degradation and tumor metastasis [63]. The expression of MMP-9 is associated with metastasis of many human cancers because they play an important role in the degradation of type IV collagen, which is a major component of the basement membrane [64]. Therefore, MMP-9 may be involved in the process of cancer metastasis [65]. Meanwhile, VEGF is a signal protein produced by cells that stimulate vasculogenesis and angiogenesis that function as oxygen supply to tissues [66]. The role of angiogenesis in supporting tumor growth and metastasis [67].

AGE ligand–receptor interactions could play an active part in the progression of human pancreatic cancer cells (Mia PaCa-2) through the induction of autocrine platelet-derived growth factor-B (PDGF-B) [68]. Additionally, RAGE binds to oncogenic KRAS facilitates hypoxia-inducible factor-1 (HIF1α) activation and promotes pancreatic tumor growth [69]. HIF-1 potentiates the expression of proteins that promote angiogenesis and cell survival [70]. HIF1α is a transcription factor induced by low oxygen conditions and involved in the activation cancer cell angiogenesis and metastasis [71]. Increased HIF-1 activity promotes tumor progression, and inhibition of HIF-1 could represent a novel approach to cancer therapy [72].

Counteract the ROS-induced oxidative stress

Activation of RAGE by S100P stimulates several cellular signalling pathways, including MAP kinase and NFκB [44] inhibiting S100P-RAGE interactions significantly reduce basal levels of NFκB activity in PDA [59]. Excessive ROS production can lead to oxidation of macromolecules and has been implicated in mitochondrial DNA (mtDNA) mutations, aging, and cell death. Mitochondrial generated ROS play an important role in the release of proapoptotic proteins,

which can trigger caspase activation and apoptosis [73]. Exposure of pancreatic tumor cells to H2O2 provoked a nuclear factor kappa B (NF-κB)-dependent increase in RAGE expression [74] that decreases ROS-induced oxidative injury [20].

Mitochondrial ATP production

Tumor cells have increased energy requirements. ATP production occurs through glycolysis and oxidative phosphorylation within mitochondria. The STAT3 has a role in mitochondrial function, regulating complex I activation and ATP production [75], promoting the oncogenic property of Ras-mediated cellular transformation [76]. RAGE expression appears to enhance the cancer cell survival that depends on autophagy, autocrine IL-6 production, and IL-6–promoted mitochondrial STAT3 phosphorylation and localization, which in turn promotes enhanced ATP production in pancreatic cancer cells [1].

RAGE and HMGB1 coordinately enhanced tumor cell mitochondrial complex I activity, ATP production that promote tumor cell proliferation and migration. Lack of RAGE or inhibition of HMGB1 diminished ATP production and slowed tumor growth *in vitro and in vivo* [69]. The role of HMGB1 in pancreatic tumor survival might involve alterations in tumor bioenergetics [69]. RAGE-mediated autophagy is required for IL-6-induced mitochondrial translocation of STAT3 and subsequently, IL-6/STAT3-mediated ATP production [1]. There are at least two different mechanisms involved in RAGE-mediated ATP production: mitRAGE dependent and RAGE-mediated autophagy dependent [69].

Down-regulation of apoptotic molecules

RAGE knockdown was associated with increased apoptosis that reversed in part by treatment with pan-caspase inhibitors [33]. In cells treated with a pharmacologic inhibitor of p53, pifithrin α, and p53 knock out tumor cell lines we observed abrogation of the increased cell death observed with RAGE knockdown [77].

Conclusion

From this review, we can conclude that RAGE and its ligands have the crucial role in pancreatic carcinogenesis through up-regulation of some anti-apoptotic molecules. Besides, more studies have been in need to understand the mechanisms by which RAGE induces the pancreatic cancer development and survival by further studies to know the relationship between RAGE and other anti-apoptotic and apoptotic molecules by molecular and proteomic tool through:

Study the relationship between RAGE and apoptotic molecules such as p53, p21, caspases and BAX.

Study the relationship between RAGE and anti-apoptotic molecules like Akt, BCL2, PARP and inhibitors of apoptosis proteins.

Drug discovery of new novel anti-RAGE agents.

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