Seminars in Cancer Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

The receptor for advanced glycation end products: A fuel to pancreatic cancer

Uzma Shahab[a,*], Mohd. Kaleem Ahmad[a], Abbas Ali Mahdi[a], Mohd. Waseem[a,b,c], Binish Arif[d], Moinuddin[e], Saheem Ahmad[b,c]

[a] Department of Biochemistry, King George Medical University, Lucknow, U.P., India
[b] IIRC-1, Laboratory of Glycation Biology and Metabolic Disorders, Integral University, Lucknow, U.P., India
[c] Department of Biosciences, Integral University, Lucknow, U.P., India
[d] Department of Biochemistry, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India
[e] Department of Biochemistry, J.N. Medical College, A.M.U., Aligarh, U.P., India

ARTICLE INFO

Keywords:
Hypoxia
Pancreatic cancer
RAGE
Signalling
Tumourigenesis

ABSTRACT

The receptor for advanced glycation end products (RAGEs) was first illustrated in the year 1992. RAGE is a single-transmembrane and multi-ligand component of the immunoglobulin protein super family. The engagement of RAGE turns out to an establishment of numerous intracellular signalling mechanisms resulting in the progression and perpetuation of many types of cancer including, the pancreatic cancer. The present review primarily focuses on the multi-ligand activation of RAGEs leading to the downstream signalling cascade activation. The kick start of the RAGEs activation leads to the several anomalies and includes multiple types of cancers. The RAGE expression correlates well with the survival of pancreatic cancer cells leading to the myeloid response. RAGEs assist in the tumourogenesis which enhance and thrive to its fullest in the stressed tumour microenvironment. An improved perceptive of its involvement in pancreatic cancer may offer novel targets for tumour supervision and risk measurement.

1. Introduction

The pancreatic cancer is distinguished by delayed diagnosis, premature metastasis and resistance to chemotherapy hence it wouldn't be incorrect to call it a 'deadly disease' [1]. Recently in 2017, the American Cancer Society (ACS) have estimated approximately 53,670 individuals will be diagnosed with pancreatic cancer in USA, out of which 43,090 are expected to succumb to death. Pancreatic cancer contributes to three percent of all cancers in the USA and about seven percent of all the cancer deaths. However, the trend of the pancreatic cancer in India is quite low. As per Delhi cancer registry data, the projected figure of pancreatic cancer was recorded to be approximately 17,000 in 2016. The incidence of the same is less and the average incidence in men and women ranges from 0.35 to 2.1. However, the global prevalence rate of pancreatic cancer is 1 per 100,000 people per year. The demise of Apple co-founder Steve Jobs owing to pancreatic cancer has brought into notice the rare and belligerent cancer type; this cancer type is causing concern in India following a rise in occurrence of the disease. According to Delhi Cancer registry, Mizoram in India has the highest prevalence of pancreatic cancer.

Reports suggest that pro-inflammatory pathways in pancreatic cancer are mediated by the transcription factor NF-κB which can also be activated by the pattern recognition receptor RAGE, receptor for advanced glycation end products [2]. RAGE is a multiligand transmembrane receptor belonging to the immunoglobulin superfamily [3]. Its genetic location is on chromosome 6 within the major histocompatibility class III (MHC III) locus in humans and mice [4]. The receptor has been first identified in 1992 on macrophages for the uptake of advanced glycation end products (AGEs) and hence derived its name [5,6]. AGEs are formed by non-enzymatic reaction of proteins, nucleic acids and lipids with reducing sugars to form an early glycation product also known as an 'Amadori product' [7–10]. The early glycation product are further oxidized, dehydrated and cross-links to yield highly heterogeneous AGEs which accumulate during glycative stress and build up inflammatory hotspots [11–14]. Later on RAGEs were also known on monocytes, microglia, astrocytes, neurons, smooth muscle and endothelial cells including T and B lymphocytes [15].

Constitutive activation of oncogenic Kras and its over-activated downstream signalling factors, such as B-Raf, phosphatidylinositol-3-kinase (PI3 K) and Akt are strong promoters of pancreatic cancer

* Corresponding author.
E-mail address: uzmashahab@gmail.com (U. Shahab).

http://dx.doi.org/10.1016/j.semcancer.2017.07.010
Received 28 April 2017; Received in revised form 23 July 2017; Accepted 31 July 2017

tumourigenicity [16]. Oncogenic Ras-driven signals propel abnormal chain of metabolic alterations [17] including glycolysis and autophagy, consequently contributing to the extensive development, survival and invasiveness of pancreatic tumour cells.

The activation of RAGEs instigates actuation of the transcription factor NF-κB and some of its downstream target genes that are notable controllers of the adaptive and innate immune system [18]. There is an utilitarian NF-κB restricting site in the proximal promoter of RAGE which has been appeared to be an immediate gene of NF-κB signalling [19]. Additionally, tumours relay essentially on anaerobic metabolism and demonstrate a higher rate of glucose uptake and thus glycolysis. This higher rate of glycolysis may bring about non-enzymatic glycation of proteins, prompting the development of AGEs [20]. The experimental data running from *in-vitro* examinations to mouse models and clinical information bolster an immediate connection between RAGE actuation and expansion, survival, migration, and intrusion of tumour cells [21,22]. Additionally, gene expression analysis with tests of human patients and mouse tumour models revealed over-expression of RAGE ligands in many sorts of solid tumours [23,24].

Besides AGEs, RAGEs were also found to be recognised by various other ligands such as β-sheet fibrils like amyloid proteins, high-mobility group B (HMGB or amphoterin) and S100/calgranulin [25,26]. Damaged-Associated Molecular Pattern molecules that originate from damaged cells and alert the immune system to tissue trauma were also found to be the ligands for RAGEs. This property of RAGE to bind to different families of ligands is referred to as pattern recognition receptor (PRR) that recognizes common features rather than ligand. Many RAGE ligands are expressed and secreted by malignancy cells and additionally by numerous cell types inside the tumour microenvironment, including fibroblasts, leukocytes and vascular cells. These ligands cooperate in both autocrine and paracrine manners and downregulates cell signalling that control different cell forms, including inflammation, proliferation, apoptosis, autophagy, and migration [27].

Although RAGE expression has been extensively reported in many, it is now emerging as a relevant element that can continuously fuel the stressful milieu at the tumour microenvironment, thus changing our perception of its contribution to cancer biology. This review focuses on the role of multiligand/RAGE axis, particularly at the multicellular cross talk built up in different stress situations in pancreatic cancer.

2. RAGE promotes pancreatic cancer cell survival

The principal method through which programmed cell death takes place within multi-cellular organisms is, 'apoptosis'. In cancerous tissues, there is a loss of equilibrium between cell division and cell death which results in inconsistent division of cells [28]. For example, down regulation of p53, a tumour suppressor gene, may lead to decreased apoptosis rate, enhanced tumour growth and development [29]. p53 inactivation can act in several ways to aid cancer development including pancreatic cancer [30–32]. When it acts as a transcription factor, it stimulates the expression of pro-apoptotic 'Bcl-2' family, residing or performing in the mitochondria [33]. p53 can itself, directly act in the cytosol and mitochondria to promote apoptosis through transcription-independent mechanisms [34]. In the recent past, RAGE has been linked to the progression and development of cancer as well as to increased chemotherapy resistance [35–38]. RAGE knockdown mice are resistant to DMBA/TPA-induced skin cancer, exhibiting enhanced apoptosis and diminished inflammatory responses [39]. Thus RAGE finds its molecular correlation with p53 as both regulate the steps of apoptosis. Pifithrin α, a pharmacologic inhibitor of p53 induces increased cell death when RAGE is knocked down [40]. Scheme 1 depicts the association of p53 and RAGE. Moreover, RAGE knockdown in pancreatic cancer cells, boosts phosphorylation of p53 [40], which is a prominent feature governing the ability of p53 to induce apoptosis [41]. Additionally, loss of RAGE lowered the expressions of anti-apoptotic Bcl-2 family members (e.g., Bcl-2 and Bcl-XL), keeping the p53-target genes such as PUMA and Bax unaffected. Besides this, absence of RAGE also promotes increased translocation of p53 to the mitochondria to the mitochondria, which induces mitochondrial outer membrane permeability (MOMP) [42] that leads to increased cytochrome *c* release to the cytoplasm consequently leading to increased apoptosis [40].

Autophagy and apoptosis, the programmed process of cell survival and cell death respectively, have always been a soft topic in cancer research. Normally, autophagy and apoptosis are both tumour suppressing pathways. Autophagy is engaged in degrading oncogenic molecules while apoptosis prevents survival of cancer cells. Thus a defect in either of the process can lead to cancer development. Although the relationship between autophagy and apoptosis is very complicated and has not been characterized in detail still, the molecular mechanisms that control this relationship are considered to be a relevant target therapeutic strategy for tumour treatment [43]. RAGE is one of the potential mediators of the crosstalk between autophagy and apoptosis in pancreatic cancer [44]. In one of the study it was shown that RAGE provides resistance to murine and human pancreatic tumour cell line against cytotoxic insults. Moreover, targeted silencing of RAGE significantly increases cell death. Moreover, targeted silencing of RAGE significantly increases cell death, while enforced over expression promotes survival [40]. This study provides a direct example of RAGE dependent enhanced autophagy and apoptosis in pancreatic cancer.

Autophagy when studied in cells reacted from pancreatic cancer was found to be directly linked to poor patient outcome [45]. On the other hand RAGE expression was also found to be directly related to autophagic response in pancreatic cancer cells. RAGE knockout leads to attenuation of Kras driven development of PDA precursor lesions by decreasing signalling through the IL6-pSTAT3 autophagic pathway. Mammalian target of rapamycin (mTOR) controls autophagy in mammalian cells [46] and in response to chemotherapy, its enhanced phosphorylation is observed, which suppresses autophagy and enhances transcriptional activities in response to nutrient availability [47–49] in RAGE knockdown pancreatic cancer cells.

3. RAGE regulates the myeloid response in pancreatic cancer

A healthy individual's adaptive immune system performs tumour immune-surveillance that keeps check of any abnormal growth [50]. Despite exerting a key role in host protection, tumour surveillance by the immune system may eventually fail. Tumour cells are initially eliminated by the immune system before becoming clinically detectable. This is then followed by an equilibrium phase where a selection process for less immunogenic tumour variants takes place until the tumour finally escapes surveillance. The heterogeneous population of myeloid-derived suppressor cells (MDSCs) is immature myeloid cells that suppress innate and adaptive immunity. These cells prevent the *in vivo* and *in vitro* activation of T cells. MDSCs are also chemo-attracted to the tumour microenvironment (TME) by tumour-produced vascular endothelial growth factor (VEGF) [51,52] expressing the granulocyte and macrophage markers Gr1 and CD11b/Mac1, respectively. Their accumulation correlated with tumour-produced granulocyte/monocyte-colony-stimulating factor (GM-CSF) [53], and they inhibited antigen-specific CD8+ T cell activation in a contact-dependent manner [54]. The recruitment and retention of MDSCs prevents the successful immune responses against pancreatic neoplasms [55] by hampering the immune effectors cells through several mechanisms, including nutrient deprivation and reactive nitrogen and oxygen species production [56].

In pancreatic ductal adenocarcinoma (PDAC), the progressive accumulation of MDSCs is widely recognised, while their immunosuppressive effect is clear. Oncogenic Kras-dependent granulocyte macrophage colony stimulating factor (GM-CSF) secretion, controls the MDSCs recruitment to the tumour microenvironment. Its presence allowed the recruitment of MDSCs in the tumour microenvironment and it suppresses cytoxic T lymphocytes (CTL) cell action and thus allow