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AGE-RAGE synergy influences programmed cell death signaling to promote cancer

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Abstract

Advanced glycation end products (AGEs) are formed as a result of non-enzymatic reaction between the free reducing sugars and proteins, lipids, or nucleic acids. AGEs are predominantly synthesized during chronic hyperglycemic conditions or aging. AGEs interact with their receptor RAGE and activate various sets of genes and proteins of the signal transduction pathway. Accumulation of AGEs and upregulated expression of RAGE is associated with various pathological conditions including diabetes, cardiovascular diseases, neurodegenerative disorders, and cancer. The role of AGE-RAGE signaling has been demonstrated in the progression of various types of cancer and other pathological disorders. The expression of RAGE increases manifold during cancer progression. The activation of AGE-RAGE signaling also perturbs the cellular redox balance and modulates various cell death pathways. The programmed cell death signaling often altered during the progression of malignancies. The cellular reprogramming of AGE-RAGE signaling with cell death machinery during tumorigenesis is interesting to understand the complex signaling mechanism of cancer cells. The present review focus on multiple molecular paradigms relevant to cell death particularly Apoptosis, Autophagy, and Necroptosis that are considerably influenced by the AGE-RAGE signaling in the cancer cells. Furthermore, the review also attempts to shed light on the provenience of AGE-RAGE signaling on oxidative stress and consequences of cell survival mechanism of cancer cells.

Keywords AGEs · RAGE · AGE-RAGE signaling · Cell death · Cancer

Abbreviations

AGE	Advanced glycation end products
Akt	Protein kinase B
DAMPs	Damage-associated molecular patterns
ERK	Extracellular-signal-regulated kinase
HMGB1	High-mobility group box 1
JAK	Janus kinase
MAPK	Mitogen-activated protein kinase
NF-kB	Nuclear factor kappa B
NOX	NADPH oxidase
Nrf-2	Nuclear factor erythroid 2-related factor 2
PAMPs	Pathogen-associated molecular patterns
PI3K	Phosphoinositide 3-kinases
RAGE	Receptor of advanced glycation endproducts
ROS	Reactive oxygen species
STAT-3	Signal transducer and activator of transcription 3
TLRs	Toll-like receptors

Introduction

Advanced glycation endproducts (AGEs) are the byproducts of metabolism and harmful substances produced non-enzymatically from glycation reaction between proteins, lipids, or nucleic acid with free reducing sugars [1]. AGEs are formed as the result of the reaction between the electrophilic carbonyl group of reducing sugars with free amino group of different proteins, which resulted in the formation of unstable Schiff's bases that eventually undergo further rearrangements to form stable Amadori products. The stable

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amadori products undergo further modification (oxidation, dehydration, or polymerization) in the presence of transition metals to form more stable AGEs [2]. The production of AGEs increases manifold under the conditions of chronic hyperglycemia and diabetes due to the availability of free sugars [3]. Since the past decade, multiple AGEs have been identified which includes (but not limited to) GOLD (glyoxal lysine dimer), MOLD (methylglyoxallysine dimer), Nε-carboxyethyl-lysine (CEL), pentosidine, and non-cross linking Nε- carboxymethyl-lysine (CML). Despite having different types or status of cross-linkings, the consequences of all AGEs remain similar in the progression of different pathologies [2].

Although the cross-linked AGEs appear to be inert per se, they exert their effects in the development or progression of different pathologies through their interaction with non-specific surface receptors known as the Receptor of advanced glycation endproducts (RAGE) [4–6]. RAGE is a multi-ligand-specific receptor that binds to AGEs and other danger signaling molecules known as DAMPs to exert their pathophysiological roles in multiple disorders. These DAMPs include High-mobility group box proteins (HMGB1), calgranulins (S100 proteins), and amphoterin, to name a few [6]. RAGE can also activates an innate immune response against microbial pathogen-associated molecular pattern molecules (PAMPs) including bacterial endotoxin, microbial DNA, and viruses. RAGE is expressed at low levels under normal physiology conditions, but it is upregulated under pathological conditions including, diabetes, cancer, and chronic inflammation. The synergy of RAGE with their ligands can influence NF-κB activation and inflammatory responses [7]. The consistent perpetuation of NF-κB activation and inflammatory responses mediated through the RAGE signaling accelerates oxidative stress and pathological consequences. Moreover, RAGE triggers various signaling molecules that activate downstream signal transduction pathways directed to NF-κB activation and stimulates the production of various cytokines and growth factors that may be responsible for chronic inflammation and progression of cancer.

Synergy of AGE-RAGE signaling and cancer

Cancer is a multifactorial disease, which is associated with multiple aberrant signaling pathways in a non-transformed cell [8]. Due to the aberrant signaling pathways, non-transformed cells acquire various characteristics including limitless replicative potential, genomic instability, evasion to apoptosis, angiogenesis, invasion, and metastasis to become cancerous, which are commonly known as the hallmarks of cancer [9]. Inflammation can contribute to tumorigenicity and tumor promotion by supplying bioactive molecules to the tumor microenvironment, including growth factors that sustain proliferative signaling, survival factors that limit cell death, invasion, pro-angiogenic factors, metastasis, extracellular matrix-modifying enzymes that facilitate angiogenesis, and inductive signals that lead to activation of epithelial-to-mesenchymal transition [10, 11]. Furthermore, inflammatory cells can release chemicals, especially reactive oxygen species, which are actively mutagenic for the neighboring cancer cells, accelerating their genetic evolution towards states of heightened malignancy [12, 13]. Therefore, inflammation has been considered as an emerging hallmarks of cancer [14]. Reinforced of cellular reprogramming, activated immune cells orchestrate production of pro-inflammatory cytokines and various signal transduction pathways to continuous cell proliferation of cancer cells [15]. The aerobic glycolysis is one of the major phenotypes of cancer cells that allows cancer cells to adapt higher glucose uptake and thus continuously exposed to hyperglycemic conditions which are majorly involved in the synthesis of AGEs [16]. Apart from its constitutive expression in immune cells and lung tissues, RAGE is inducibly expressed in cancer cells [17]. Binding of AGEs with RAGE activates various signaling pathways including MAPK, ERK1/2, PI3K, Akt, JAK-STAT, and NF-κB associated with cell survival, inflammation, and cancer progression [18]. Besides promoting cell survival and inflammation around the tumor microenvironment, RAGE and its ligands also promote angiogenesis, cell migration, cell proliferation, invasion, and metastasis by restricting cell death from apoptosis [19–21]. Due to insufficient availability of oxygen in the tumor, the cancer cells remain under continuous deprivation of oxygen, which is known as hypoxia. The hypoxic condition promotes angiogenesis, invasion, metastasis, drug resistance phenotype, and restricts apoptotic machinery during cancer progression. Hypoxia also induces AGE-RAGE-mediated activation of HIF1α, NF-κB, ERK, and Akt signaling pathways which contribute to the progression of cancer [22]. The tumor hypoxia also accumulates RAGE expression. In addition, the HIF1α (a master regulator of hypoxia) and RAGE are closely associated with cancer. A recent report suggests that the NF-κB-RAGE-KRAS-HIF-1α pathway underlies the progression of pancreatic cancer [23]. Moreover, the involvement of the AGE-RAGE axis has been shown to promote the autophagic flux with simultaneous inhibition of apoptotic signaling in cancer cells. The activation of autophagic proteins such as Beclin-1 promote the survival of cancer cells through autophagy [17]. Activation of AGE-RAGE signaling also generates oxygen-free radicals, causes oxidative stress, and activates NF-κB that secrets pro-inflammatory cytokines, growth factors, and adhesion molecules such as ICAM-1 and VCAM-1 eventually leading to cancer progression. AGEs may alter the extracellular matrix (ECM) through engagement of cell surface receptors and pro-inflammatory

cytokines production, and ROS may lead to oxidative stress and cancer. Synergy of AGE ligand with their receptor is associated with upregulation of vascular endothelial growth factor (VEGF) and metalloproteinase-2 (MMP-2) as well as the disruption of VE-cadherin/catenin complex that may favor angiogenesis [24]. Current report revealed that overexpression of RAGE augments cell migration, invasion, and epithelial-to-mesenchymal transformation in human lung adenocarcinoma cells through ERK signaling [25]. A recent report suggests that the AGEs also promote cell proliferation and cell migration in breast cancer cells [26]. The previous report revealed that activated Akt, PCNA, and MMP signals further support the inhibition of apoptosis in cancer cells [27]. Inhibition of RAGE signaling in cancer cells has been successful in curbing cancer growth in multiple studies [28–30]. The association of AGE-RAGE signaling with various molecular mechanisms involved in the progression of cancer is shown in Fig. 1.

AGEs, RAGE, and ROS

Accumulation of AGEs accelerates the production of reactive oxygen species (ROS) and oxidative burden in cells and tissues. ROS is an array of reactive molecules that play an important role in maintaining cellular homeostasis. ROS regulates various cell signaling pathways directly or indirectly, which regulates various physiological processes including cell proliferation, differentiation, cell death, inflammation, and immunity [31]. ROS is mainly generated either by mitochondrial ETC or through intracellular enzyme systems such as NOX, LOX, Xanthine oxidase, Cyclooxygenase, NOS, and Cytochrome p450 monooxygenase [32]. The cellular ROS generation is also induced by various growth factors, intra and extracellular toxin substance, AGEs, and cytokines. The H_2O_2 and O_2^- are major reactive oxygen species involved in cellular signaling. A low-level of ROS regulates various physiological functions, but an elevated level of ROS leads to oxidative stress and cell damage. The ROS is generally metabolized by intracellular antioxidant enzymes and prevent the adverse effects of excessive ROS in a normal cell. Moreover, ROS target various cellular redox-sensitive proteins and other biological macromolecules and alter their normal functions thereby resulting in the progression of pathological consequences. An elevated level of ROS is associated with several pathologies including cardiovascular diseases, diabetes, neurodegenerative diseases, inflammation-associated injuries, aging, and cancer [33]. Previous reports revealed that the cancer cells accumulate ROS due to high metabolic rate, activity of various enzyme systems, and mitochondrial dysfunction [12]. Moreover, elevated ROS results in oxidative stress and altered gene regulation leading to the progression of abnormal cell growth, proliferation, invasion, and metastasis. The cancer cells maintain a relatively higher redox state compared to normal cells that sustain proliferative pathways and inhibit programmed cell death signaling. Indeed, AGEs-RAGE signaling generates ROS and initiates various signaling pathways during the onset of cancer [34]. Oxidative stress plays a crucial role in the activation of AGEs-RAGE signaling and pathogenesis of

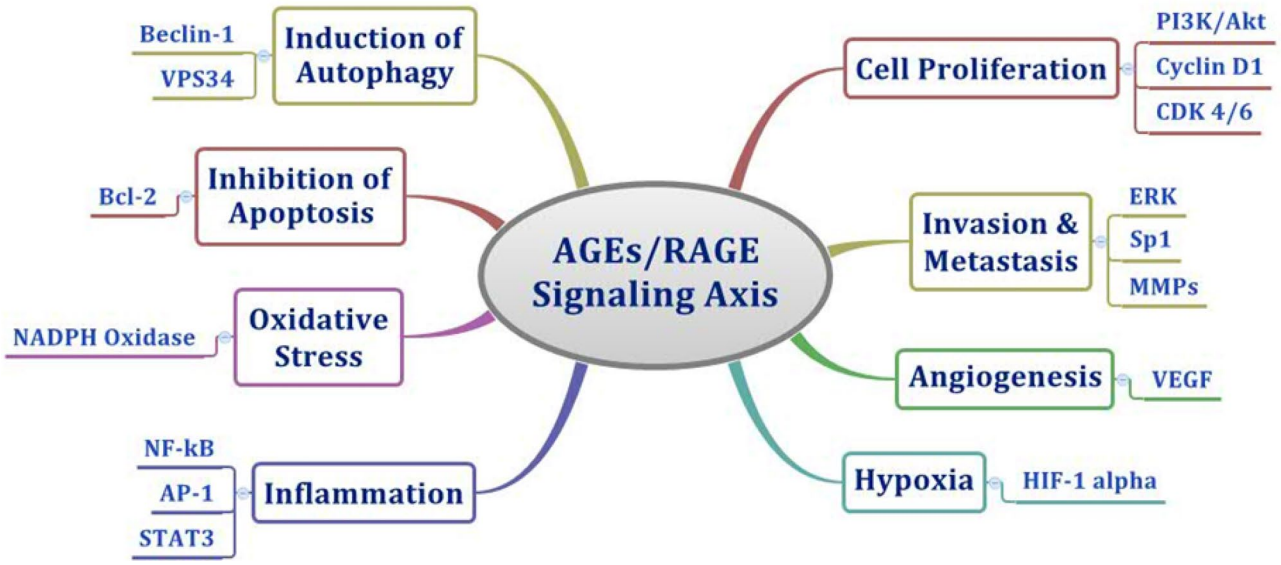

Fig. 1 The association of the AGE-RAGE signaling with molecular mechanisms involved in the progression of cancer. The figure shows an association of the AGE-RAGE signaling with different pathological conditions involved in the progression of cancer including cell proliferation, invasion, metastasis, and angiogenesis. This even influences cellular redox homeostasis, tumor-associated inflammation, and programmed cell death signaling

diabetes, chronic inflammation, and cancer. Initially, it regulates the downstream pathways and later on it promotes the synthesis of more AGEs [35, 36]. AGEs-RAGE-generated ROS accomplishes cell survival and evades programmed cell death signaling during the progression of cancer. Although, AGEs-RAGE-mediated ROS promotes apoptotic cell death in normal cells, accumulation of AGEs and RAGE promotes NF-κB activation, release of pro-inflammatory cytokines, and oxidative stress that may cause various pathological consequences. Accumulation and activation of AGE is one of the key pro-inflammatory factors in the progression of cancer, diabetes, and diabetic retinopathy. Synergy of AGE-RAGE induces the activation of MAPK signal transduction pathway with NOX-mediated ROS generation and activation of NF-κB, which leads to upregulation of transcriptional activity of target genes including growth factors (VEGF), adhesion molecules (ICAM-1, VCAM-1), and pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) and chemokines MCP-1) [37]. Role of ROS in AGEs-RAGE signaling is an emerging interest to shed light on insight molecular mechanisms to understand the complex biology of programmed cell death and survival signaling in cancer.

Synergy of AGE-RAGE influences programmed cell death signaling in cancer

Programmed cell death (PCD) is a physiologically conserved process for the development and removal of unwanted damaged cell for maintaining cellular homeostasis. Programmed cell death is broadly categorized into three types: Type I—Apoptosis, Type II—Autophagy, and Type III—programmed necrosis. Different types of cell deaths exhibit multiple cellular phenotypes that affect many intracellular organelles, cell nucleus, and membrane [38]. Apoptotic cell death (Type I) eliminates the damaged, harmful, unwanted, and senescent cells and is also involved in the function and regulation of the immune system, differentiation, homeostasis/proliferation, and development. Apoptotic cell death is executed by two major pathways, namely, extrinsic and intrinsic apoptotic pathways via caspase cascades to drag the cells towards death [39]. Autophagic cell death (Type II) is the catabolic process that acts as a quality control mechanism for organelles and proteins to favor survival during starvation or scarcity conditions [40]. Necroptosis or programmed necrosis (Type III), is a caspase-independent cell death that is stimulated by tumor necrosis factor receptor 1 (TNFR1), TLRs, IFN receptors (IFNR), and intracellular RNA- or DNA-sensing molecule upon impairment of apoptosis [41]. Necroptosis induces an innate immune response against the infection caused by viruses [42]. All these orchestrated mechanisms of cell death get altered under pathophysiological condition such as cancer. The deficiency of cell death is significantly involved in tumor development and resistance against radiations as well as chemotherapy [38]. ROS plays an intermediate role in cell death and survival signaling. An intracellular level of ROS determines the fate of the cell. Therefore, induction of cell death by manipulating the redox balance in the cancer cells has been considered as one of the promising approaches for cancer therapy.

The AGE-RAGE signaling and apoptosis

The role of AGEs and its receptor RAGE has been investigated for induction of apoptosis in different types of cells [43–47]. The propagation of apoptosis through the AGEs-RAGE axis involves pro-apoptotic factors and caspase cascades. The apoptotic signaling channelizes through death receptor activation and mitochondria disintegration followed by the activation of executioner caspase-3 [48]. The expression of RAGE modulates the death receptor and mitochondrial pathways of apoptosis by regulating the expression of pro-apoptotic caspase-3, caspase-9, and anti-apoptotic Bcl-2 [49, 50]. It has been shown that RAGE-deficient cardiac cells have enhanced Bcl-xL expression and reduced cytochrome c release [51]. An earlier investigation also demonstrates that exogenous α-Fas together with AGE aggravate the release of cytochrome c, activation of caspase-8, and caspase-3. Moreover, AGEs may activate Fas-FasL signaling in human retinal ARPE-19 cells [52]. In addition, AGEs-RAGE interaction activates NF-κB to stimulate TNF-α secretion in cell lines including the macrophages [53] and microvascular endothelial cells [54]. Furthermore, AGE-mediated apoptotic signaling in pericytes orchestrates through initiator caspase-10 and is executed through caspases-3, -6 -7, or 9 [55]. One of the primary mediators through which the AGE-RAGE axis induces apoptosis is elevated reactive oxygen species (ROS) level in the cells [46, 56]. Earlier studies highlighted that AGEs-mediated cell death may influence cellular alterations that may cause pathological complications [57, 58]. The oxidative burden within the cells further perturbs several signaling pathways involved in cellular homeostasis. For instance, AGEs-induced oxidative stress leads to the activation of NF-κB and MAP kinase (MAPKs) pathways [59, 60]. The MAPKs are a family of serine/threonine kinases that participate in apoptotic signaling. In addition, the JNK and p38 MAPK are the well-versed intermediates that activate apoptosis in response to cellular stress and chemotherapeutic drugs [61–64]. It has been shown that AGEs activate apoptosis via JNK and p38 MAPK in osteoblast [65, 66] and in Schwann and mesangial cells [67, 68]. Furthermore, the AGEs-ROS mediated p38 MAPK and JNK activation and in turn orchestrate pro-apoptotic caspase-3 cascade [60]. Importantly, AGEs have been reported as the pro-apoptotic

factors for the cellular culture of microvascular cells, neuronal cells, fibroblasts, and renal mesangial cells [68–71]. In contrast, the AGEs cognate partner S100P/RAGE itself activates apoptosis signaling through the MAPK pathways [72]. On the other hand, RAGE ligand HMGB1 under reduced condition induces Beclin-1-dependent autophagy, while in oxidized state promotes apoptosis [73, 74]. Indeed, ROS triggers cell death signaling through the mitochondrial and endoplasmic reticulum stress-mediated pathway [75, 76]. AGEs-RAGE axis further extends the signaling to mitochondrial functioning. It has been shown that AGE-RAGE interaction leads to mitochondrial dysfunction and altered mitochondrial dynamics [77–79]. The fractions of RAGE have been identified in the extract of mitochondrial complex I and II [80]. The damaged mitochondria accumulate ROS that leads to the disintegration of mitochondrial membrane potential (MMP) and prefers apoptotic instigation in the absence of autophagy signaling [74, 81]. It is observed that AGEs lead to the exacerbation of mitochondria associated pro-apoptotic protein Bax that leads to the mitochondrial alteration and caspase-9 activation in mesangial cells [82]. Interestingly, AGEs-induced disintegration of MMP may be restored with supplementation of glutathione together with an antioxidant N-Acetyl cysteine (NAC) [83].

On the contrary to the pro-apoptotic roles of RAGE in normal cells, cancer cells tend to employ RAGE signals for their proliferative purposes. Apoptosis is the most prominent form of programmed cell death that cancer cells manage to evade by disrupting numerous cellular mechanisms. RAGE and its ligand HMGB1 is known to be upregulated in many types of tumor and promotes invasion and metastasis by activating diverse cellular signaling pathways [84]. The induced expression of RAGE associated with cancer serves multiple purposes to assure the survival of transformed cells via the activation of NF-κB [2]. RAGE-mediated activation of NF-κB is associated with angiogenesis, cell migration, proliferation, and evasion of cell death [85]. Multiple studies suggest that RAGE meticulously perpetuates the survival signaling in cancer cells by promoting the "programmed cell survival" (Autophagy) and suppressing "programmed cell death" (Apoptosis) under metabolic and oxidative stress [86]. In a study carried out by Kang R et al. [86], RAGE knockdown resulted in increased apoptosis with diminished autophagy in pancreatic cancer cells under high oxidative stress. Supportively, RAGE overexpression was positively associated with reduced apoptosis and sustained autophagy. Moreover, RAGE overexpression restricted the mitochondrial translocation of p53 and prevented apoptosis [17]. The release of HMGB1 from autophagic cells and its subsequent binding to RAGE support the cancer cell proliferation via ERK1/2 and MAPK activation [87]. HMGB1/RAGE interaction also prevents apoptosis in cancer cells through the activation of Akt and MMP-9 [88]. A study conducted by Elangovan et al. suggests that downregulation of RAGE by RNA interference (RNAi) reduced the survival of prostate cancer cells by downregulating RAGE as well as its physiological ligand HMGB1 [89]. Our previous report demonstrates that quercetin promotes apoptosis by attenuating the expression of RAGE and its ligand HMGB1 in human breast adenocarcinoma cells [85]. In addition, the quercetin inhibits RAGE/PI3K/Akt/mTOR axis and increases gemcitabine chemosensitivity in pancreatic cancer cells [90]. The sustained autophagic response in cancer cells under stress (along with the inhibition of apoptosis) is also largely attributed to the decreased phosphorylation of mammalian target of rapamycin (mTOR) accompanied by the simultaneous interaction of autophagic protein Beclin-1 with Vps34 [91]. Thus, upregulated expression of RAGE promotes cancer cell survival by sustaining autophagy and inhibiting apoptosis.

A possible explanation for the functional disparity of RAGE in normal and cancer cells to regulate apoptosis can be attributed to the ability of cancer cells to display high intracellular glyoxalase activity. In the case of normal cells, the induced apoptosis is the result of intracellular accumulation of glycation products. However, the survival pathways mediated through the AGE/RAGE axis in cancer cells are mainly sustained through receptor-governed signaling present on the cell surfaces. Moreover, since a high glyoxalase activity is maintained in cancer cells, apoptosis due to the intracellular glycation is seldom observed in such cells. Furthermore, the generation of ROS through AGE/RAGE interaction in normal cells generally results in apoptotic cell death due to free radical-induced DNA damage. However, cancer cells have a characteristic feature to survive under high oxidative stress. Cancer cells scrupulously maintain a relatively higher oxidative burden to regulate their signaling pathways. In that view, AGE/RAGE-mediated oxidative stress can result in apoptosis in normal cells while showing an opposite (anti-apoptotic) effect in cancer cells. (Fig. 2) Taken together, AGE/RAGE-mediated signaling has a close connection in the regulation of programmed cell death.

The AGE-RAGE signaling and autophagy

Autophagic cell death is pertinently suggested as a double-edged sword for programmed cell death and survival. Autophagy is an essential catabolic process for the degradation of cellular components to sustain cellular metabolism under nutritional deprivation conditions. The autophagic process involves various upstream regulators, initiation, and nucleation of autophagophore and autophagolysosome formation, a sequence of events that ultimately aims at the degradation of intracellular components. It plays a vital role in cellular energy balance and homeostasis. However, the defects in autophagic machinery cause several pathologies

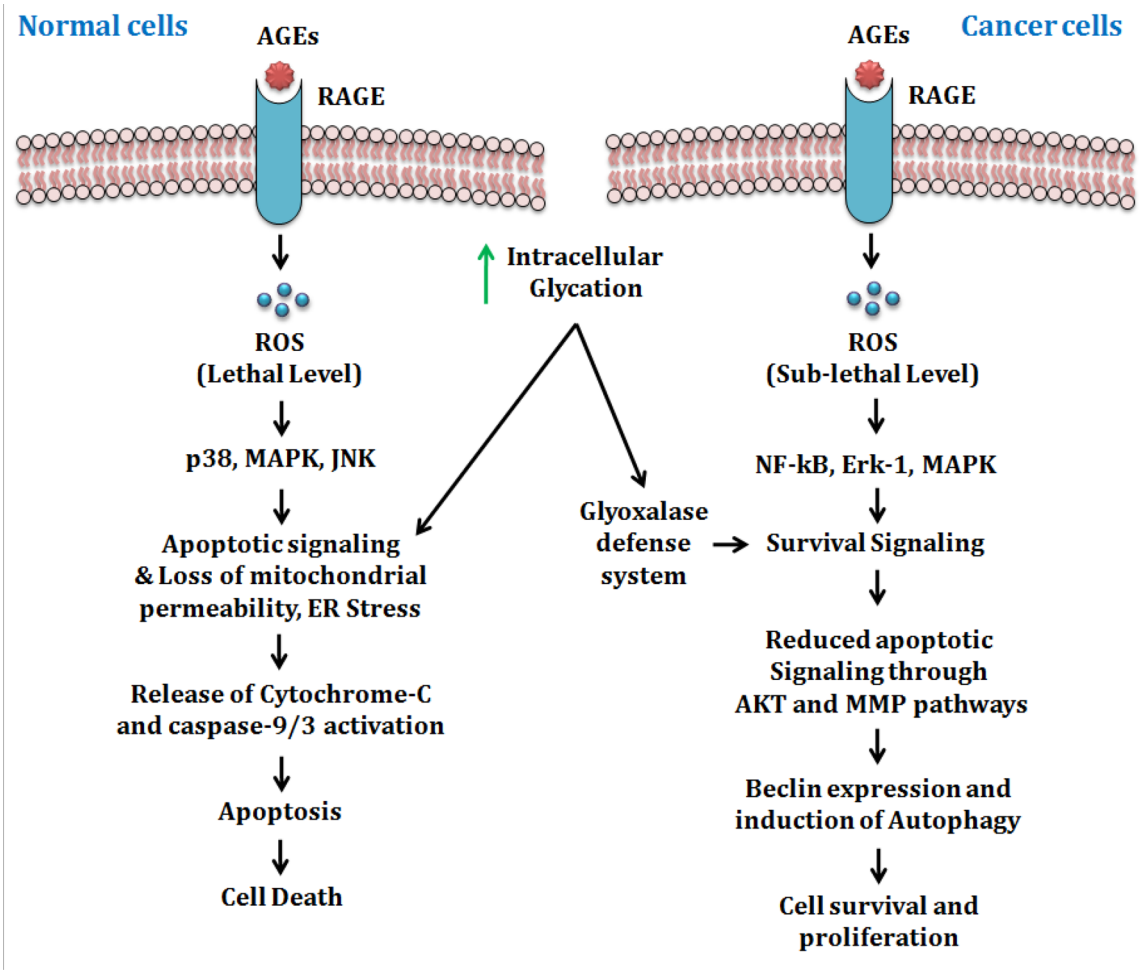

Fig. 2 Role of AGE-RAGE signaling in apoptotic cell death in normal cells and cancer cells. The AGE-RAGE signaling promotes cellular ROS generation and plays an important role in apoptotic cell death in normal cells and cancer cells. Once the AGEs are synthesized it circulates through the system and binds to RAGE. The binding of AGEs to the RAGE activates the number of signaling molecules which promote ER stress and loss of mitochondrial permeability subsequently induces apoptotic cell death in normal cells. On the other hand, the AGE-RAGE signaling promotes survival signaling by inhibition of apoptosis and induction of autophagy in cancer cells. AGE-RAGE signaling may intricate dual role in apoptotic cell death and cell survival signaling. Dysregulated activation of AGE/RAGE signaling may contribute various pathological conditions

including cancer. Moreover, Autophagy has been reported to play dual roles in cancer. Cancer cells possess a high proliferation and growth rate resulting in nutrient stress conditions in the tumor microenvironment. In addition, oncogenic mutations like KRas lead to metabolic adaptation in cancer cells to sustain in the tumor microenvironment [92]. The role of Ras in autophagy in cancer cells largely appears to be paradoxical [93]. A plethora of literature suggests that autophagic signaling acts as an adaptive stress response that enables cancer cells to survive under nutrient-deprived conditions [94]. Additionally, the tumors are deprived of oxygen, forcing them to evolve mechanisms to survive during hypoxic conditions. Hypoxia plays a key role in cancer metastasis and is also intricately related to autophagy machinery in cancer cells [95]. Moreover, autophagy sustains cancer cells under therapeutic stress and enables drug resistance mechanisms. A recent report suggests that the inhibition of autophagy restrains the chemosensitivity in cancer cells [96]. In addition, the induction of autophagy also inhibits apoptosis in cancer cells [97].

AGEs and RAGE are reported to accumulate during the progression of cancer. AGEs participate in autophagy signaling in a wide variety of cells and are involved in cellular dysfunction [98, 99]. Previous reports have highlighted that AGE-RAGE signaling mediates ROS generation and is associated with autophagy in cancer cells to resist apoptosis [22, 100]. In combination, ROS and oxidative stress help to progress autophagy that may favor cancer cells for cell survival and growth [101]. AGEs induce autophagy via the ERK pathway and increase the proliferation of VSMCs. The

knockdown of RAGE in the tumor cell diminishes autophagy and tumor cell survival, which in turn results in the induction of apoptotic cell death. On the contrary, overexpression of RAGE promotes autophagy and diminishes apoptosis to support tumorigenesis. Moreover, RAGE-mediated autophagy is also associated with decreased phosphorylation of mTOR and increased Beclin-1/VPS34 autophagosome formation [17]. In addition, the AGEs-RAGE potently induces autophagy more than the known inducers such as TNF or doxorubicin. However, the potency of AGE-mediated autophagy also depends upon the expression of RAGE. AGE-RAGE activates PI3K, a kinase that plays vital roles in autophagy. Few evidence also suggests that the accumulation of AGEs leads to the ROS generation. NF-κB is intricately involved in autophagy as it controls the transcription of many autophagic genes including Beclin-1. AGE-RAGE signaling also activates PKC and/or RAF kinase and downstream p38/MAPK and ERK pathways to mediate autophagy [102]. As oxidative stress generates oxidative injury and cell death, there are evidences that AGEs activate Nrf-2, a master regulator of antioxidant genes and provide defense against oxidative stress in diabetes [103]. Recent report suggests that the AGEs regulate Nrf-2 and Bcl-xL signaling and promotes survival of oral cancer cells in diabetic patients [104]. It has been also suggested that the AGEs/RAGE signaling axis leads to excessive autophagy and impairs the cell viability of cardiomyocytes, causing cardiac dysfunction [105]. Apart from that, AGEs are also known to mediate autophagy in cardiomyocytes via ERK1/2, whereas prolonged exposure of AGEs to cardiomyocytes leads to apoptotic cell death via the p38/MAPK pathway [106]. Moreover, PI3K/Akt/mTOR signaling pathway negatively regulates autophagy. AGEs-RAGE interaction also inhibits the PI3K/Akt/mTOR signaling pathway and results in autophagy [107].

Interestingly, RAGE avidly regulates p65 and BNIP3 to promote autophagy and cell survival [105]. A contradictory result is also evident from a study where RAGE-deficient HCC represents the onset of autophagy through the AMPK/mTOR signaling pathway [108]. The mechanistic pathways that confer to autophagy via AGE-RAGE interactions also show large diversity and remain to elucidate. The Role of AGE-RAGE signaling in pro-survival autophagy during cancer progression is shown in Fig. 3.

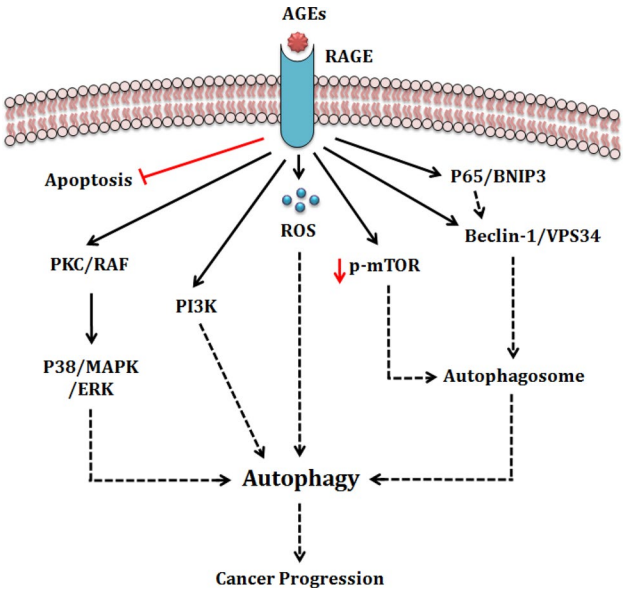

Fig. 3 Role of AGE-RAGE signaling in Pro-survival autophagy during cancer progression. The AGE-RAGE signaling promotes autophagy that mediates cancer cell survival. The binding of AGEs with RAGE activates PKC/RAF, PI3K, and p65/BNIP3 which promotes pro-survival autophagy and inhibits apoptotic signaling in cancer cells. AGE- and RAGE-mediated generation of cellular ROS may contribute stress-associated pro-survival autophagy in cancer

The AGE-RAGE signaling and necroptosis

Necroptosis is a caspase-independent cell death that is morphologically analogous to necrosis, but mechanically resembles to apoptosis [109]. Oxidative metabolism generates reactive oxygen species (ROS) via mitochondrial respiratory chain and redox-active during the execution of cell death via necroptosis. AGEs are formed due to the synthesis of methylglyoxal, toxic derivatives, dihydroxyacetone phosphate (DHAP), and from the fragmentation of glyceraldehyde-3-phosphate during the process of glycolysis. An interesting study shown that the increased level of cellular glucose possibly induces necroptosis [110]. Receptor-Interacting Protein 1 (RIP1), RIP3, and Mixed Lineage Kinase domain-like (MLKL) are the key mediators of Necroptosis. The assembly of RIP1 and RIP3 result in the formation of the "Necrosome", which is one of the significant characteristics of necroptosis [111]. The subsequent phosphorylation of MLKL by necrosome releases cell damage-associated molecular patterns (DAMPs) with the loss of plasma membrane integrity. The release of DAMPs evokes the inflammatory responses and favors the progression as well as the survival of tumor cells. High-mobility group box 1 (HMGB1) is a distinctive DAMP molecule. The intracellular HMGB1 is present within all nucleated cells and plays a significant role in the nuclear and cellular homeostasis, whereas the extracellular HMGB1 commence and protract the inflammatory response via the ligation of the RAGE and TLRs [112]. Furthermore, the release of HMGB1 and AGEs during necroptosis may interact with RAGE present on the surrounding tumor cells that support inflammation and cancer progression. (Fig. 4) The HMGB1 is a part of the family of the High-mobility group of non-histone chromosomal proteins. It is expressed as a single chain of the polypeptide consisting of 215 amino acids [113]. HMGB1 maintains the

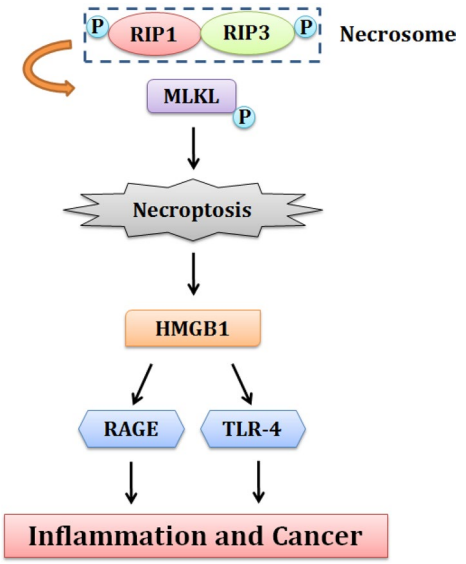

Fig. 4 The association of the RAGE signaling with necroptosis during the progression of inflammation and cancer. The intracellular HMGB1 plays a significant role in cellular homeostasis. Upon necrotic insult, the assembly of RIP1 and RIP3 forms necrosome which subsequently releases HMGB1. This extracellular HMGB1 binds with RAGE or TLR-4 that may influence inflammation and cancer progression

chromosomal structure and stability inside the nucleus of a cell. During stress condition, HMGB1 translocates to the cytoplasm from the nucleus to protect the cell from death via mechanism of autophagy by dissociation of Beclin-1/Bcl-2 interaction for competitive binding with Beclin-1. Once HMGB1 is secreted out or released from the cells, it activates a different set of pathways by binding with Toll-like receptors (TLR-2,TLR-4 and TLR-9) and Receptor of Advanced Glycation Endproducts (RAGE) for induction of inflammation and cell survival [114]. Several cytokines and inflammatory mediators promote tumor growth through TLR-mediated signaling pathways, which lead to activation of transcription factors: NF-κB and STAT-3 for marinating tumor microenvironment consisting of an inflammation [115]. HMGB1 released from necrotic cells orchestrate TLRs and RAGE signaling amplifies inflammatory response by creating functional tripod to maintain chronic inflammatory state [116]. TLRs are evolutionary conserved transmembrane protein found in the cell surface of immune cells. TLRs are key components of the innate immune system that direct detection of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [117]. DAMPs released from injured or dying cells behave as endogenous ligands for TLRs and are recognized by specific TLRs on immune cells; subsequently, TLR signaling will lead towards the inflammatory response. The immune cells including macrophages and dendritic cells consist TLR and RAGE receptor on their cell surface and binding of HMGB1 resulted release of inflammatory mediators including IL-6 and TNF-α. Inconsistent release of IL-6 and TNF-α leads to necrotic or apoptotic cells and maintain the HMGB1 release, resulting a cascade amplification of inflammation [118]. HMGB1 also interacts with TLR5 and initiates MyD88-dependent activation of NF-kB signaling pathway resulting in production of pro-inflammatory and perception of pain [119]. Previous report suggests that the core component of TLR signaling is activation of an IL-1-like pathway dependent upon the adapter MyD88, coupling via an intricate series of kinases and scaffolding proteins to activation of NF-κB [120].

HMGB1 is a damage-associated molecular pattern (DAMP), which contributes progression of inflammation and cell survival of cancer [121]. HMGB1 is passively released from the damaged cells during necrotic cell death. An active release of HMGB1 during the angiogenic or inflammatory condition promotes cell survival [113, 122]. HMGB1 can activate diverse sets of signaling components, including AKT and MAPKs and play an important role in cell proliferation via synergy of RAGE and hasten cell cycle progression [84]. Interaction of HMGB1 with their receptor RAGE and TLRs influences three major signal transduction pathways including NF-kB, PI3K/Akt, and MAPK/ERK1/2/p38 [114]. It has been noticed that HMGB1 influences cell proliferation of diffused large B cell lymphoma cells by activation of ERK1/2, Akt, and STAT-3, Non-Receptor Tyrosine Kinase (Src), and SRC Proto-Oncogene. However, obstruction of HMGB1 signaling may inhibits tumorigenesis [123]. Over expression of HMGB1 directly or indirectly influences hallmarks of cancer, that includes the limitless potential to divide, angiogenesis, evasion of apoptosis, compromised sensitivity to growth inhibitors, increased response to growth signals (self-sufficiency), inflammation, invasion, and metastasis [122]. Taken together, release of HMGB1 and other pro-inflamatory cytokines during necrotic insult orchestrates cell survival and enhances the stemness of resident cancer cells for continuous cell proliferation.

Role of miRNAs in regulation of oncogenic AGE-RAGE axis

MicroRNAs (miRNAs) are endogenous, single-stranded family of non-coding RNAs, implicated in regulation of target genes at the transcriptional and translational level [124, 125]. Over the past decade, several studies highlighted the importance of miRNAs in regulation of various human diseases, including, cancer [126–128]. Dysregulated miRNAs signaling in cancer cells up and/or downregulate oncogenes, which, in turn, leads to tumor proliferation, angiogenesis, and apoptotic evasion [129, 130]. Moreover, a systematic

profiling of cancer-associated miRNAs provides an informative insight to monitor cancer progression and therapeutic response in patients [131, 132]. The intriguing role of miRNAs in modulation of cancer gene expression attributed a significant attention in recent past years; however, a mechanistic linkage between miRNAs and pathways associated with tumor progressing remains enigmatic.

Given the importance of miRNAs in cancer gene regulation and AGE-RAGE signaling in cancer proliferation, several studies have identified novel miRNAs involved in the tuning of the AGE-RAGE axis. The oncogenic miR-21, which is reportedly upregulated in various cancer cells, activates though SP100P/RAGE signaling pathway and leads to cancer progression [133, 134]. Indeed, miR-221 and miR-222 is reportedly involved in cell proliferation, through inhibiting cell cycle regulator p27kip1 [135]. In this context, an interesting study showed that HMGB1-RAGE axis induces the oncogenic expression of miR-221 and miR-222 in papillary cancer cell line, to promote cellular malignancy [136]. Moreover, exogenous HMGB1 interacts with RAGE and activates miR-221/miR-222 expression, which in turn, inactivates oncosuppressor PTEN (Phosphatase and tensin homolog) in thyroid carcinoma cell lines, suggesting that HMGB1/RAGE pathway promotes oncogenic miRNAs expression to favor cancer proliferation and targeting these pathways could be a promising approach against tumor growth [137]. An interesting study showed that the treatment of human monocytes with AGEs induces the expression of miR-214, which specifically target tumor suppressor PTEN to delay apoptosis of monocytes [138]. In contrast, an interesting study demonstrated that AGE-induced miR-223 expression target insulin-like growth factor-1 receptor (IGF-1R) expression and leading to apoptosis in osteoblast-like MC3T3-E1 cells [139]. In addition, a dysregulated expression of miR-205 has been inversely associated with the invasive traits of triple-negative breast cancer (TNBC); moreover, ectopic expression of miR-205 in MDA-MB-231 cells significantly target HMGB1/RAGE signaling pathway to attenuate cell growth and metastatic invasion, following studies that suggest that apart from oncogenic transformation, certain miRNAs contributes in regulation of cell proliferation through distinct signaling [140].

RAGE inhibitors as a therapeutic agent

The synergy of AGE-RAGE accomplishes downstream signaling of NF-κB activation and other molecules, which leads to oxidative stress and pathological consequences. Multiple evidences suggested that the elevated expression of RAGE considerably evades cell death in cancer cells. Moreover, the activation of RAGE in cancer cells stimulates diverse sets of signaling pathways that support tumor growth. In addition, AGE-RAGE signaling promotes survival mechanism (pro-survival autophagy) and evades cell death (apoptosis) which appears to be major pathways during cancer progression. In the recent past, several reports highlighted that RAGE inhibitors significantly inhibited tumor growth and induces cell death. An inhibition of AGE-RAGE signaling by natural or synthetic inhibitors can be considered as therapeutic targets. We have explored various databases to find out RAGE inhibitors those are identified to inhibit cell proliferation in

Table 1 RAGE inhibitors that induce apoptosis or inhibit cell survival in various malignancies

RAGE inhibitor	Mechanism involved	Type of cancer	References
Papaverine	Inhibition of RAGE dependent NF-κB activation	Human fibrosarcoma	[141]
Curcumin	Inhibition of ERK1/2 and NF-κB, Increases ROS to induce apoptosis	Lung cancer, Nasopharyngeal carcinoma	[2]
Quercetin	Inhibition of HMGB1 and promotes apoptosis, Increases ROS to induce cell death	Breast cancer	[85, 142]
Withaferin A	Increases ROS to induce cell death	Breast cancer, Head and neck cancer	[2, 143, 144]
Small RAGE antagonistic peptide	Decreases interactions of RAGE ligands (S100s, HMGB1) with RAGE, Inhibition of NF-κB	Pancreatic ductal adenocarcinoma	[145]
Hispidin	Inhibition of NF-κB and RAGE expression	Pheochromocytoma	[146]
Ergothioneine	Inhibition of NF-κB and RAGE expression	Pheochromocytoma	[146]
Ethyl pyruvate	Inhibition of NF-κB, STAT-3, HMGB1, and RAGE expression	Human mesothelioma	[147]
Acetylated apurinic apyrimidinic endonuclease 1/redox factor-1 (Ac-APE1/Ref-1)	RAGE-mediated apoptosis induction through unknown mechanisms	Breast cancer	[148]

For compounds that inhibit NF-κB, further studies may be warranted to examine the pathways involved in apoptosis (or inhibition of cell proliferation) induction through nuclear factor κB in cancer cells

cancer cells either directly or indirectly. Table 1 summarizes different RAGE inhibitors that can be further explored for a possible intervention in anticancer therapy.

Conclusion

The accumulation of AGE and RAGE orchestrate diverse set of signal transduction pathways for progression of oxidative stress to manifest pathological key events. Nevertheless, dysregulated activation of various set of genes and protein directly or indirectly influences cellular homeostasis via accelerated generation of free radicals and ROS. An accumulated ROS favors production of AGEs and activation of nuclear transcription factor NF-κB, with increases expression and release of pro-inflammatory cytokines resulting in the cellular damage, which triggers the release of intracellular component to the rapid activation of an array of signaling cascade culminating tumor microenvironment for cell survival. The tumor microenvironment is mainly comprised of cancer cells surrounded by inflammatory milieu with hyperglycemic and hypoxic environment which concomitantly enhances the formation of AGEs. The association of hyperglycemia and AGEs formation during cancer progression requires extensive research to decode the complex mechanism of cell proliferation of cancer cells. Beside, that the upregulation of RAGE expression is well documented in various pathological conditions. The binding of AGEs with their receptor RAGE augments oxidative stress and inflammation that collectively promotes tumorigenesis. Moreover, the programmed cell death pathway is dysregulated during cancer progression. Based on the available reports discussed above, it is inclined to believe that AGEs-RAGE signaling promotes survival pathways in cancer cells by negative feedback regulation of apoptosis and positive regulation of pro-survival mechanism such as autophagy and necroptosis mediated release of DAMPs. Moreover AGEs-RAGE signaling-mediated pro-survival autophagy limits apoptosis in cancer cells. However, in normal cells, the activation of AGEs-RAGE signaling induces cell death to balance tissue homeostasis. Dysregulated activation of AGE-RAGE signaling may lead to pathological consequences. The paradigm of AGEs-RAGE signaling-mediated diversion from cell death (apoptosis) to cell survival (pro-survival autophagy) requires extensive research. An inhibition of AGE-RAGE signaling may be beneficial to counteract progression of inflammatory cascades responsible for various pathological conditions. Further deciphering sequence of events involved in regulation of AGE production and identification of potential inhibitors of AGEs/RAGE may be of immense benefit for cancer prevention and therapeutics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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