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Review

Targeting receptors of advanced glycation end products (RAGE): Preventing diabetes induced cancer and diabetic complications

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ABSTRACT

Cancer and diabetes are the two major disorders that affect a large proportion of the world's population. Results from multiple epidemiological studies have concluded that diabetes and cancer are linked, and diabetic patients live at much higher risks of developing cancer and diabetic complications at the later phase of disease. Inflammation is the central pathway that mediates both diabetic complications as well as cancer. Receptor of advanced glycation end products (RAGE) is a non-specific multi-ligand pattern recognition receptor that induces the inflammatory responses by binding with multiple ligands. RAGE and its ligands are upregulated in diabetes, inflammation and cancer. Advanced glycation end products (AGEs), high mobility group box protein-1 (HMGB1) and S100 proteins are the major RAGE ligands that contribute to these consequences and an increased release of RAGE ligands during diabetic conditions can be a possible mechanism leading to diabetic complications and cancer. Moreover, further release of RAGE ligands from cancer cells can be a possible mechanism behind the worsening of diabetic complications in diabetic cancer patients. Inhibition of RAGE signaling can prevent diabetic complications and cancer in diabetic patients and can be helpful in the management of worsening diabetic complications and cancer in diabetic cancer patients. Curcumin, Quercetin and Withaferin A are known to inhibit multiple molecular pathways that are involved in RAGE signaling. The combined effects of these molecules can be explored to achieve the complete inhibition of RAGE signaling in diabetic patients.

1. Introduction

Cancer accounts for 9.6 million deaths in 2018. Every 1 in 6 deaths in the world occurs due to cancer; making it the second most leading cause of deaths globally. Lung cancer, breast cancer and colorectal cancer are the most common cancers that affect the population worldwide [15]. Diabetes, on the other hand, is also one of the major causes of deaths worldwide. The latest reports published by WHO revealed a figure of 1.2 million deaths in a year caused by diabetes making it the 8th major cause of deaths globally. A recent report generated by international diabetes federation revealed that more than 422 million people are affected by diabetes globally [140]. A Growing body of evidence suggests that cancer and diabetes are interlinked and diabetic patients live at much higher risks of developing cancer in the later stages of diabetes. Diabetes is a common comorbidity in cancer patients [160,167]. An observational study conducted using population based registries suggested cancer incidences were 15–30% higher in diabetic patients in comparison to non-diabetic patients [8]. Inflammatory pathways promote cancer cell proliferation [30]. Hyperinsulinemia, hyperglycemia and inflammation are the major assumed pathways that link diabetes to cancer [46]. On the other hand, diabetic patients also live at high risks of developing diabetic complications. The development of major diabetic complications including the vascular calcification, retinopathy, neuropathy and nephropathy in diabetic patients is also supported by inflammatory responses generated during the hyperglycemic conditions [206]. Cancer and diabetic complications appear during the later stages of diabetes [139,171]. The late stage occurrence of these complications in diabetic patients and the mediatory role of inflammation in these pathologies suggest the involvement of a common central inflammatory pathway.

Receptors for Advanced Glycation End products (RAGE) are non-specific multiligand pattern recognition receptors that exist on the cell

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surfaces [168]. In addition to binding with advanced glycation end products (AGEs), these receptors also show binding with a variety of ligands including the beta-amyloid, beta sheet fibrils, high mobility group box proteins (HMGB), Amphoterin, S100, C3a and advanced oxidation protein products (AOPPs) [51,155,168]. RAGE belongs to the immunoglobulin or Ig superfamily [214] and exists in very low concentrations on different cell surfaces including the macrophages, endothelial cells and smooth muscle cells under the normal physiological conditions [155,173]. The expression of RAGE increases in pathological conditions such as diabetes, inflammation and cancer [50,116] and unlike other receptor proteins, where an increase in the concentration of ligands results in the down-regulation of receptor expression, RAGE receptors are up-regulated in a ligand rich environment [214].

2. RAGE mediated signaling pathways

A variety of signaling pathways are stimulated when ligand binding to RAGE occurs including the MAP, ERK, JAK and stress-induced protein kinase pathways [214]. Interaction of RAGE with advanced oxidation protein products signals the oxidative stress-regulated ligand generation [173]. RAGE stimulation activates nuclear factor kappa B associated transcription of proinflammatory genes which increase the synthesis and release of IL-1, IL-6 and TNF- alpha [50,168]. Activation of nuclear factor also stimulates the further synthesis of RAGE which in turn activates more nuclear factor, thus, forming a positive loop to increase the transcription of proinflammatory genes. The key players of inflammation i.e. monocytes, neutrophils, macrophages and other leukocytes release the RAGE ligands during the inflammatory responses [214]. In various studies that are conducted to determine the role of RAGE ligands in inflammation, inhibition of RAGE activity retarded the inflammatory pathway; suggesting a potential role played by RAGE in inflammation [69].

3. Intracellular recruits of RAGE

The cytosolic domain of RAGE (ctRAGE) lacks the tyrosine kinase activity and therefore recruits the other intracellular component proteins to execute its signal transduction. One such important intracellular protein component is mammalian Diaphanous-related formin 1 (mDia1) encoded by the gene Drf1/ Diaph1 (5q31). The expression of mDia1 proteins increases with the increase in RAGE concentration. However, the expression of RAGE is found to be independent of mDia1 proteins expression suggesting the presence of other intracellular recruitable proteins for RAGE signal transduction. The src protein of sarcoma family is another recruited protein in RAGE signaling [214]. A study conducted by Natrajan and group concluded that the src is activated by S100B through RAGE in vascular smooth muscle thus initiating a cascade of downstream signal transductions including phosphorylation of MAPK, ERK and NF-κB [155]. The Signal transducers and activators of transcription 3 (STAT3) are also activated by a direct src action or by Janus Kinases (JAK) [69]. Suppression of src retards the cellular inflammation and migration induced by S100B suggesting that src plays a crucial role in cell inflammation induced by RAGE [60].

4. RAGE and inflammation

4.1. NF-κB activation

Nuclear factor-κB (NF-κB) is a transcription factor for inflammation that regulates the expressions of over hundreds of genes that are involved in multiple cellular changes such as cell transformation, survival, proliferation, invasion, angiogenesis, metastasis and most importantly inflammation [55]. Under the normal physiological conditions, this protein complex exists in an inactivated state due to its inhibition by the inhibitor of κB (IκBα) present in the cytosol [155]. Another complex called IκB kinase complex (IKK) composed of α, β and regulatory γ subunits also exists in the cytosol. The regulatory γ- subunit of IKK, also known as NF-κB essential modulator (NEMO) phosphorylates and degrades the IκBα in an ubiquitin-dependent manner and blocks its inhibitory action on κB thus activating the signal transduction molecule NF- κB protein complex [115,214]. Upon activation, NF-κB protein complex translocates to the nucleus to activate a variety of inflammatory genes [155]. NF-κB is one of the initial signal transduction molecules that gets activated during the RAGE binding to exhibit inflammatory responses [156].

The mitogen-activated protein kinases (MAPK) are a group of intracellular components that consist of a set of signaling molecules working in unison to produce the associated cellular response. RAGE signaling induces inflammation through the MAPK pathways [141,214]. Binding of ligand to RAGE leads to the activation of the MAPK pathway that eventually activates the IKK to phosphorylate and inactivate the IκB, thus, activating the process of NF-κB signal transduction [214]. Upon sensitization by an appropriate ligand, RAGE receptors induce the activation of NF-κB by the MAPK pathway through the activation of ERK1/2 or P38 MAPK [109].

4.2. The p38 MAPK pathway of inflammation

The P38 MAPKs are mainly known for the regulation of cytokine expressions. Four major subtypes of P38 MAPKs (α, β, γ & δ) are known [80]. The p38α MAPKs are the most abundantly present kinases in the cells [97]. These kinases are expressed in a tissue-selective fashion. While p38 α & β are present in the majority of cells, p38 γ & δ are found to be present on skeletal muscles and testis, pancreas, small intestine respectively [164]. P38 MAP kinases are phosphorylated and activated by the upstream signaling from MKK3 and MKK6 kinases. Studies have also suggested that P38 can also be phosphorylated by JNK activator kinase, MKK4 [177]. Once activated, P38 translocate from the cytosol to the nucleus and activates a number of responder genes along with the activation of NF-κB protein complex [177,214].

4.3. The Ras/ Raf/ Mek/ Erk signaling pathway of inflammation

The extracellular signal-regulated kinases or ERKs are expressed by two genes: ERK1 and ERK2 [98]. When the inhibitors of MEK1/2 (The MAPK kinases regulating ERK phosphorylation) were added to *C. trachomatis* infected HeLa 161 cells, reduction in the levels of IL-8 mRNA transcription was observed, suggesting a potential role of ERK pathway in the production of IL-8 during inflammation [17]. The MAPK ERK signaling pathway follows after the phosphorylation of the RAGE receptor by the ligand binding. The cytosolic domain of RAGE gets phosphorylated through its tyrosine domain upon activation. The phosphorylated receptor domain then binds with an initiator complex called GRB2-SOS complex. This complex activates another downstream kinase called Ras by facilitating the exchange of bound GDP by GTP on Ras. The active Ras then stimulates the subsequent downstream kinase called Raf or MAP kinase kinase kinase (MAPKKK or MAP3 K). The MAP3 K then causes a further downstream phosphorylation of MAP Kinase Kinase (MAP2K) or MEK that finally phosphorylates the ERK or MAP kinase [61]. The phosphorylated ERK then leads to the transcription of NF-κB through the degradation of κB inhibitor. The NF-κB then translocates into the nucleus and regulates the expression of inflammatory genes [214].

4.4. MAPKs pathways in cancer and diabetic complications

Different Mitogen Activated Protein Kinases (MAPKs) tend to act in diverse ways to promote the cell proliferation in cancer. While P38 MAPKs are known to be apoptotic and antiproliferative that negatively regulate the cell cycle, studies on several cell lines also proposed a paradoxical involvement of P38/MAPKs in positively regulating the cell

cycle and supporting the cancer cell proliferation [197]. The P38δ isoform is overexpressed in all types of breast cancer. A delayed formation of primary tumor with reduced lung metastasis was observed in mice deleted with P38δ. Interestingly, improved cell adhesion and reduced detachment was noticed in these mice [196]. In a similar study conducted to examine the effects of norepinephrine on proliferation, invasion and migration of pancreatic cancer cells, the events were found to be positively regulated by β1 and β2 adrenergic receptor mediated P38/MAPK pathway [68]. In another study, overexpression of growth factors receptors was observed in colorectal cancer cells. These receptors activate the epidermal growth factor via ERK/MAPK pathway thus supporting the cancer growth [41]. Metastasis associated lung adenocarcinoma transcript-1 (MALAT-1), a non-coding RNA is associated with metastasis in cancer. Knockdown of MALAT-1 in gall bladder cancer cells resulted in attenuated cancer growth by the inactivation of ERK/MAPK pathway [213]. In another study, inhibitor of ERK/MAPK prevented the effects of hepatocyte growth factor to promote the growth of colon cancer cells [229]. Results from multiple studies therefore support the view that inhibition of MAPKs can prevent cancer cell proliferation, invasion and migration.

Studies have also demonstrated that chronic exposure of human mesangial cells to hyperglycemia causes diabetic nephropathy through the activation of P38/MAPK pathway [207,227]. Monocyte chemo attractant protein-1 (MCP-1) is known to cause cardiovascular diabetic complications. The production of MCP-1 increases manifold under hyperglycemic conditions. In a study that was carried out to determine the signaling pathways leading to MCP-1 production, it was observed that chronic hyperglycemia induced ROS production resulted in the overexpression of MCP-1 protein through P38/MAPK pathway [179]. In another similar study, downregulation of P38/MAPK pathway by resveratrol restored the diabetes induced cardiac dysfunction in streptozotocin induced diabetic rats [45]. Inhibitor of P38/MAPK also inhibited the early development of diabetic retinopathy in experimental animals [36]. Carnosine, an endogenous peptide is known to have beneficial effects in the prevention of diabetic retinopathy. In a study conducted to reveal the mechanical approaches, an ERK/MAPK inhibitory effect of carnosine was observed to prevent retinopathy [54]. ERK/MAPK pathway is also observed to play important roles in kidney fibrosis and diminished collagen degradation under hyperglycemic conditions in animal models [26].

5. RAGE signalling and diabetic complications

The production of advanced glycation end products (AGEs) increases manifold in diabetic conditions [168]. AGEs and other RAGE ligands have shown to play a crucial role in the genesis and maintenance of diabetic complications. Vascular calcification is a diabetic complication that causes increased vascular stiffness and reduced vascular integrity [211]. The administration of AGEs in RAGE knockout db/db diabetic animal model showed insignificant calcification while the similar administration in normal diabetic db/db mouse resulted in a substantial amount of calcification [85]. AGEs binding to RAGE leads to P38 induced expression of Tissue Growth Factor (TGF) beta 1 proteins and TGF-beta 1 signaling via smad2/3- P27 pathway causing cell hypertrophy and expansion of extracellular matrix [104,106] (Fig. 1). A positive relation between CML levels and calcification of arterial walls was also evident from another study where the CML/RAGE signalling in diabetic patients exacerbated the atherosclerotic calcification through the CML/RAGE- reactive oxygen species (ROS)-p38MAPK-cbfα1-ALP and NADPH/ROS pathways [204,205] (Fig. 1). Intracellular recruits of RAGE receptor called mDia stimulate the downstream signaling through RAC-1-JNK- AP-1 signaling pathway to induce the RAGE expression, inflammation and atherosclerosis in diabetic conditions [120]. Stimulation of RAGE receptor also induces the cleavage of Phospholipase-C (PLC) into IP3- DAG and increases the intracellular Ca^{+} signaling leading to vascular complications by the activation of PkC ERK1/2 pathway [86,132]. PkC also induces the vascular dysfunction by the activation of earlier growth response-1(EGR-1) pathway [217]. Vascular dysfunction in diabetes is also caused by the activation of PKC Beta II [92]. Induction of JAK STAT pathway also induces vascular remodeling by the activation of Nuclear factor of Activated T – cells (NFAT) and Proto-oncogene serine/threonine-protein kinase (Pim-1) when stimulated by RAGE ligands [4,147] (Fig. 1). High glucose levels in diabetic conditions induce the release of HMGB1 proteins from the nucleus to the cytoplasm of the cell and in extracellular spaces. In a study conducted, HMGB1 resulted in the calcification of vascular smooth muscle cells via the activation of NFκB and BMP-2 (Bone morphogenetic protein- 2) expression in the saphenous vein [203]. In addition to HMGB1, expression of calcium-binding proteins S100A8 and S100A9 also increases significantly in inflammatory conditions [6]. These proteins increase the vascular calcification process by their interaction with RAGE to signal the MAPK pathway. ApoE mice with ablated S100A9 or RAGE receptor showed less progression of atherosclerosis [135]. Renal protective effects of interventions against AGEs and their cross-linked products are also observed in animal models of diabetic nephropathy [14,43]. A potential role of HMGB1 protein was observed in the development of nephropathy in diabetic rats, where a high amount of protein accumulation was observed in the nucleus as well as in the cytosol of renal glomerular cells [88]. Results from a clinical study also showed the increased expression of TLR-2 and TLR-4 in the circulation of diabetic patients [34]. A possible mechanism behind the HMGB1 induced diabetic nephropathy is its interaction with Toll-like receptors-4 (TLR-4) to activate the inflammatory pathways in renal cells [112]. The association of Toll-like receptor-2 (TLR2) with inflammation is also inferable from another study conducted where the TLR-2 overexpression along with HMGB1 and HSP10 proteins was observed that lead to the inflammatory infiltration and renal damage in diabetic rats [105]. miR-92**b-**3p are the proteins that are involved in the process of cell proliferation, differentiation and various other signal transduction processes. Exogenously administered AGEs in rat models increased the expression of miR-92**b-**3p in renal epithelial cells of the animal model of diabetic nephropathy [113]. Vascular endothelial growth factor (VEGF) induces retinopathy by the induction of preretinal neovascularization [189]. A substantial role of AGEs in the pathogenesis of diabetic retinopathy is also evident from the results of an *in- vitro* study where a time-dose and hypoxic condition dependent action of AGEs in the overexpression of (VEGF) was observed in the inner nuclear and retinal pigment epithelial layers of retinal cells [117] (Fig. 1). Significant reduction in vasopermeability, leucostasis and microglial activation in retinal cells were also observed in diabetic RAGE -/- rats suggesting the RAGE blockers as therapeutic alternatives in diabetic retinopathy [124]. Similar responses are also produced by HMGB1 protein through their interactions with TLR9 and RAGE receptors resulting in inflammation, neovascularization and a high apoptosis rate in retinal cells of diabetic rats [75,223]. RNA interference against S100A4 mRNA resulted in significant attenuation of diabetic retinopathy by suppressing the expression of brain-derived growth factor (BDNF), VEGF and hypoxia-inducible factor-1*α* (HIF-1*α)* [162]. Two other members of S100 proteins, myeloid-related protein-8 (MRP8) and MRP14 were also found to be overexpressed in endothelial cells, leukocytes and myofibroblasts of proliferative diabetic retinopathy (PDR) membranes in diabetic patients. Moreover, the calprotectin complex formed by MRP8/ MRP14 proteins also increased the expression of adhesion molecules-1 intracellularly to produce the inflammatory response in PDR [1]. Significant participation of RAGE and its ligands is also observed in diabetic neuropathy. Presence of AGEs in cytoskeleton proteins and myelin components in peripheral neurons are observed in patients with diabetic neuropathy [128]. The possible mechanism behind the AGEs induced neuropathy is its interaction with RAGE to generate oxidative stress and create an inflammatory milieu in the neuronal cells by upregulating the NF-κB and stimulating the production of other glycation products such as Nepsilon-(carboxymethyl)

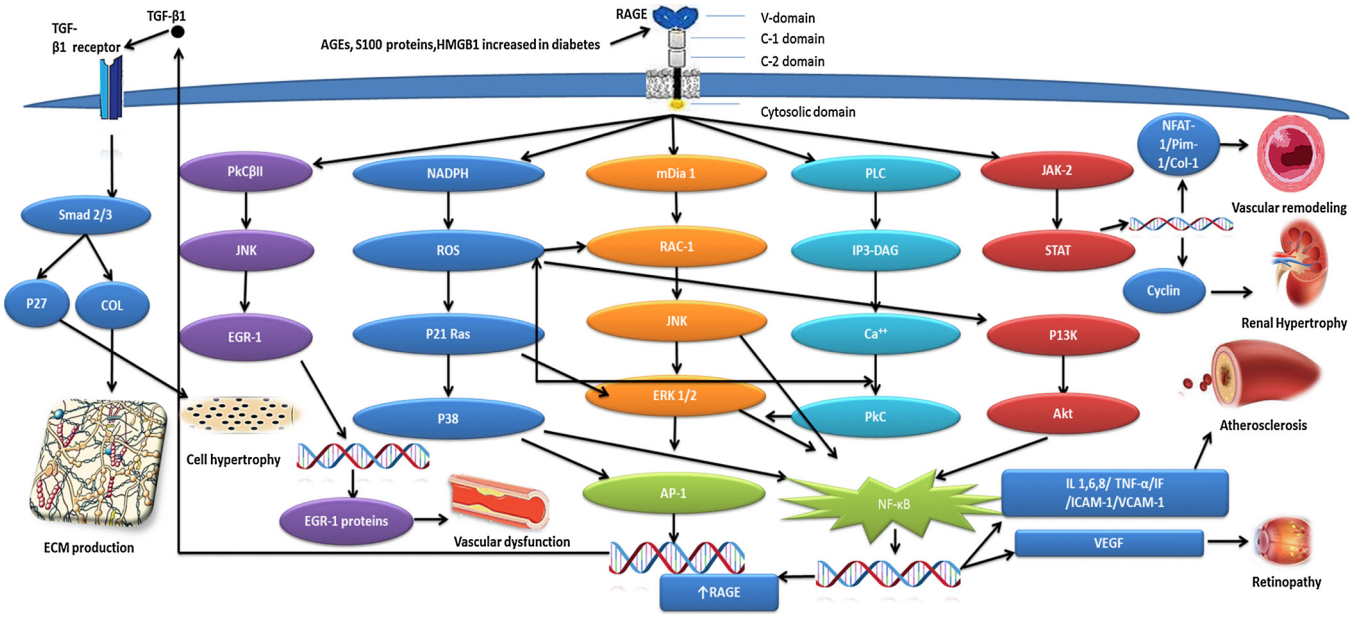

Fig. 1. RAGE signaling pathways leading to diabetic complications under increased release of RAGE ligands in hyperglycemic conditions. Majority of signaling pathways results in the activation of NFkB, its subsequent translocation into the nucleus and expression of inflammatory genes including ILs/TNF-α/IF/ICAM-1/VCAM-1 leading to inflammation and atherosclerosis. NFkB activation also results in the expression of VEGF that supports angiogenesis and diabetic retinopathy. AP-1 is the other transcription factor that is activated by RAGE signaling pathways that leads to the production of TGF-beta 1 proteins that are released in extracellular space to interact with TGF-beta 1 receptor. TGF-beta 1 binding activates intracellular smad2/3 proteins that result in downstream signaling causing cell hypertrophy and production of extracellular matrix. Activation of JAK-STAT and RAGE induced production of EGR proteins results in vascular remodeling and compromised vascular functions in diabetic conditions. RAGE, Receptor of Advanced Glycation End products; NFkB, Nuclear Factor kappa B; ILs, Interleukins; IFs, Interferons; VCAMs, Vascular cell adhesion molecules; ICAM, Intracellular adhesion molecules; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, Reactive Oxygen Species; PkC, Protein Kinase C; ERK, Extracellular-signal-Regulated Kinase; PLC, Phospholipase C; IP3- DAG, Inositol trisphosphate- Diacylglycerol; JAK-STAT, Janus kinases-Signal Transducer and Activator of Transcription proteins; NFAT, Nuclear factor of Activated T – cells; Pim, Proto-oncogene serine/threonine-protein kinase; TGF, Tissue Growth Factor; COL, collagen; ECM, Extracellular matrix; EGR, Early growth response proteins.

lysine and pentosidine [176]. TLR4 receptor signalling contributes substantially in the development and maintenance of peripheral neuropathy [108] by interacting with HMGB1 proteins to result in neuroinflammation and neuropathic pain [119].

6. RAGE signaling in cancer

A variety of tumors including brain, breast, colon, colorectal, lymphomas and melanoma have shown an increased presence of RAGE on their cell surfaces except in certain tissues such as in lung and esophageal epithelial cells, where the presence of RAGE is physiologically constitutive and a surprising reduced levels of RAGE is observed in their cancer pathologies [116,134]. The paradoxical involvement of RAGE in tumor development in specific tissues can be attributed to its inducible presence in these tissues. For example, the presence of RAGE in the alveolar epithelium is constitutive while in other tissues such as in colon epithelium the expression of RAGE increases with an increase in ligand binding through a positive loop mechanism [156]. A substantial involvement of RAGE in cancer genesis was witnessed in a study conducted by *Twak et al.* to determine the cell proliferation pattern in the presence and absence of RAGE signaling in breast cancer cells. The results not only suggested the potential role of RAGE in cell proliferation but, it was also observed that RAGE signaling contributes to angiogenesis and metastasis [95]. The induction of angiogenesis and VEGF production in cancer microenvironment occurs through mDia/RAC1/JNK/ AP1 pathway [13,214]. A key role played by RAGE signaling in cancer is the development of microenvironment suitable for cancer cell proliferation [156]. However, studies have also suggested other mechanisms involved in cancer cell proliferation. Stimulation of RAGE ligand by an appropriate ligand also activates the JAK STAT pathway that promotes mitogenesis in cell proliferation in cancer cells [65,89]. In a study that was conducted to determine the cell proliferation pathway in prostate cancer cells, it was observed that the AGE-RAGE interaction causes the phosphorylation of retinoblastoma (Rb) proteins to contribute to cell proliferation [10]. The specific involvement of AGE in cell proliferation is also disputed; as a number of other RAGE ligands are also found in increased levels in tumor cells along with AGEs [116]. Multiple changes, therefore, occur through RAGE mediation to progress cancer signaling.

7. RAGE ligands in cancer

7.1. HMGB1 protein

High mobility group box 1 (HMGB1) is a RAGE ligand that is found in elevated levels in cancer cells [22,74]. It induces the inflammatory signaling in cells resulting in overexpression of NF-κB in association with the generation of cytokines and adhesion molecules [172]. HMGB1 is found to have a poor inflammatory activity per se but its engagement with cytokines and toll like receptors (TLRs) ligands (TLR2,4 and 9) leads to exhibit the inflammatory response by NF-κB expression [166] (Fig. 2). Autophagy is another mechanism through which cancer cells survive, at least for a few days. When a tumor growth is initiated, its proliferation is prevented by the poor availability of blood supply. The cells in this metabolically stressed condition survive through autophagy. In the later phase, angiogenesis around the hypoxic and metabolically stressed cells restores the normal pathway for cell proliferation [122]. In a recent study conducted by *Liu et al.* [114], Adriamycin (ADM) resistant breast cancer cells (MCF-7/ ADM) were found to show resistance due to the overexpression of mediator complex subunit 19 (Med19). Med19 mediated resistance was found to be due to the induction of autophagy through HMGB1 signaling. Autophagic stimuli promote the translocation of HMGB1 to the cytosol to interact with the autophagic protein, beclin1. Binding of HMGB1 to

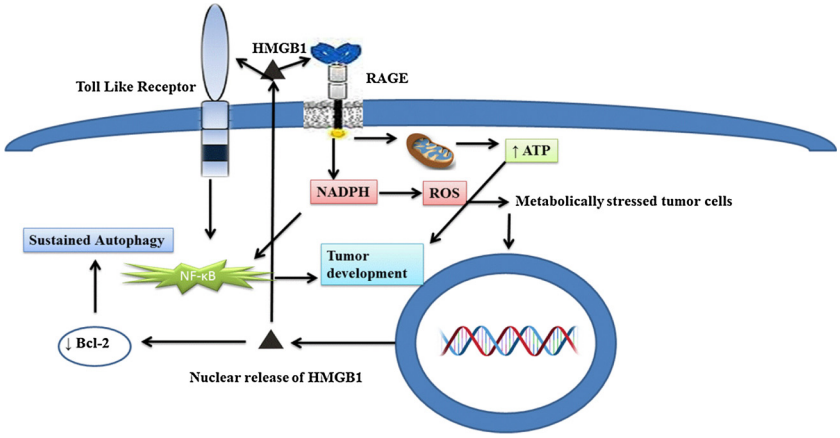

Fig. 2. Schematic representation of role of HMGB1 proteins in cancer. Metabolically stressed tumor cells leads to nuclear release of HMGB1 in the cytosol. HMGB1 displaces Bcl-2 protein in the cytosol and leads to sustained autophagy in metabolically stressed cancer cells. HMGB1 proteins are also released in the extracellular space and act on TLR and RAGE . The extracellular binding of HMGB1 on cell surfaces further stimulates the downstream signaling. HMBG1 binding with TLR signals the downstream pathways that activate the NFκB and aid in the development of tumor microenvironment. HMGB1 binding with RAGE also stimulates the downstream signaling that results in increased ATP production in mitochondria to overcome increased energy demands in cancer cells. RAGE stimulation also activates the NADPH ROS pathway that further adds to metabolic stress and sustained autophagy in cancer cells. HMGB1, High mobility group box protein-1; RAGE, Receptor of advanced glycation end products; TLR, Toll like receptor; NFκB, Nuclear factor Kappa B; ROS, Reactive Oxygen Species; ATP, Adenosine Triphosphate.

RAGE receptors intracellularly and displacing the Bcl-2 proteins is thought to be the possible mechanism behind sustained autophagy induced by HMGB1 [181,182] (Fig. 2). Treatment with endogenous peroxide (H2O2) or knockdown of superoxide dismutase by small interfering RNA caused an increased cytosolic expression of HMGB1 molecule and promoted autophagy suggesting a positive relation between ROS levels and HMGB1 expression in the cell [183]. Another study suggested that NADPH/ROS mediated pathways support cancer growth and development when RAGE receptors are stimulated [205] (Fig. 2). The nuclear release of HMGB1 during the necrosis in an apoptosis-defective cancer cell also stimulates the activation of NFκB and increases tumorigenesis [122] (Fig. 2). It is also worth mentioning that only the reduced form of HMGB1 produces the apoptosis-inhibiting effects in malignant cells, whereas the oxidized form produces the apoptosis supporting effects [150]. Molecular targets against HMGB1 results in the inhibition of cancer cell proliferation. Suppression of HMGB1 expression by recombined humanized endostatin inhibited the proliferation of A549 lung cancer cell [125]. Apart from the intracellular events mediated by HMGB1 leading to cell proliferation, extracellular release of HMGB1 from necrotic cells and its binding with RAGE receptors leads to NF-κB activation and subsequent inflammatory response [5]. Extracellular release of HMBG1 may also occur through pyroptosis, ROS generation and autophagy but not apoptosis [84,116]. HMGB1 is considered as a major damage-associated molecular pattern (DAMP) [33,35] and its Interaction with RAGE results in cell proliferation [84,184] (Fig. 2). In a recent study conducted to determine the extracellular effects of HMGB1 released from dying cells during radiotherapy or chemotherapy, binding with RAGE stimulated the downstream ERK and P38 signaling pathway that encouraged the proliferation and repopulation of surviving tumor cells [58]. Knockdown of RAGE or depletion of extracellular HMGB1 caused a significant amount of pancreatic tumor suppression with increased apoptosis and diminished autophagy [184]. Moreover, it was also observed that HMGB1- RAGE binding in the mitochondria of pancreatic tumor cells causes changes in bioenergetics by increasing the mitochondrial complex 1 activity and ATP production to promote tumor progression and migration [83] (Fig. 2). In a study that aimed to determine the consequence of HMGB1- RAGE signaling in the differentiation of Nurse-like cells (NLCs) in patients with chronic lymphocytic leukemia (CLL), increase in the concentration of NLCs was in direct proportion with passively released HMGB1 by CLL cells. Blocking the HMGB1-RAGE-TLR9 axis was also successful in preventing the differentiation of NLCs in CLL cells suggesting that HMGB1 induced signaling plays a crucial role in the maintenance of tumor microenvironment in CLL [74]. Interventions against HMGB- RAGE axis have significantly retarded the proliferation of cells in a variety of cancers including leukemia [74], breast cancer [114], pancreatic tumors [184] and certain malignant mesothelioma [82].

7.2. S100 proteins

S100s is a family of proteins consisting of 22 members that are involved in intracellular calcium signaling and a variety of extracellular responses [16]. The intracellular functions of S100 proteins promote cell cycle, cell differentiation and cell motility while their extracellular interactions with cell surface receptors including the Toll-like receptors4 (TLR4), fibroblast growth factor receptors (FGFR), interleukin-10 receptor (IL-10R) and RAGE exert a cytokine type response [16,24]. Extracellular binding of S100 proteins with RAGE triggers different cellular signaling including the MAP Kinase, NF-κB, and phosphatidylinositol 3-kinase (PI-3 K)/AKT signaling pathways to promote inflammation and cancer [24] (Fig. 3). S100 proteins are implicated in a variety of malignancies including breast, lung, bladder, kidney, thyroid, gastric, prostate and oral cancers [161]. Different members of S100 proteins tend to act through different mechanisms to encourage cell proliferation, angiogenesis and metastasis in cancer. Moreover, these proteins show tissue specificity with different members involved in tumorigenesis in different tissues [16]. Overexpression of S100A6 by plasmid transfection in panc-1 cells promoted the invasion and migration by inducing the expression of β-catenin [25] (Fig. 3). In another study, depletion of S100A from head and neck patient-derived xenografts (PDX) cells inhibited the tumor formation and invasion in animal models [136]. S100A8 and S100A9 proteins released in copious amounts from acute myeloid leukemia (AML) cells arrest the myeloid differentiation and accumulate the myeloid-derived suppressor cells (MDSCs). Blocking the two proteins with antibodies and recombinant peptides reduced the leukemic cell proliferation and prolonged the survival in animal models [180]. A recent finding revealed that S100AA along with its partner protein Annexin-2 is involved in plasma membrane repair in metastatic breast cancer cells [72]. Transfection of S100A2 in NSCLC cells induced metastasis in *in-vitro* and *in vivo* models with least alterations in cell proliferation pattern [19]. A similar migratory and invasive effect was observed in colorectal cancer cells through the induction of MAPK/ ERK and hypoxia signaling pathway by the S100A4 protein through its interaction with RAGE, while the signaling was reversed by the use of recombinant sRAGE and RAGE-specific antibodies [32].

7.3. Advanced glycation end products (AGEs)

AGEs are non-enzymatically produced glycated products of the reaction between proteins, amino acids and lipids with reducing sugars such as glucose [50]. The electrophilic carbonyl groups of reducing sugars react with free amino groups of different biomolecules in the

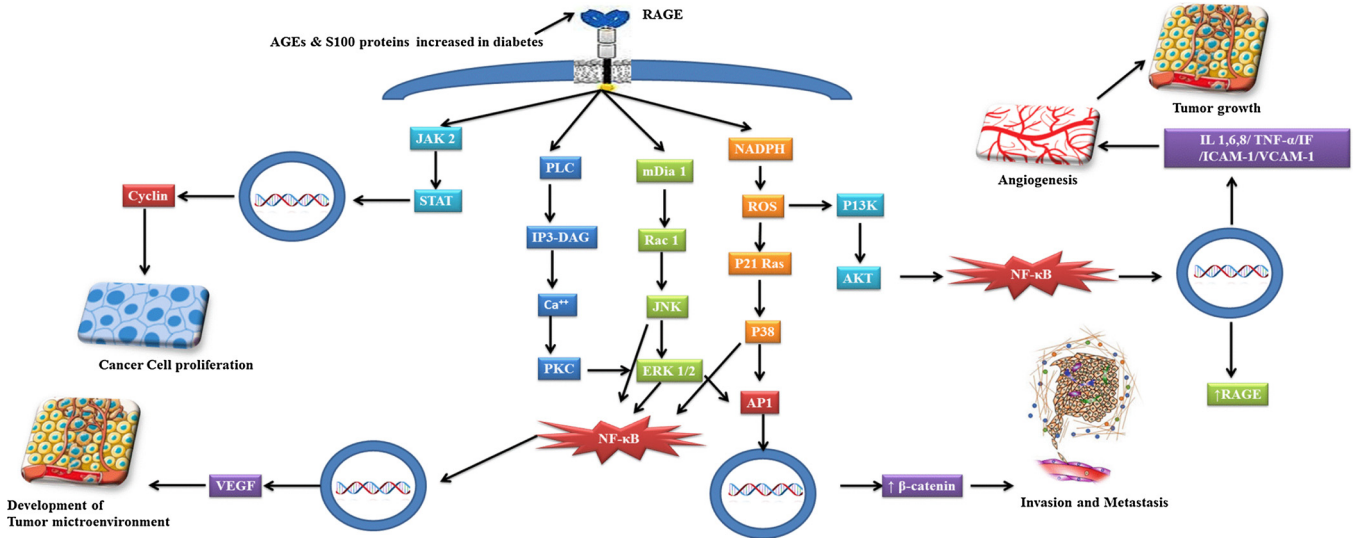

Fig. 3. Schematic representation of RAGE signaling in cancer. Binding of RAGE ligands (AGEs and S100 proteins) stimulate multiple signaling pathways. Ligand binding to RAGE stimulates the JAK/STAT pathway that increases the overexpression of cyclins. This leads to increased proliferation signals in cancer cells. Majority of downstream signaling pathways result in the activation of NF-κB that supports cancer development and proliferation. Stimulation of NADPH/ ROS pathway also activates transcription factor AP1 that increases the expression of β catenin to support tumor invasion and metastasis. Unlike other Ligand- Receptor binding, the binding of RAGE ligands further stimulates the production of RAGE ligands intracellularly.

body to form Schiff's bases which are generally unstable and undergo further rearrangement reactions to form the stable Amadori products. These products in the presence of transition metals undergo oxidation, polymerization or dehydration to form the more stable AGEs [173]. The resulting cross-linking between proteins results in tissue damage [168]. Around 20 chemically different AGEs are identified. The most important of them include the 'cross-links' pentosidine, MOLD (methylglyoxal lysine dimer), Nε-carboxyethyl-lysine (CEL) GOLD (glyoxal lysine dimer) and hydroimidazolone AGEs and non-cross linking Nε-carboxymethyl-lysine (CML) [188]. Metabolic discrepancies such as diabetes that result in chronic hyperglycemia increase the formation of AGEs [50]. Extracellular matrix (ECM) that surrounds the tumor growth gets irreversibly glycated in high amounts in hyperglycemic conditions that triggers the RAGE to exhibit its variety of mechanisms to induce cell growth. Stiffening of ECM through glycation and cross-linking promotes tumor progression and invasion through mechanotransduction mechanisms where the exogenous forces induce intracellular signaling to activate ERK, P13 K, Rac and cyclin D1 to encourage the cell cycle progression [157] (Fig. 3). A number of epidemiological studies and meta-analysis indicated a positive link between diabetic conditions and the occurrence of colorectal cancer [216]. Treatment of diabetic cancer patients with hypoglycemic agents such as metformin and thiazolidinediones successfully increased their survival rate [185]. Moreover, recent reports further suggested the association of Type-II diabetes with the occurrence of a number of solid cancers including the breast, endometrial, liver, pancreas and bladder cancer [12]. Moreover, as the tumor cells have a characteristic feature of increased glucose uptake and glycolysis capability [116], an increased generation of AGEs from glycated cellular components and their intracellular responses to promote cancer is undoubtedly conceivable. Interaction of N^{ϵ}-CML with RAGE resulted in the development and progression of pancreatic cancer in *in-vitro* and animal models [126]. A similar effect was observed on triple negative breast cancer cells where the interaction of AGE with its receptor promoted the cancer development, invasion and migration through the ERK and NF-κB signaling pathways [103] (Fig. 3). In addition, increased circulating levels of AGE in breast cancer patients contributed to tamoxifen therapy resistance [198]. Multiple mechanisms, therefore, can come into play to induce cancer cell proliferation, invasion and metastasis by AGE-RAGE signaling.

8. Single nucleotide polymorphism (SNP) and RAGE signaling

8.1. SNPs in RAGE and its association with cancer

Association of SNP in RAGE and its ligands with higher risks of cancer is evident from a number of investigations. The association of different RAGE SNPs with the higher risks of cancer is observed to be cancer type specific. Relation of four SNPs of RAGE gene namely rs1800625 (T-429C), rs1800624 (T-374A), rs2070600 (Gly82Ser) and rs184003 (G1704 T) with higher risk of cancer progression was studied through a hospital based case control study involving gastric cancer patients. The RAGE gene SNP rs1800625 (T-429C) with TT genotype and T allele was associated with reduced risk of gastric cancer. Moreover, rs1800625 (T-429C) and rs184003 (G1704 T) were linked significantly with tumor clinical stages [62]. However, in case of urothelial cell carcinoma, the rs1800625 (T-429C) polymorphism with C allele was found to be linked with higher risks of cancer development [71]. In another similar study, rs2070600 (Gly82Ser) with genotype was associated with higher risks of gastric and colorectal cancer [53,153] while the rs184003 (G1704 T) represented the reduced risk of the gastric cancer. Importantly, subjects carrying rs2070600 polymorphism with AG genotype have poor ability to produce sRAGE while those with rs184003 (G1704 T) polymorphism showed better sRAGE production [53,107]. Interestingly, in case of breast cancer, both rs184003 (G1704 T) and rs2070600 (Gly82Ser) polymorphisms were significantly associated with higher risks of cancer development and metastasis [143,153]. In addition to association of RAGE polymorphism with risks of different types of cancer, the implication of RAGE ligands polymorphism (HMGB-1) in influencing the risks of cancer development is well established. In a meta-analysis study carried out to assess the association of polymorphism in HMGB-1with higher cancer risk, out of four genotypes of HMGB-1 (rs1045411, rs2249825, rs1360485 and rs1412125), the gene rs1045411 was associated with high cancer susceptibility [93]. However, the association of rs1045411 gene in cancer development is not well clear. In other studies, the presence of rs1045411 (CT genotype) polymorphism reduced the chances of lung cancer, hepatocellular carcinoma and gastric cancer [9,63,199]. In addition, rs1412125 polymorphism was significantly associated with patients responding well to platinum based chemotherapy in lung cancer patients [202]. In another case control study, the incidence of

colorectal cancer was more in participants carrying rs2249825 SNP with G allele [200].

8.2. SNPs in RAGE and its association with diabetic complications

Multiple studies have also suggested the varying association of single nucleotide polymorphism in RAGE gene with diabetic complications. In a study conducted among Han Chinese diabetic patients to derive a relationship between 2184A/G polymorphism in RAGE gene and diabetic nephropathy, the results suggested the protective roles of AG + GG genotype of 2184A/G polymorphism in diabetic nephropathy [20]. Polymorphism in the promoter regions of RAGE gene (−374 T/A) is also observed to be an influencing factor in diabetic nephropathy, retinopathy, proteinurea and cardiovascular complications. Diabetic Patients with AA genotype of −374 T/A polymorphism had fewer incidences of proteinurea, peripheral vascular disease, acute myocardial infarction and coronary heart disease [149,191]. The −429 T/C and rs2070600 (Gly82Ser) polymorphisms were also found to be positively associated with the development of micro and macrovascular complications in diabetic patients [191]. Results from multiple studies have also suggested that the −429 T/C polymorphism located at the promoter region is associated with increased incidences of diabetic retinopathy and nephropathy in diabetic patients [70,165,191]. In a study conducted to assess the association of SNPs with diabetic nephropathy in diabetic patients, it was observed that C allele of rs1800625 and the T allele of rs184003 in RAGE gene is associated with increased risk of diabetic nephropathy [226]. In another study, diabetic patients with G/G genotype of rs2070600 (Gly82Ser) had high levels of sRAGE in their circulation in comparison to G/S genotype [73]. The A allele of rs2070600 (Gly82Ser) is also found to be associated with increased risks of diabetic retinopathy [225].

9. Body defense against RAGE signalling

Proteolytic cleavage of RAGE by metalloprotein sheddases results in the formation of soluble RAGE or sRAGE that differs from RAGE by lacking the active C terminal signaling domain in their structure. As a result, sRAGE bind to AGE ligand but fails to signal the associated pathway. A small amount of sRAGE is also produced by the splicing of RAGE. Such products are known as esRAGE [188]. Soluble receptors of RAGE (sRAGE) are the natural decoy receptors of RAGE [188]. Multiple studies suggest sRAGE to be a potential therapeutic intervention in diabetic complications and cancer. In a study that was carried out, diabetic mice when treated with soluble form of RAGE showed suppression of accelerated atherosclerosis [146]. In another short report, low levels of sRAGE in diabetic patients were associated with micro vascular complications. Diabetic patients with low levels of sRAGE developed more microvascular complications in comparison to patients with normal levels of sRAGE [52]. An inverse relationship between the levels of circulating sRAGE and the risk of cancer is evident from a number of experimental studies. Epidemiologic studies conducted among Finnish male smokers suggested an inverse relationship between the serum levels of sRAGE and occurrence of pancreatic cancer and colorectal cancer such that the higher prediagnostic levels of sRAGE were indicative of lower risk of both types of cancer [76,77]. Low levels of circulating sRAGE are also indicative of advanced stages of cancer. In another study, patients suffering from advanced stages of lung cancer had low levels of circulating sRAGE [18,79]. Meta-analysis of sRAGE gene variants indicated the association of genotype 82Ser/ 82Ser with low levels of sRAGE and high risk of cancer. Reduction in the levels of circulating sRAGE by 100, 200 and 300 pg/ml increased the risk of cancer by 1.11, 1.24 and 1.38 times respectively [66]. Pancreatic cancer patients with a stable or remissive disease after chemotherapy had low circulating sRAGE in comparison to patients with progressive disease responding poorly to chemotherapy [208]. sRAGE was also decreased in patients with locally confined breast cancer (LBC) responding well to neoadjuvant chemotherapy. In addition, a combination of sRAGE with CA 15-3 (a breast cancer biomarker) enabled better discrimination of healthy patients from LBC patients with 70% sensitivity [174].

Another defensive mechanism of the body against RAGE action is the expression of AGER receptors (AGER 1, 2, 3). These receptors, through endocytosis, cause the degradation of AGEs. AGERs also decrease the oxidative stress by inhibition of RAGE signaling [50,168]. AGE-R1 receptors are involved in the clearance of AGEs by eliciting AGE-specific ligand binding and their subsequent degradation. AGE- R3 or galectin-3 receptors are carbohydrate-binding proteins that belong to the family of lectin proteins [214]. These receptors are increased in hyperglycemic patients after their exposure to AGEs. Diminished levels of both these receptors lead to diabetic and renal complications [51].

10. RAGE ligands as biomarkers of cancer

10.1. HMGB1

Overexpressed HMGB1 is associated with poor prognosis and overall survival in patients with different types of cancer [212]. In patients receiving the oncolytic therapy, response to immunogenic transgene coding virus and T- cell activity in blood was associated with low baseline levels of HMGB1 levels [110]. High serum levels of HMGBI were also associated with poor outcomes of radioembolization therapy in liver metastases from colorectal cancer [39]. A similar relation was also observed in advanced pancreatic cancer patients taking chemotherapy; where high levels of serum HMGB1 was indicative of poor prognosis and decreased overall survival [209]. However, no such relation was observed between serum HMGB1 and transarterial chemoembolization therapy in liver cancer patients [91]. In another study, high serum HMGB1 levels were related to Asbestos related diseases (ARD) and malignant mesotheliomas (MM) [222]. Serum levels of hyper-acetylated from of HMGB1 were found to be higher in MM patients in comparison to asbestos- exposed patients, therefore representing as a differential marker of MM and ARDs. Combining the HMGB1 levels with fibulin-3 (a known biomarker of MM) increased the sensitivity and specificity of diagnosis of MM [130]. A direct correlation between serum HMGB1 levels and tumour size, invasion and progression of gastric cancer was observed [28]. When the diagnostic efficiency of HMGB1 was compared with the carcinoembryogenic antigen (CEA) in the detection of colon cancer, the accuracy was almost similar. In addition, HMGB1 was found to be more efficient in the detection of stage 1 colon cancer. Combining the two markers (HMGB1 and CEA) showed more accurate overall diagnostic sensitivity when compared to the CEA alone [102]. Expression of high levels of RAGE and HMGB1 (78.8% and 68.2% respectively) in patients with advanced prostate cancer was found to be independent of gender. Moreover, coexpression of both the proteins in prostate cancer was associated with progression and poor prognosis of disease [228]. In a study conducted on patients with colorectal cancer, a direct relation between HMGB1 expression and metastasis was observed [178]. In another case study comprising of 119 non- diabetic patients with colorectal cancer, 55% of patients were having a high expression of RAGE along with Amphoterin. The overexpression of RAGE was evident in all advanced stages of colorectal cancer (Dukes B, C and D) [94]. Although, the coexpression of RAGE with amphoterin showed poor prognosis in Dukes' B and C patients [94,163]. Albeit, no relation between the protein expression and age, gender and tumour invasion depth was evident from the study; suggesting that high serum levels of HMGB1 are associated with migration and progression of colorectal cancer [178]. Circulating levels of HMGB1 can, therefore, be indicative of advanced stages of cancer [28], metastasis [178,228], success rates of anticancer therapy [39,110] and improved diagnostic procedures for cancer detection [102,130].

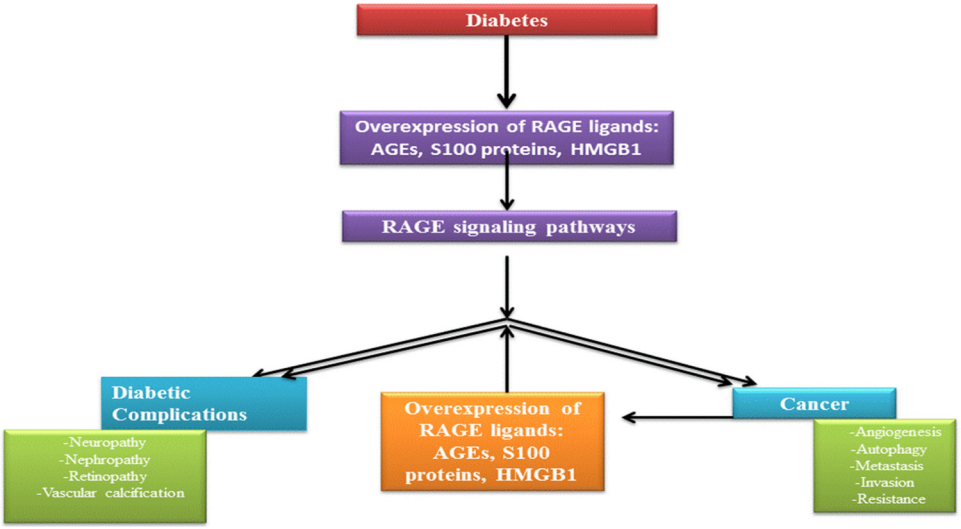

Fig. 4. Involvement of RAGE signaling in diabetic complications and cancer: Overexpressed RAGE ligands during the diabetic condition induce diabetic complications and cancer in diabetic patients through RAGE signaling. RAGE ligands released from the cancer cells further worsen the diabetic complications and cancer in diabetic cancer patients. RAGE, Receptors of Advanced glycation end products; AGEs, Advanced glycation end products; HMGB1, High mobility group box protein 1.

10.2. S100 proteins

Increased expression of intracellular calcium-binding S100 proteins is observed in different cancers [57]. In a serial analysis of gene expression, calcium-binding proteins (S100A7, S100A8, S100A9, and S100A10) were among the most up-regulated genes in gastric cancer [129]. Immunohistochemistry of tissue specimens of patients with prostate cancer of different grades revealed a high expression of S100A8 and S100A9 in intraepithelial neoplasia and high-grade adenocarcinomas while their expression in benign tissue was poor. Increased expressions of the two proteins were observed more towards the invaded stroma [59]. Similar results were also observed in another study where the two- dimensional gel electrophoresis of colorectal malignant tissues of 23 patients revealed a high expression of S100A8 and S100A9 in 16 tissue specimens [175]. Microarray analysis of breast cancer tissue indicated a high expression of S100A6, S100A8 and S100A9 (32%, 12% and 28%) [31]. S100A4 is a RAGE ligand released extracellularly from colorectal cancer cells (CRC) that acts on over-expressed RAGE receptors in the surrounding region. The specific association of S100A4 with CRC cells represents a potential biomarker for colorectal cancer prognosis [32]. S100A2 is a tumour suppressor protein. Low levels of S100A2 were observed in immortal human bronchial epithelial cells (HBE) in comparison to normal human bronchial epithelial cells (NHCE). Moreover, the protein was undetectable in tumorigenic HBE cells ($< 10\%$); suggesting that S100A2 can be a potential biomarker of early changes in lung cancer [42]. Calgranulins are intracellular calcium-binding S100 proteins that are expressed in multiple cell types [29,101]. Two-dimensional electrophoresis of cystic fluids collected from the malignant and benign ovarian tumours showed the additional expression of calgranulin A and B in malignant tissues. The similar additional presence of the two proteins was also seen in the serum of patients with malignant ovarian cancer [142]. S10A11 is another intracellular calcium-binding protein that remains confined in nuclear boundaries of normal cells. Cytosolic translocation of S100A11 was observed in almost all common cancer [31].

10.3. Advanced glycation end products (AGEs)

Carboxymethylysine (CML) is an advanced glycation end product that interacts with RAGE to promote cancer development and progression. High plasma levels of CML are seen in patients with pancreatic cancer [126]. In a prospective case-control study carried out among 48 men (24 prostate cancer cases and 24 control), plasma levels of CML were significantly higher (182 vs. 152 μg/mL) in prostate cancer patients. Increase in CML was also indicative of increased prostate cancer risks (relative risk: 1.79) among patients with the history of benign prostate hyperplasia, hypertension and smoking [220].

11. RAGE signaling causes cancer in diabetic patients

A number of epidemiological studies have suggested that diabetic patients live at higher risks of developing several types of malignancies including the liver, pancreatic and breast cancers being the most common [46,81]. Hyperinsulinemia, hyperglycemia and inflammation are considered as the major contributors to cancer risks among diabetic patients [44,46,49,158]. Insulin resistance in type-II diabetes results in hyperinsulinemia [81]. Multiple studies provide a link between hyperinsulinemia and cancer [148,192]. Insulin supports tumour growth by interacting either with its own receptor or with Insulin like growth factor-1 (IGF-1) proteins expressed on cancer cells [81]. Hyperglycemia provides a favorable environment to cancer cells by overcoming the ever-increasing demands of cancer cells for nutrients to run its cellular machinery in increased metabolic conditions [37,158]. Importantly, hyperglycemia also accelerates the formation of advanced glycation end products (AGEs) that play a crucial role in the development of a variety of cancers [103,126,157,216]. The supportive roles of inflammation in the genesis of cancer are well-established. Inflammation contributes to tumorigenesis through various mechanisms including the maintenance of tumor microenvironment and angiogenesis [24,122,166,172] via the activation of NF-κB along with the production of cytokines and adhesion molecules [81,172]. Moreover, RAGE ligands including the S100 and HMGB1 proteins that are released in enormous amounts during diabetic conditions [105,203] have shown to contribute significantly in the development of inflammatory responses in both diabetic complications and cancer in various studies conducted [24,133,172,218,219] (Fig. 4). In that view, RAGE signaling is an important pathway that contributes to cancer in diabetic patients.

12. Cancer aggravates diabetic complications through RAGE signaling

Patients having both diabetes and cancer lead to worse outcomes [195]. In a study conducted among diabetic and non-diabetic patients with colorectal cancer, neuropathic symptoms were more in patients having both the disorders [194]. Similar results were obtained in diabetic patients with prostate cancer where the urinary function was lowered in diabetic cancer patients [100]. The involvement of cancer in the exacerbation of diabetic complications was evident from a recent study conducted among 817,060 diabetic cancer patients where the rates of diabetic complications were much higher in diabetic cancer

Table 1
Table representing molecular targets of Curcumin, Quercetin and Withaferin A in cancer, inflammation and diabetic complications. Majority of targets that are involved in the RAGE signaling are inhibited by these molecules.

Molecules		Targets	Pathology Targeted
1	Curcumin	2 PKc/NADPH oxidase/ decrease ROS [40,67]	Atheroscelrosis, lung cancer
		3 Increase ROS to induce cell death [99]	cancer
		4 Inhibits ERK-1/2 [215]	Nasopharyngeal carcinoma
		5 TLR-4 inhibition leading to NFkB inhibition [118]	Colitis
		6 TNF inhibition [169]	Tumor cells
		7 Suppression of RAGE expression by elevation of PPAR gamma activity [111]	Hepatic stellate cells proliferation (Hepatitis)
		8 Inhibition of TGB1 and SMAD 2/3 [33,64,90,186]	HK2 cells, profibrotic action, Benign Prostatic Hyperplasia, lung cancer cells, cervical cancer cells
		9 Inhibits expression of VEGF [90]	Benign Prostatic Hyperplasia
		10 TNF, IL-6 and other cytokines [2,47]	Inflammation
2	Quercetin	1 Inhibits HMGB1 and promotes apoptosis [35]. Induces phosphorylation of kinases and subsequent cytokines (TNF and IL) expression. Inhibits degradation of IKB and nuclear translocation of NFKB [87,201]	Inflammation, Breast cancer
		2 Inhibits NADPH oxidase to decrease ROS generation [78]	Vascular smooth muscle cells
		3 Increases ROS to induce cell death [48]	Cancer cells
		4 Decrease NADPH oxidase and RAGE expression to inhibit cell death in nephropathy [224]	Diabetic Nephropathy
		5 Inhibition of P21Ras [154] to decrease cell survival and proliferationand provide chemoprevention [152]	Cancer
		6 Inhibits the expression of cytokines (IL1, 6 &8, TNF-alpha) by downregulating P38 MAPK and NFKB [127,201]	Inflammation
		7 Downregulates the activity of AP1 and AP1 induced VEGF expression to inhibit	Temoxifen resistant breast cancer cells and angiogenesis [138]
		8 Reduces inflammation induced expression of adhesion molecules (ICAM and VCAM) [190]	Endothelial cells
		9 Decreases miR21 expression [144,151]	Chromium induced carcinogenesis, MCF cells
		10 Inhibition of TGB1 and SMAD2/3 to decrease cell proliferation [21]	Epithelial mesenchymal transition in retinal cells
2	Withaferin A	1 Inhibits Nuclear translocation of NF-kB and inflammasome complex [38,170]	Inflammation
		2 Inhibition of Angiogenesis by inhibiting VEGF [159]	Cancer
		3 Inhibition of TGF-β1 induced Smad2/3 activation and TNFα-induced translocation of NFkB into the nucleus by inhibition of phosphorylation of Smad2/3 and NFkB [7,23,96]	Cancer, Inhibition of endothelial to mesenchymal transition in NSCLCs, Angiogenesis, Fibrosis, inflammation
		4 Dual inhibition of NF-kappaB and AP-1 Fra-1 transcription factors and silencing of IL-6 promoter chromatin accessibility [131]	Angiogenesis in breast Cancer
		5 Decrease ROS and inflammation [11]	Endothelial dysfunction
		6 Decrease TNF-α and IL-6 production in endothelial cells by suppressing IKKβ/NF-κβ phosphorylation [11]	Insulin resistance and endothelial dysfunction
		7 Elevates ROS generation to induce apoptosis and activates P38 MAPK. Inhibits Akt activation [145]	Head and neck cancer
		8 Apoptosis involving ROS production and activation of Bax/Bak. [56]	Breast cancer
		9 Inhibition of STAT3 [221]	Neuroblastoma and multiple myeloma
		10 Inhibits the efficiency of NF-κB nuclear translocation in large B cell lymphomas [123]	B cell lymphoma
		11 Inhibitor of STAT3 for the treatment of HCT116 [27]	Colon cancer
		12 Inhibits P38 MAPK [121]	Activated leukemic cells of lymphoid and myeloid
		13 Inhibits constitutive and IL-6-induced phosphorylation of STAT3 (on Tyr705), but not IFN-γ-induced STAT1 phosphorylation. Withaferin- A induced down-regulation of STAT3 activation is associated with a reduction in Janus-activated kinase 2 (JAK2) activity. [193]	Renal cancer
		14 Inactivation of Akt and NF-κB in human pulmonary epithelial cells (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in human lung epithelial A549 cells stimulated with tumor necrosis factor α(TNF-α), resulting in the suppression of leukocyte adhesion to lung epithelial A549 cells. Also inhibited phosphorylation of Akt and extracellular signal-regulated kinase (ERK) [137]	Lung cancer
		15 Inhibition of nuclear translocation of NFkB and its DNA binding activity to downregulate VEGF expression [187]	Angiogenesis
		16 Downregulation of PKC, VEGF, TNF and IL [3]	Diabetic nephropathy

patients in comparison to normal diabetic patients [210]. A possible mechanism behind the aggravation of these complications in diabetic cancer patients can be attributed to the mutual presence of RAGE and its ligands in both the diseases. RAGE and its ligands mediate the development of diabetic complications [133,218,219]. In addition RAGE ligands are released in diabetic conditions [105,203] as well as in cancer [22,57,74]. The manifold increase in RAGE ligands in the presence of both the contributing diseases is quite possible; making the diabetic cancer patients much prone to the development of these complications (Fig. 4). Inhibition of RAGE signaling in diabetic cancer patients is a potential approach to manage the diabetic complications in these patients.

13. Phytoconstituents as multi targeting interventions

Since the time immemorial, medicinal plants and herbs are utilized as a major source of medications for the treatment of diverse disorders. Progress in the understanding of molecular targets of phytoconstituents has led to the advent of multi- targeted approach. An interesting characteristic of a number of plant derived phytoconstituents is their ability to target multiple pathways simultaneously. The implication of RAGE signaling in diabetes leading to cancer and diabetic complications is mediated by a diverse set of molecular pathways. Thus, targeting a single pathway would not necessarily halt the RAGE signaling and its associated effects. From our recent search through different databases, it has been observed that Curcumin, Quercetin and Withaferin A inhibit maximum number of molecular pathways that are involved in RAGE signaling. A brief outline of molecular targets of these molecules is given in the Table 1:

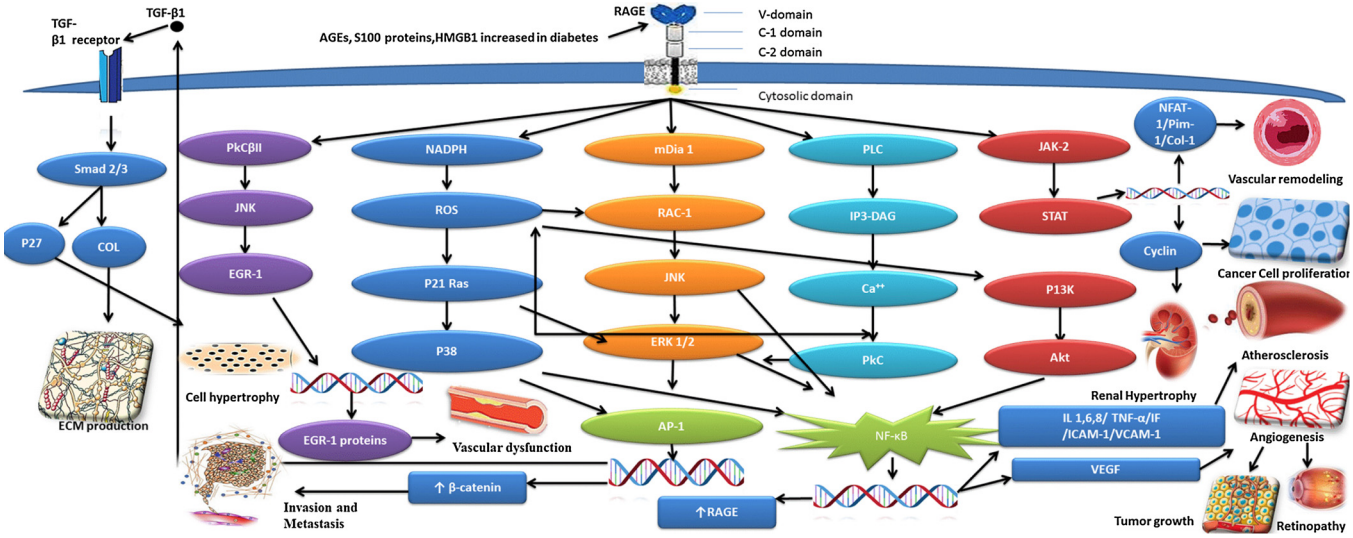

Fig. 5. Possible roles of RAGE signaling in diabetic complications and cancer in diabetic conditions. Release of RAGE ligands increases during hyperglycemia or diabetes. Multiple signaling pathways induced by RAGE ligands result in the activation of NFkB, its subsequent translocation into the nucleus and expression of inflammatory genes including ILs/TNF-α/IF/ICAM-1/VCAM-1 causing inflammation and atherosclerosis to support the cancer cell proliferation and diabetic complications respectively. NFkB activation also results in the expression of VEGF leading to angiogenesis around the cancer cells. AP-1 is the other transcription factor protein that is activated by RAGE signaling pathways leading to production of TGF-beta 1 proteins that are released in extracellular space to interact with TGF-beta 1 receptor. TGF-beta 1 binding activates intracellular smad2/3 proteins that result in downstream signaling causing cell hypertrophy and production of extracellular matrix. Increased expression of β catenin leads to invasion and metastasis of cancer cells. Activation of JAK-STAT signaling results in cell proliferation as well as vascular remodeling. RAGE signaling induced production of EGR proteins also results in compromised vascular function in diabetic condition. RAGE, Receptor of Advanced Glycation End products; NFkB, Nuclear Factor kappa B; ILs, Interleukins; IFs, Interferons; VCAMs, Vascular cell adhesion molecules; ICAM, Intracellular adhesion molecules; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, Reactive Oxygen Species; PkC, Protein Kinase C; ERK, Extracellular-signal-Regulated Kinase; PLC, Phospholipase C; IP3- DAG, Inositol trisphosphate- Diacylglycerol; JAK-STAT, Janus kinases-Signal Transducer and Activator of Transcription proteins; NFAT, Nuclear factor of Activated T – cells; Pim, Proto-oncogene serine/threonine-protein kinase; TGF, Tissue Growth Factor; COL, collagen; ECM, Extracellular matrix; EGR, Early growth response proteins.

14. Discussion and conclusion

Inflammation is the central pathway that leads to a number of complications in the living body. The process is mediated by a number of receptor and through diverse mechanisms. The roles of inflammation in the development of diabetic complications and cancer are well established [30,75,119,223]. Targeting an inflammatory pathway involved in these pathologies can provide significant results in their prevention and management. The Receptor for advanced glycation end products (RAGE) is one such receptor that exerts its inflammatory actions by interacting with multiple ligands.

Multiple studies including several epidemiological surveys have shown that diabetic patients live at a much higher risk of developing cancer in the later stages of their lives [8,46,81]. As already discussed, the abnormal conditions of hyperinsulinemia, hyperglycemia and inflammation in diabetes are highly supportive to tumor growth and development. Of particular interest is the observation that the production and release of advanced glycation end products (AGEs) [157,216] and other RAGE ligands (S100 and HMGB1 proteins) is accelerated under hyperglycemic conditions [105,203]. RAGE ligands have shown to induce inflammatory responses and cancer genesis by interacting with RAGE [24,172] (Fig. 1). Therefore, the release of RAGE ligands and the upregulation of RAGE expression in diabetes and cancer can be conceived as a possible link between diabetes and cancer.

On the other hand, diabetic complications including the vascular calcification, retinopathy, neuropathy and nephropathy are all mediated directly or indirectly by RAGE and its ligands that are released in diabetes [133,218,219] (Fig. 5). Targeting the RAGE ligands in diabetic patients can therefore reduce the risk of diabetic complications and cancer. Moreover, a high release of RAGE ligands is also observed in cancer patients [22,57,74]. An increased incidence of diabetic complications in diabetic cancer patients in comparison to normal diabetic patients is easily conceivable and is also evident from multiple studies [100,194,195,210] and is attributable to manifold increase in RAGE and its ligands in the presence of both the diseases in these patients. Inhibition of RAGE in cancer can not only reduce the cancer progression but can also reduce the susceptibility of diabetic cancer patients to develop complications during the vulnerable period.

Phytoconstituents from plant sources have proved to be beneficial in the treatment of various disorders. A major advantage of these phytoconstituents is their ability to target multiple pathways that are associated with a particular disorder. In our present discussion, we have discussed three phytomolecules namely curcumin, quercetin and withaferin A. As evident form multiple studies conducted on these molecules, multiple molecular pathways are blocked by them. The implications of multiple pathways in RAGE signaling that are mutually involved in the genesis of cancer and diabetic complications in diabetic conditions suggest that a multi-targeted therapeutic approach is needed imperatively to control these consequences. As discussed already, multiple nodes in different molecular pathways are blocked by curcumin, quercetin and withaferin A. The combined effect of these molecules is the complete blockade of RAGE signaling pathways. Thus, interventions including these molecules may prove beneficial in controlling these complications and may prove to be helpful in controlling cancer growth and proliferation as well as diabetic complications in diabetes.

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