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Hypoxia Driven Glycation: Mechanisms and Therapeutic Opportunities

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Abstract

Tumor masses are deprived of oxygen and characterized by enhanced glucose uptake followed by glycolysis. Elevated glucose levels induce non-enzymatic glycosylation or glycation of proteins which leads to accumulation of advanced glycation end products (AGE). These AGE molecules bind to their respective receptors called the receptor for advanced glycation end products (RAGE) and initiate several aberrant signaling pathways leading to onset of diseases such as diabetes, Alzheimer's, atherosclerosis, heart failure and cancer. The role of AGE in cancer progression is being extensively studied in recent years. As cancer cells are hypoxic in nature and adapted to glycolysis, which induces glycation, its effects need to be understood in greater detail. Since AGE-RAGE signaling is involved in cancer progression, inhibition of AGE-RAGE interaction could be a potential therapeutic target. The purpose of this review is to highlight the role of AGE-RAGE interaction in hypoxic cancer cells.

Keywords

Glycation; Advanced Glycation End Products; RAGE; Cancer; Hypoxia; Hif1α

1. Introduction

Cancer is rated as one of the most prevalent diseases around the globe and several factors are responsible for its progression. Over the past few decades, glycation has emerged as one of the important factors whose role has been discussed extensively in cancer progression [1]. Glycation is the non-enzymatic reaction between the reducing sugars and amino groups of proteins, lipids and nucleic acids [2]. This reaction is known as Maillard reaction [3, 4] and is distinct from glycosylation which is an enzymatic process. The final products generated during glycation are known as Advanced Glycation End Products (AGE) which are mainly derived from arginine and lysine groups of proteins after reaction with the carbonyl group of the sugar moiety [5]. Detailed mechanism of Maillard reaction is schematically presented in

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figure 1. Involvement of AGE in cancer progression is yet to be fully understood, however, a few reports explain AGE-mediated cancer progression in different types of cancer. One recent finding showed involvement of AGE in enhancing proliferation, migration and invasion during breast cancer progression [6] while another report explained its crucial role in prostate cancer progression through inducing invasiveness [7]. Jiao et al. [8] observed that dietary consumption of AGE was associated with a modest increased risk of pancreatic cancer in men. Apart from cancer, accumulation of AGE has been linked to multiple diseases including diabetes, cardiovascular disease, renal failure, arthritis and neurodegenerative disorders [9].

The inner mass of solid tumors is hypoxic in nature and this creates a pre-metastatic niche which further enhances the aggressiveness of cancer cells [10]. AGE accumulation mediates various disorders. Diabetes, inflammation and acute ischemia/perfusion (I/R) in heart are previously reported but hypoxia-driven AGE accumulation in cancer cells is not yet fully discussed [11]. Here, we review the extensive role of AGE and the Receptor for Advanced Glycation End Products (RAGE) in cancer progression.

2. AGE and RAGE: Brief overview

AGE are generated through non-enzymatic glycation and oxidation of proteins that play a significant role in the pathogenic progression of several metabolic disorders. These compounds are also known as glycotoxins [4, 12, 13]. Formation of Schiff base and Amadori products are considered as the first step in glycation where aldoses are coupled with free amino groups of proteins, lipids, nucleic acids. These intermediate forms are the dicarbonyls such as glyoxal (GO), methylglyoxal (MG), or 3-deoxyglucosone (3-DG) which is highly reactive [14, 15]. Finally, Amadori products react non-enzymatically with lysine or arginine residues to produce AGE. These dicarbonyls are also derived from lipid peroxidation, glycolysis as well as protein degradation [16]. AGE are either extracellular, derived from food items or intracellular that are derived from sugars [17]. AGE are broadly categorized into three types summarized in table 1. Apart from protein glycation, DNA glycation also produces AGE, which act as potential carcinogens [18]. The glycated DNA accumulates several structural changes including depurination, strand breaks, and mutations such as insertions, deletions, and transpositions [19]. RAGE is expressed on the cell surface and when bound to AGE initiates further signaling events. RAGE is a 35 kDa pattern recognition receptor and transmembrane protein belonging to the immunoglobulin (Ig) superfamily [20]. RAGE is also a receptor for **Damage**-Associated Molecular Pattern (DAMP) molecule that originates from damaged cells and alerts the immune system to tissue trauma. RAGE acts as a receptor for high mobility group box 1 (HMGB1), the prototypical DAMP, and S100 proteins along with AGE [21]. The detailed structure of RAGE is illustrated in figure 2. RAGE is composed of one extracellular domain, one transmembrane domain, and one cytoplasmic tail. The extracellular domain of RAGE consists of three immunoglobulin-like regions: one “V”-type followed by two “C”-type regions [22]. The transmembrane-spanning domain connects the intracellular region with the 43-amino acid cytosolic tail. The V-domain is critical for ligand-binding, whereas the cytosolic tail is essential for RAGE-mediated intracellular signaling. The V-domain of RAGE facilitates AGE binding which further activates an array of signaling pathways [23,

24] involved in tumorigenesis. The ligand and receptor bond in between RAGE-AGE is mediated by charge-charge interaction [25]. Binding of AGE to RAGE initiates several downstream events that lead to cell proliferation, autophagy, and carcinogenesis [26–28].

3. Role of AGE-RAGE complex in cancer progression

AGE-RAGE axis plays a critical role in tumor growth and metastasis when RAGE is activated upon binding with AGE [29]. There is a growing body of evidence that supports a correlation between AGE-RAGE expression and cancer malignancy. Few of them are melanoma [30], oral cancer [31], breast cancer [32, 33], gastric cancer [34], colorectal cancer [35, 36], pancreatic cancer [8, 37, 38], intestinal cancer [39], prostate cancer [40, 41], renal cancer [42] and leukaemia [43]. One contradictory finding [44] that needs to be studied in detail proposes tumor suppressive function of RAGE in lung cancer.

AGE-RAGE axis plays a pivotal role in cancer cell proliferation. One recent report explains AGE-RAGE-mediated cell proliferation in rat vascular smooth muscle cells [45]. Another study on breast cancer cell lines revealed RAGE-mediated cell proliferation and cancer progression [46]. RAGE also plays a key role in various metabolic activities of the cells. The proliferation of myeloid cells is regulated by AGE-RAGE interaction followed by MAPK, PI3K, JAK/STAT-mediated pathways [43]. Mammalian target of rapamycin (mTOR) which is a serine/threonine protein kinase is a potential RAGE target and regulates transcription, cell growth, cell proliferation, cell motility, cell survival and protein synthesis [47]. AGE-RAGE interaction also induces cancer promoting vascular endothelial growth factors (VEGF) in breast cancer cells [33]. Another study suggests that RAGE activation by AGE induces VEGF production and inflammatory response in human synoviocytes by modulating RAGE-NF-κB pathway [48]. Autophagy is the programmed cell survival process by which organelles and proteins are degraded after being engulfed by the autophagic vesicles followed by fusion with lysosomes [49]. This is recognized as a mechanism for tumor cell survival, which provides resistance to apoptosis [50]. AGE-RAGE-mediated autophagy induction is also reported in the literature. AGE-RAGE-mediated autophagy induction is associated with tumor cell survival. This pathway is operated through reactive oxygen species (ROS) generation. RAGE is considered as a positive regulator of autophagy and negative regulator of apoptosis during oxidative stress conditions. ROS generation is enhanced during AGE-RAGE interaction and hence induces the autophagy process [51]. The same paper also reported apoptosis-mediated enhanced cell death and diminished cell survival by autophagy during the H2O2 induced oxidative injury by suppressing RAGE expression. Studies have also established the fact that RAGE is a positive feedback regulator for NF-κB. This is so because knockdown of RAGE decreases H2O2-induced activity of NF-κB. Collectively, these findings suggest that RAGE is an important regulator of oxidative injury. These findings also provide the mechanistic insight of apoptosis-autophagy crosstalk mediated via ROS signaling during a process involving RAGE [52].

Apart from autophagy cellular senescence which limits the cell proliferation process can also play a significant role during cancer progression [53]. Stress induced premature cellular senescence is a biological process which is different from replicative senescence and induced during oxidative stress conditions [54–58]. It is believed that senescent cells show

bimodal mode of action during cancer progression which includes suppressed tumour growth at early stage [54, 59–62] and tumor promoting effect during later stage [53]. These cells enhance the proliferative property of cells by secreting metalloproteases, growth factors and cytokines which are known as Senescence-Associated Secretory Phenotype (SASP) or Senescence Messaging Secretome (SMS) [54–56, 58, 63]. Involvement of senescence-mediated disease progression is also observed in other conditions such as diabetes [64], cardiovascular disease [65, 66], renal failure [67], arthritis [68] and neurodegenerative disorders [69]. Cancer cells acquire senescence bypass mechanism which overrides the replicative senescence process and escape from senescence mechanism [70, 71]. Recently RAGE-mediated premature senescence activation [72] has explained in the literature. Liu et al. [72] describe RAGE-mediated ER stress which further activates premature senescence via p21 signaling in diabetic nephropathy. However, detailed role of bimodal action of RAGE-mediated cancer progression as well as suppression needs to be studied under senescence activated conditions. Cancer cells possessing invasive property are metastatic in nature. Metastatic property of cancer cells is also influenced by AGE-RAGE interaction. Growth and invasion of melanoma cells was enhanced after AGE-RAGE interaction [73]. Kang et al. [74] provided evidence for upregulation of RAGE in cells forming a primary melanoma tumor that could contribute to the metastatic switch. The experimental analysis also suggested that the metastatic human melanoma cells, G361 exhibit higher levels of cellular proliferation and migration in the presence of RAGE activating AGE ligands. AGE-RAGE interaction also induces migratory potential of oral cancer cells by up-regulating MMP2 and 9 in an ERK-mediated manner [31]. Angiogenesis is the hallmark of cancer metastasis. The role of AGE-RAGE complex in angiogenesis is well documented in the literature [75, 76]. A very recent finding explains AGE-mediated angiogenesis process by moesin phosphorylation which is a ezrin-radixin-moesin (ERM) protein family protein through a RhoA/ROCK pathway in human umbilical vein endothelial cells [77]. Similarly, AGE-RAGE interaction enhances angiogenic potential in hepatocellular carcinoma cells by upregulating VEGF expression [78]. In addition, RAGE activation also increases endothelial permeability to macromolecules which is very common condition in tumor microvasculature. In a study by Tsuji et al. [79] promotion of angiogenesis in lymph node metastasis by latent membrane protein 1 is associated with an increased expression of RAGE. Autocrine VEGF is found to be a major mediator of AGEs driven angiogenesis. AGE–RAGE interaction reduces the pericyte number which in turn relieves the restriction on endothelial cell replication and facilitates angiogenesis [80].

RAGE plays diverse roles in the proliferation of cancer. For example in osteosarcoma cells, RAGE is over expressed and it further induces cell migration by ROS mediated mechanism [81]. AGE bind to and activate RAGE, which is a predominant modulator of inflammation-associated cancer and induces ROS that are an important regulator of cancer [16]. The mechanism of AGE-RAGE complex mediated cancer progression is different in different cancers and summarized in table 2.

4. Hypoxia: an inducer for AGE-RAGE mediated cancer progression

Hypoxia is a physiological condition which arises inside a solid tumor mass due to insufficient oxygen supply and links to multiple oncogenic pathways [82]. Hypoxia

contributes to chemoresistance, radioresistance, angiogenesis, vasculogenesis, invasiveness and metastasis in solid tumors [83, 84]. Metabolic parameters like low glucose concentration, low oxygen concentration as well as low pH lead to the development of hypoxic regions within the tumor mass [85, 86]. These hypoxic cells also induce angiogenesis and evade the apoptotic mechanism of the cell [87].

Hypoxia-driven AGE accumulation and RAGE activation is well documented [88]. Gopal et al. [88] observed hypoxia-induced accumulation of fluorescence AGE such as LW-1 and s-RAGE. Hypoxic tumor cells shows metabolic shift from mitochondrial aerobic respiration to anaerobic glycolysis process [89]. These hypoxic cells induce accumulation of di-carbonyls which act as a precursor for AGE synthesis [16]. MG which is a major intermediate compound formed from glycolysis can also act as a precursor molecule for AGE [90]. MG readily reacts with proteins, lipids and nucleic acids to form AGE. Shinohara et al. [91] observed significant accumulation of MG at high glucose concentrations. Chang et al. [92] reported rapid generation of AGE after hypoxia exposure in endothelial cells which further activated RAGE-mediated signaling. These oxygen deficient cells actively participate in tumor growth and metastasis through activating several signaling events [93]. Another report demonstrated hypoxia-induced AGE formation and RAGE activation in macrophages [94]. RAGE-AGE interaction also mediates myocardial injury after ischemia attack [95]. Previously, hyperglycemia induced AGE activation followed by retinal neovascularization was studied by Shin et al. [96].

Cancer cells are hyperglycemic in nature and the enhanced glucose uptake induces aerobic glycolysis or Warburg’s effect [97]. Hyperglycemic condition is also linked with cancer migration, invasion as well as proliferation [98] and induces AGE accumulation. Detailed understanding of the AGE mediated cancer onset could open avenues in cancer therapeutics. The relation between hyperglycemia and epigenetic modification of oncogenic pathways has been recently studied. A finding by Dong et al. [99] demonstrated epigenetic silencing of fructose-1, 6-biphosphatase which is one of the critical gluconeogenic enzymes, increases glycolysis and NADPH production via the pentose phosphate pathway and a reduction in oxidative phosphorylation. This pathway is regulated by the transcription factor snail which also plays a major role in EMT progression. These metabolic alterations induce survival pathways that lead to cancer stem cell phenotype through lowering ROS generation and inducing β-catenin/TCF4 activation [99].

Further, AGE-RAGE interaction activates several signaling pathways that are involved in cancer progression during oxygen deficient condition. For example, AGE-RAGE interaction activates JNK as well as stat1 signaling during insufficient blood supply [100]. Hypoxia-induced RAGE upregulation was discussed in some recent findings, which further explain the role of AGE-RAGE interaction in hypoxic cancer cells. A recent report described hypoxia-induced RAGE expression in oxygen deficient hepatocellular carcinoma (HCC) [101]. This study showed that RAGE positive cell lines are more resistant to hypoxia as compared to RAGE negative cell lines in HCC. Suppression of RAGE expression by siRNA enhanced susceptibility towards hypoxia. This finding clarifies the significance of RAGE in adapting to the hypoxic resistant phenotype which is very critical for the survival of hypoxic cancer cells. Another study explained that hypoxia-mediated RAGE induces

phosphorylation of Erk1/2, Akt and nuclear translocation of NF-κB. Once in the nucleus, NF-κB would contribute to cell survival and invasion under hypoxia, by maintaining RAGE and P2X7R expression levels and matrix metalloproteinases 2 and 9 synthesis [102]. Hypoxia induced AGE-RAGE mediated activation and their downstream signaling pathways are illusttrated in figure 3. These observations highlight the significance of hypoxia in AGE-RAGE signaling and cancer progression. Treatment of hypoxic cancer cells by targeting AGE-RAGE interaction will gain more attention in near future. One recent addition to the hypoxia-mediated AGE-RAGE activation is involvement of senescence-mediated malignancy in hypoxic cells. Several pro-senescent pathways are regulated in hypoxic cells [103]. Senescent cells showed SASP which induces secretion of immunomodulatory cytokines as well as several cell survival factors. Reports are there that explain role of hypoxic senescent fibroblasts in cancer progression [104]. Work done by Taddei et al. [104] showed correlation between hypoxia-induced senescent stroma and malignant property of prostate cancer cells. Their work further showed that hypoxia-induced miR-210 mediates tumor vessel formation as well as enhances aggressiveness of cancer [104].

Hypoxia leads to development of aggressive phenotype and various hypoxia-driven factors actively participate in tumor cell survival and hamper clinical response to therapy [87]. Hypoxia inducible factor 1 (Hif1) is one of the major transcription factors upregulated in hypoxic microenvironment and it induces several downstream genes involved in cancer progression and metastasis [105]. The Hif1 expression is also regulated by AGE-RAGE mediated signaling which is explained in subsequent sections.

5. Hif1: a key player in AGE-RAGE complex mediated carcinogenesis

Hif1 is one of the major factors induced during hypoxia exposure and maintains oxygen homeostasis in the body. It helps to adapt in the oxygen deprived condition by regulating glucose uptake and anaerobic respiration of cells. Erythropoiesis, angiogenesis, cell survival, growth, metabolic adaption are influenced by Hif1-mediated pathways [106, 107]. Hif1 is a heterodimeric transcription factor composed of oxygen dependent alpha (α) subunit and constitutively expressed beta (β) subunit. The α subunit is stabilized in hypoxic condition and translocated to the nucleus where it interacts with the β subunit to form the complex which further activates transcription of various proteins involved in survival of cancer cells [108]. So the alpha subunit plays a critical role in the regulation of cell survival machinery in hypoxic cells. Both α and β subunits have similar structure [109] and the whole gene is subdivided into several domains. The amino-terminal domain consists of basic helix-loop-helix (bHLH) and PAS (Per-ARNT-Sim homology) domain. The carboxy-terminal domain (CTD) has two transactivation domains separated by one inhibitory domain (ID) [109, 110]. Hif1α has one oxygen-dependent degradation domain (ODD) towards its CTD which senses oxygen concentration inside the cells. As both Hif1α as well as AGE are upregulated in hypoxic cells, correlation between these two might have immense importance in cancer therapeutics.

Recently RAGE-mediated Hif1α activation was extensively studied. Kang et al. [111] showed that the interaction between RAGE and oncogenic KRAS induces Hif1α activation in pancreatic cancer cells. They found a novel mechanism of Hif1α activation involving NF-

κB-RAGE-KRAS-Hif1α–mediated pathway in hypoxic pancreatic cancer cells. Inhibition of RAGE expression downregulates KRAS activation followed by Hif1α expression. Hence, RAGE-mediated signaling is necessary for downstream Hif1α activation. This upregulated Hif1α further induces aggressiveness of the pancreatic cancer mass. Further, knock down of RAGE as well as Hif1α decreased cell viability and induced apoptosis. These results suggest a role of RAGE in maintaining the viability of cancer cells [111]. It was further demonstrated that both mRNA and protein level of RAGE were increased in a hypoxic rich environment. This study further showed upregulation of RAGE expression in primary neurons subjected to hypoxia or oxygen-glucose deprivation, an in vitro model of ischemia [112]. AGE-mediated regulation of Hif1α transcriptional activity has also been reported [113]. The relation between RAGE-Hif1α was explained in another study that demonstrated RAGE mediated-Hif1α activation by suppressing p53 protein expression [114]. Correlation between AGE induced oxidative stress and Hif1α stabilization in Leidig's cells was recently studied [115]. Bala et al. [116] demonstrated AGE-RAGE expression mediated Hif1α expression in HUVEC cells. In this study HUVEC cells were exposed to glycation modified human serum albumin (AGE-HSA) and expression of RAGE was measured. This study revealed upregulation of RAGE in HUVEC cells which is further accompanied by induced Hif1α expression. Knockdown of RAGE by using siRNA downregulated Hif1α expression. Furthermore, Hif1α targeted VEGF expression was significantly induced upon AGE-HSA treatment. These findings support the role of hypoxia in AGE-mediated angiogenesis and cancer progression. Another study also investigated AGE mediated VEGF accumulation [117] in hypoxic cells. Hif1a also plays a major role in bypassing oncogene induced senescence and induces premalignant property of the cells [118]. However, direct link between RAGE activation, hypoxia and Hif1α-mediated cancer progression by senescence bypassing is not yet established. Hence, further research in this field will open a new arena for cancer therapeutics. Further studies are needed to find out the detailed mechanism of AGE-mediated and Hif1α induced carcinogenesis in hypoxic cells.

6. Therapeutic strategies to target AGE-RAGE complex in cancer

Targeting AGE-RAGE interaction to control AGE mediated disorders has been extensively studied. Several therapeutic approaches have been adapted that include inhibition of AGE formation, accumulation, blocking of AGE-RAGE interaction and their signaling mediated pathways, use of RAGE blockers and anti-RAGE antibodies. Enzymatic degradation of AGE precursor like α-oxalaldehyde is another potential alternative method to inhibit AGE accumulation [119]. Targeting AGE mediated pathways in diabetes treatment has been elucidated in many reports. One such report demonstrated that inhibition of AGE-RAGE interaction protects against hyperglycemia induced fibrosis of peritoneal membrane [120]. It is interesting to note that benfotiamine-mediated AGE inhibition acts as a potential therapeutic approach to control type 2 diabetes [121]. Clinical trials of several anti-AGE molecules are reported and among them TM2002 showed better AGE inhibitory effect. TM2002 protects against AGEs mediated renal injury and cardiovascular disorders [122]. Aminoguanidine and Alagebrium are two chemicals that are widely used to inhibit AGE accumulation in diabetic kidney [123]. Another compound is pigment epithelium-derived factor that partly suppresses AGE-RAGE axis and helps to cure vascular complications of

diabetic patients [124]. A pioneer work by Maeda et al. [124] showed the significant role played by aptamers to regulate AGE function. These are short single standard DNA or RNA molecules. This work demonstrated that binding of these aptamers to AGE further inhibits their binding to RAGE and reduces RAGE-mediated oxidative stress in diabetic nephropathy. These findings suggest that regulation of AGEs-RAGE axis plays a major role in the therapeutic aspects of glycation derived diabetes. In spite of significant advancement in the AGE-RAGE mediated carcinogenesis, only few therapeutic approaches are reported till date. Mizumoto et al. showed that inhibition of RAGE by using anti-RAGE antibody protects against pulmonary metastasis [125]. In another study, apoptosis induction in prostate cancer cell lines was achieved by targeted blocking of AGE receptors [126]. Food-mediated AGE accumulations are also reduced by lowering intake of food cooked at higher temperature [127]. Detection of AGE-RAGE complex has tremendous importance for the above mentioned therapeutic approaches. Different methods are used to quantify AGE accumulation, few of which are diode array detector (DAD), fluorescence detector, tandem mass spectrometer (MS/MS), gas chromatography coupled with MS and enzyme-linked immunosorbent assay (ELISA) [128]. Detection of AGE-RAGE complex is also performed by immunohistochemistry [129]. Autoantibodies are generated against glycated protein and DNA which detects AGE-RAGE complex [17, 130]. As RAGE-mediated senescence plays a pivotal role in cancer progression, detection of these senescencent cells might help to link with AGE-RAGE-mediated cancer. A pioneer work by Evangelou et al 2017 [131] identified a novel method which detects senescent cells in biological materials by using lipophilic, biotin-linked Sudan Black B (SBB) analogue. This method for detection of RAGE-mediated senescent cells could be further extended to detect AGE-RAGE-mediated complex. However, considering the significant increment in the incidence of AGE-RAGE mediated cancer, further therapeutic interventions studies are needed.

7. Conclusions and emerging questions

In this review, we summarized recent findings and advancements in AGE-RAGE mediated carcinogenesis. Hypoxia-induced regulation of AGE-RAGE-mediated carcinogenic pathway is gaining importance these days. The detailed mechanism of these signaling pathways are not yet fully explored, which will be very helpful to decipher new methods to cure cancer. There are so many open questions that remain unexplored. The most unanswered question is whether there is any direct modification in hypoxia-induced Hif1α molecule due to glycation or accumulation of AGE. As Hif1α is a major molecule involved in several carcinogenic pathways, this type of finding will create a new insight into AGE-mediated carcinogenesis. As most of the findings discussed here are based on in vitro studies, there is a need to conduct some relevant in vivo studies for accurate interpretation. It is interesting to note that diabetic patients are more prone to cancer [132]; hence correlation between these two diseases is needed to be studied in detail. As AGE are involved in both diabetes as well as cancer, another important question is whether existing therapies for AGE-mediated diabetes will be helpful for controlling AGEs-mediated cancer. Designing of selective inhibitors for AGE-RAGE mediated Hif1a signaling pathway will also prove to be an advanced strategy for cancer treatment.

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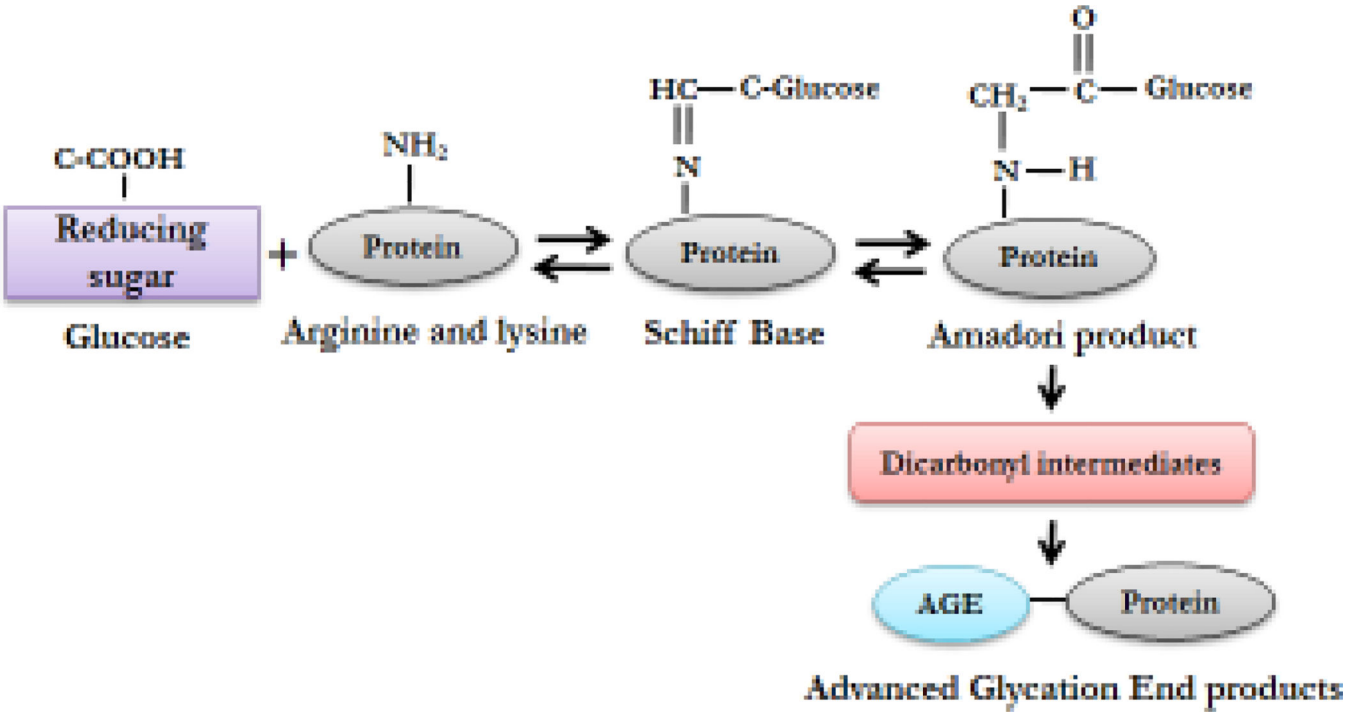

Figure 1. Schematic presentation of the Maillard reaction

Amino group of protein (arginine and lysine derivatives) react with carbonyl moiety of reducing sugars to form reversible Schiff base which further rearranges to form Amadori products. These products finally form Advanced Glycation End Products (AGE) through dicarbonyl intermediates.

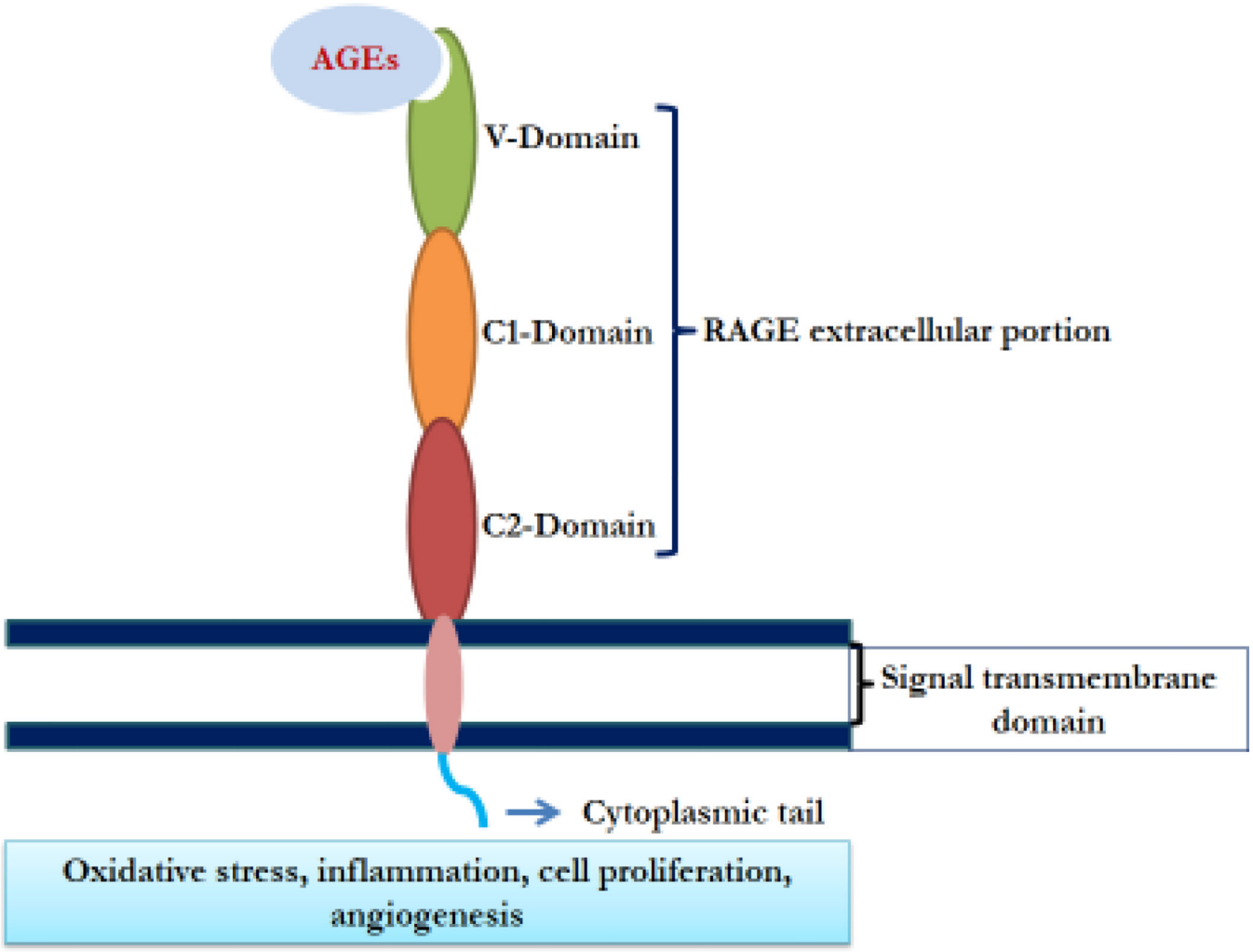

Figure 2. Structure of receptor for advanced glycation end product (RAGE)

The RAGE is composed of three extracellular immunoglobulin (Ig)-like domains, a single transmembrane helix (light pink) and a short cytoplasmic (dark sky blue) domain. The Ig domains are V (shown in dark green), C1 (orange) and C2 domain (dark brown). The V-domain is responsible for binding to the AGE (faint blue) and cytoplasmic tail responses to the signaling pathways.

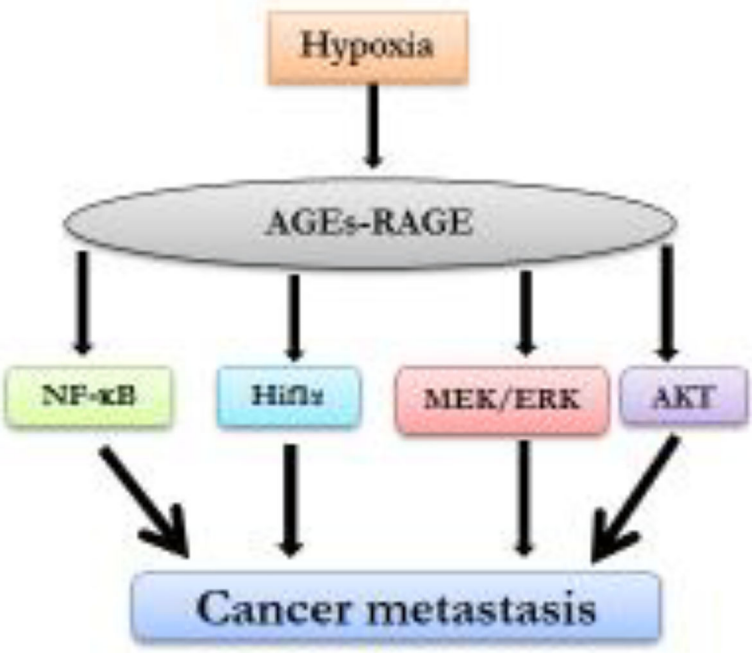

Figure 3. Hypoxia-induced AGE-RAGE-mediated signaling pathways

Hypoxia induces AGE accumulation which further formed complex with RAGE and activates several downstream pathways including NF-Kb, Hif1α, ERK and AKT signaling. These pathways further contribute to cancer metastasis progression.

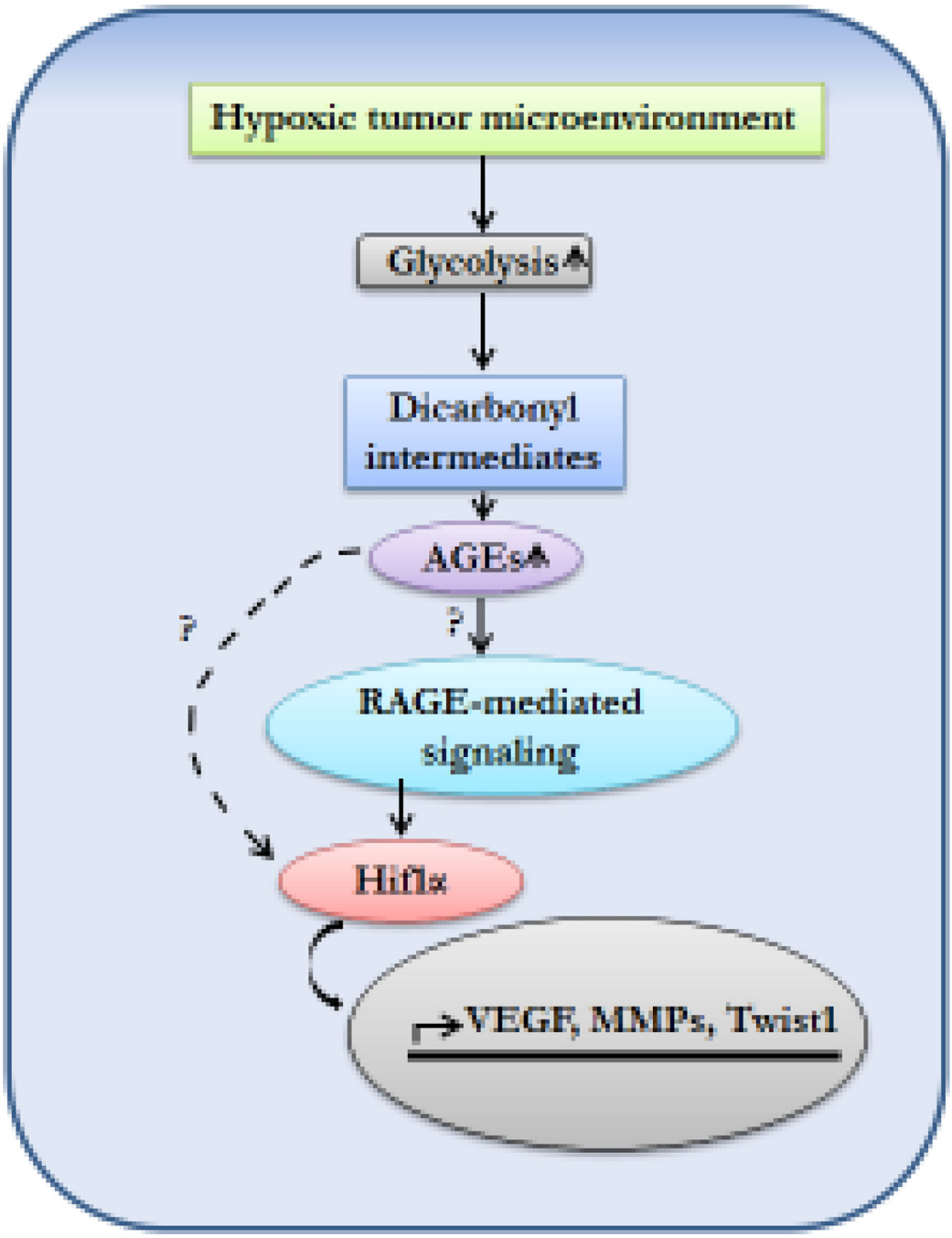

Figure 4. Hypoxia-driven AGE-RAGE-mediated carcinogenesis is induced by Hif1α

Hypoxic microenvironment induces glycolysis and dicarbonyls accumulation. These dicarbonyls further trigger AGE generation. Once AGE interact with their receptors, RAGE, they activate Hif1α signaling pathways which further act as a transcription factor for synthesis of cell survival and metastasis related genes.

Table 1

Types of advanced glycation end products (AGE)

Type of AGE	Examples
Fluorescent cross-linking	Pentosidine and Crossline
Non-fluorescent cross-linking	Imadazolium dilysine cross-links, Alkyl formyl glycosyl pyrroles and Arginine–lysine imidazole crosslinks
Non-cross-linking	Pyrraline and *N* carboxymethyllysine

Table 2

Summary of the role of AGE-RAGE complex in different cancers

Types of Cancer	Role of AGE-RAGE complex	References
Osteosarcoma	Promotes proliferation	(81)
Breast cancer	Induces proliferation, migration and invasion	(6, 32, 33, 44, 46)
Colorectal cancer	Biomarkers	(26)
Colorectal cancer	Induces tumorigenesis, cell proliferation	(35, 36)
Pancreatic cancer	Promotes tumorigenesis	(38, 74, 111)
Hepatocellular carcinoma	Enhances angiogenic potential Promotes proliferation	(27, 78)
Prostate cancer	Cancer cell proliferation	(41, 104, 126)
Oral cancer	Cancer migration	(31)
Gastric cancer	Cancer invasion	(34)