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Advanced Glycation End Products (AGEs) and RAGE in Breast Cancer: Mechanisms, Progression, and Potential Interventions

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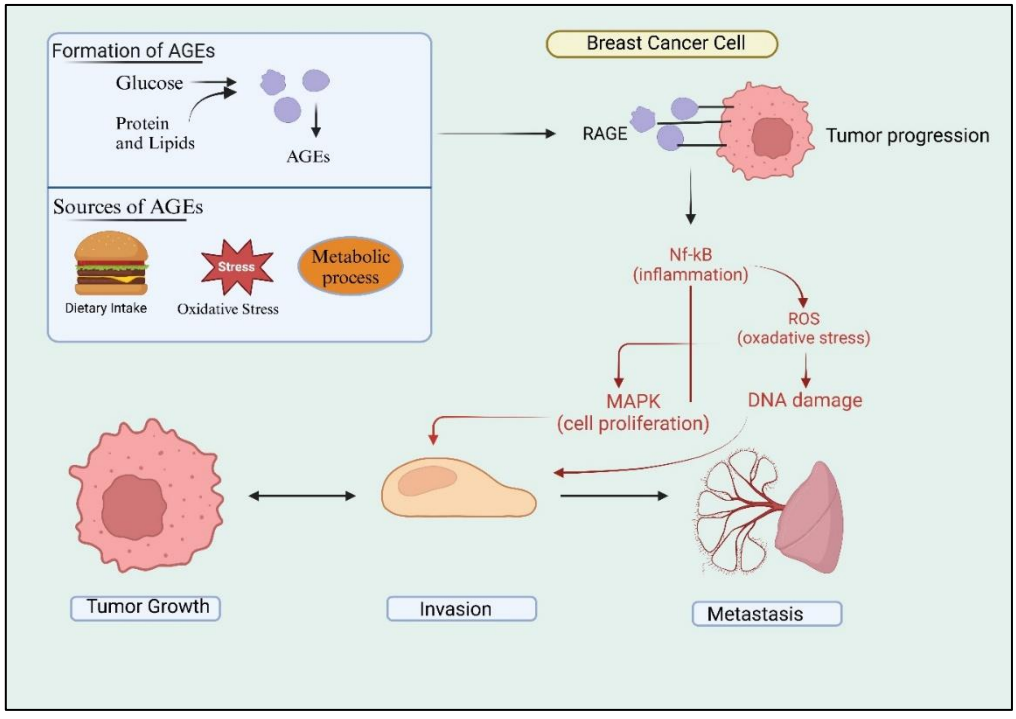
ABSTRACT

Breast cancer is still the most common cause of cancer-related death for women globally, necessitating the identification of novel molecular targets for improved diagnosis and treatment. The Advanced Glycation End Products (AGEs) and their receptor (RAGE) play a crucial role in chronic inflammation, oxidative stress, and tumor progression. The progression of breast cancer has been linked to the AGE–RAGE axis, which promotes angiogenesis, cellular proliferation, the epithelial-mesenchymal transition (EMT), and metastasis. Elevated levels of AGEs, commonly associated with diabetes, obesity, and aging, contribute to tumor microenvironment remodeling, thereby fostering an aggressive cancer phenotype. The molecular mechanisms underlying AGE–RAGE interactions in breast cancer highlight their role in activating key oncogenic pathways, including NF-κB, MAPK, PI3K/AKT, and JAK/STAT signaling cascades. The crosstalk between AGE–RAGE and other pro-inflammatory mediators, such as cytokines and reactive oxygen species (ROS), further amplifies tumor progression and resistance to chemotherapy. Given the growing evidence linking AGE–RAGE signaling to breast cancer pathogenesis, understanding its regulatory mechanisms offers a new avenue for the development of targeted therapies. This review provides a comprehensive analysis of AGE–AGE-RAGE-mediated breast cancer progression and explores its potential as a prognostic marker and therapeutic target, paving the way for future translational research and clinical applications.

Keywords – Breast cancer, Diabetes, Advance Glycation End Products (AGEs), RAGE, MAPK, S100 Protein, PI3K/AKT, JAK/STAT, NF-kB, HMGB1.



Graphical Abstract

INTRODUCTION

Cancer and diabetes are the most common diseases, globally raising concern related to significant health issues. Greater glycolytic rates associated with cancer frequently result in a higher metabolism, which in turn promotes the synthesis of advanced glycation end products (AGEs)[1]. A significant public health issue, diabetes mellitus is the seventh greatest cause of mortality in the regions of the United States, Europe, and other industrialized nations. Its incidence and prevalence are increasing[2,3, 4]. Hyperglycemia, primarily caused by untreated insulin resistance, is a symptom of type 2 diabetes, the most prevalent kind of long-term chronic metabolic disease5.The glycation triggered by hyperglycemia is a comprehensive process, and it has major structural and functional ramifications [6,7,8]. As AGEs can accelerate the advancement and spread of breast cancer, research has recently revealed the straight effects of diabetes-related hyperglycemia and hyperinsulinemia[9,9,10]. Globally, breast cancer is most rising concern of mortality for women and the second most prevalent cause. Numerous morphological, molecular, and biochemical characteristics that affect the course of the illness, prognosis, and responsiveness to treatment define this heterogeneous malignancy[11]. Breast cancer and their types are categorized according to their hormone dependence; for example, they are called ER-positive or ER-negative. Particularly, ERα-positive breast cancer accounts for over 70% of situations[12]. Based on their immunohistochemistry (IHC) features (hormone status), breast cancer can be divided clinically into three primary kinds. These are triple negative, HER2 positive (HER2+), and hormone receptor positive. Hormone receptor-positive breast cancers are those that exhibit either progesterone receptor-positive (PR+) or estrogen receptor-positive (ER+) characteristics. Approximately 85% of all instances of breast cancer are hormone receptor-positive. The hormone drugs used in the therapy include tamoxifen and the aromatase inhibitors anastrozole (Arimidex), letrozole (Femara), or exemestane (Aromasin). There are two types of hormone receptor-positive breast cancer: Luminal A and Luminal B. Luminal A cancers are often HER2-negative (HER2-) and ER+ or PR+. Luminal B cancers are often HER2+ (or HER2- with elevated Ki67) and ER+ and/or PR+[13]. In the case of Diabetes, chronic hyperglycemia is the indicator of unhealthy glycemic management. The brain and other glucose-dependent tissues require a constant, uninterrupted supply of glucose, which is maintained by the pancreas's actions in preventing both postprandial and interprandial hypoglycemia. Increased glycemic variability around healthy mean glucose levels or even brief bouts of hyperglycemia or hypoglycemia can have a substantial influence on the development and spread of diabetes sequelae, including cardiovascular disease, renal disease, retinopathy, and neuropathy [14].

Differences in the types and duration of diabetes therapies may also affect a woman's risk of getting or dying from breast cancer. There is promising proof that the most popular treatment for people with type 2 diabetes, metformin, an insulin sensitizer, may lower breast cancer risks by lowering the level of glucose produced by the liver [15]. Few studies have examined how diabetes medication affects the risk of breast cancer, and none that we are aware of have examined how diabetes therapy affects survival [16,17]. Understanding the effects of diabetes and diabetes therapies on the probability of getting breast cancer and survival following diagnosis of breast cancer becomes essential since diabetes is becoming a global health issue that places more and more women at risk [17]. Type 2 diabetes predominantly raises the breast cancer risk incidence; recent studies have found that the risk for both case-control and cohort studies increased by around 20%. However, this potentially significant route has not been well documented in studies based on survival population following a diagnosis of breast cancer, and even fewer have documented mortality specific to breast cancer. Given that several aspects of diabetes, such as obesity, resistance to insulin, and elevated plasma glucose during fasting, have been connected to the incidence and predicting of breast cancer, there is a considerable biologic plausibility of a connection with mortality [18–21]. The immunoglobulin class comprises the multiligand receptor RAGE. When a variety of ligands attach to RAGE, the renin-angiotensin-aldosterone system is activated, and pathological inflammation results [22]. RAGE affects several renal conditions, including obesity-related nephropathy, diabetic kidney injury, and hypertensive kidney damage. The concept of diabetic kidney disease (DKD) has received international attention as a result of recent developments in the management of diabetes and hypertension, which have changed the usual clinical course of kidney damage in diabetic patients. Since DKD can be brought on by a variety of intricate factors, such as diabetes, hypertension, obesity, and hyperlipidemia, RAGE is a perfect target for preventing DKD and its effects. Various factors imply that increased RAGE expression seems to be a characteristic shared by various illnesses [23].

1. RAGE: Structure, Expression, Function

For human RAGE, over 20 different alternative variants have been identified. In contrast to lung and aortic smooth muscle cells, endothelial cells are more likely to produce esRAGE mRNA, which express fl-RAGE mRNA. This shows that RAGE splicing in humans is very tissue-dependent. The nonsense-mediated decay (NMD) mechanism may target a significant amount of splice sequences, it is anticipated that they will be degraded before proteins are produced. Some others do not have the signal sequence on exon1, which might lead to early degradation of the produced protein. Only three human variations—fl-RAGE, sRAGE, and esRAGE—have been identified at the protein level in vivo [24,25]. High concentrations of the S100A6 protein are present in the brain, kidney, spleen, lungs, and muscles [26]. RAGE's unique connection to disease etiology has led to an increasing interest in it as a therapeutic target. One of the initial steps in verifying RAGE as a target was the usage of the extracellular ligand-binding region of RAGE (sRAGE), which effectively competes with the receptor for ligands. In reality, RAGE ligands belong to many families.

These comprise matrix proteins including Collagen I and IV, Aβ peptide, members of the S100/calgranulin protein family, the prototypic HMGB1/amphoterin, and certain advanced glycation end products such carboxymethyllysine [27–29]. A single of the most basic, nuclear, non-histone chromosomal HMG (High Mobility Group) proteins—HMGB1—has been demonstrated to turn on RAGE. The unrelated mevalonate pathway chemicals "HMG-CoA" (3-hydroxy-3-methylglutaryl coenzyme A) and "HMG-CoA reductase inhibitors" (statins) should not be mistaken with the HMG proteins [30]. Containing 215 amino acids, HMGB1 is a highly conserved protein. It is found in almost every mammalian cell. HMGB1, HMGB2, and HMGB3 in humans are 80% identical [31]. The full-length human RAGE is made up of the hydrophobic transmembrane (residues 343–363), cytoplasmic domains (residues 364–404), and extracellular (amino acid residues 23–342) components. Three immunoglobulin-like domains comprise the extracellular structure of RAGE: two constant C1 (residues 124–221) and C2 (residues 227–317) domains, as well as a variable (V) domain (residues 23–116) [30].

2. RAGE LIGANDS

RAGE includes ligands such as HMGB1, phosphatidylserine, S100 proteins, Lysophosphatidic Acid, advanced glycation end products (AGEs), and complement protein [33].

2.1. AGEs

Designated for its unique ability to function as an AGE receptor, RAGE was found by isolation from bovine lung in 1992. AGEs, a family of irreversible chemicals, are created by the Maillard reaction, which is the process that involves nonenzymatic glycolation and oxidation of protein besides sugar [31]. Two sources of AGEs exist: the body's synthesis of extra sugar and protein and external intake, primarily from food. Cigarette smoke has also been discovered to contain AGEs [32]. Methylglyoxal (MGO), the primary precursor of AGEs, is a highly reactive dicarbonyl molecule primarily created as a consequence of glycolysis. The glyoxalase system's detoxification of MGO to D-lactate under physiological conditions depends on the enzyme glyoxalase 1 [33].

2.2. HMGB1

HMGB1 was the first to be demonstrated as a non-AGE ligand to bind to RAGE [34]. HMGB1 consists of three functional regions: an acidic C-terminal structural domain, two N-terminal DNA-binding structural domains (A-box and B-box), and the HMGB1 B-box, which is associated with the release of cytokines and an inflammatory response-triggering functional structural domain [35].

The role of HMGB1 as a binding enhancer between RAGE and other ligands may mediate some of its functions [36]. Like S100B, it is probable that HMGB1 will form a helix-loop-helix structure and use its acidity to ligate RAGE through the C-terminal [37].

2.3. S100 Protein

A wide range of useful proteins that bind Ca2+ and are involved in apoptosis, cell division, proliferation, and the immunoinflammatory response make up the S100/calgranulin family. They initiate diverse cellular signaling processes and have varying affinities for certain RAGE domains [38]. The S100 proteins have been shown to interact with and regulate a wide range of proteins involved in cellular functions, such as calcium homeostasis, cytoskeleton dynamics, energy metabolism, and cell growth and differentiation [39–41] Increases in intracellular calcium concentration cause calcium to bind to the EF-hand, which alters the structure of the S100 protein and permits interaction with target proteins and activity regulation [42].

In an experiment, inhibiting the S100–RAGE interaction with soluble RAGE, mice's reaction to methylation BSA during the challenge phase of delayed-type hypersensitivity (DTH) was inhibited. In a model of experimental autoimmune encephalomyelitis, animals deficient in IL-10 showed reduced colonic inflammation, prevented arthritis development, and suppressed spinal cord injury and inflammatory cell infiltration [46,47]. Through an entropically mediated mechanism involving a Ca2+-dependent hydrophobic contact with the RAGE extracellular V and C1 domains, Park and colleagues showed that RAGE recognizes S100B [43].

3. Signaling Pathway Activated by RAGE

Many intracellular signaling pathways regulate different biological functions, including migration and cytoskeleton organization, are activated when the ligands interact with RAGE. Furthermore, transcriptional patterns such as adhesion-related, profibrotic, and pro-inflammatory cytokine genes are significantly impacted by RAGE activation. Following its interaction with ligands, the cytoplasmic domain of RAGE interacts with Dia-1's formin homology (FH1) domain. This connection activates the Rho GTPases Rac-1 and Cdc [42], which are crucial for regulating gene transcription and transducing signals that connect plasma membrane receptors to the cytoskeleton's structure [44].

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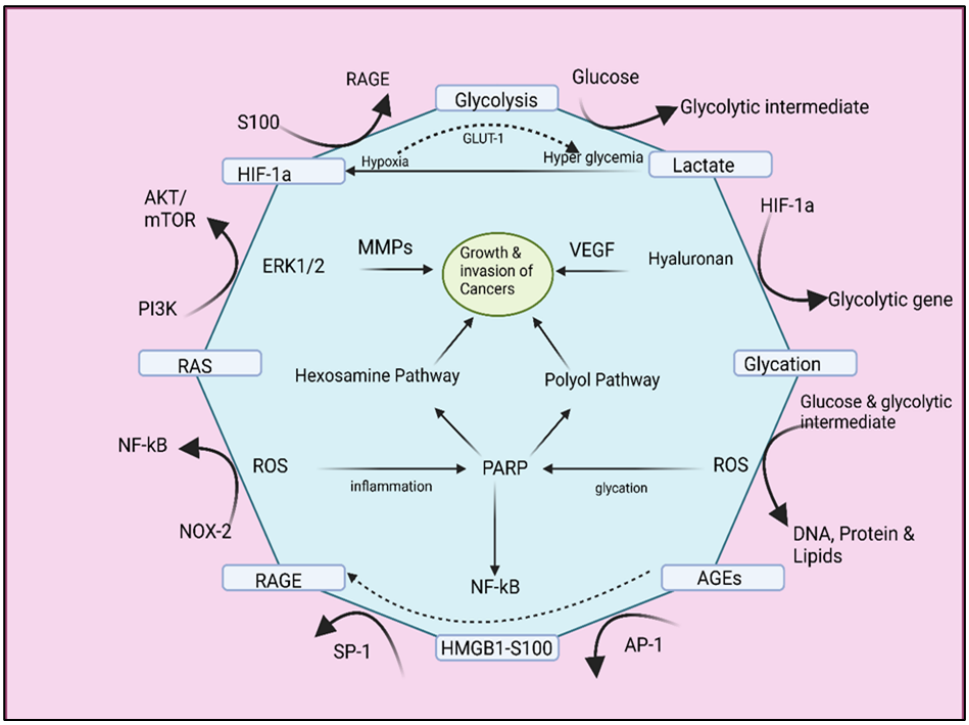

Fig. 1. Represent Various intracellular signaling pathways that control a variety of cellular processes, including migration and cytoskeleton organization, are activated when the ligands interact with RAGE.

Rac-1 or Cdc [42] activates JNK and p38 mitogen-induced protein kinase [45]. In numerous ways, RAGE affects alterations to gene expression that are ultimately caused by signal transduction pathways triggered when ligands bind to RAGE in the extracellular space. RAGE is expressed by a variety of cell types, and when it binds to a ligand, it triggers signaling cascades that include mitogen-triggered protein kinases, phosphatidylinositol 3-kinase, the Rho GTPases Rac-1 and Cdc42, and Jak/STAT (indicate transducers and stimulants of transcription) [46–48].

To find possible interaction partners in a lung library, a yeast two-hybrid test was used, using the human RAGE cytoplasmic region as bait. The lung was chosen because RAGE was initially identified in bovine lung extract to pinpoint the exact mechanisms by which RAGE signals through the cytoplasmic domain [49].

4. RAGE IN DIABETES

As hyper-glycemia in diabetes raises the formation of AGEs, the kidney and other kidney cells- such as the glomerular basement membrane, mesangial cells, podocytes, tubular cells, and vascular endothelial cells- are overloaded with AGEs, which promotes cellular damage. A guanidine derivative called aminoguanidine inhibits the production of AGE by trapping reactive dicarbonyl. Giving streptozotocin (STZ)-induced diabetic mice aminoguanidine improved diabetic glomerulosclerosis and reduced the excretion of urine albumin [50]. The connection between extracellular matrix with AGEs, including collagens, can be broken by a different family of substances called crosslink breakers, which are directed at the AGE–RAGE axis. Crosslink breakers include compounds of pyridinium bromide, N-phenacyl thiazolium, and alagebrium (ALT-711). Interestingly, alagebrium does not affect the intramolecular crosslink, peptide bonds, or conversion of natural carbohydrates to proteins that preserve the collagen chain's regular integrity. As a result, aberrant crosslink is decreased, but normal structure and function are maintained. In vitro experiments showed that AGE-regulated interconnect was significantly increased by the combination with ALT-711, reducing the amount of pepsin-mediated digestion of the diabetic rats' tail [51]. In a research, mice with RAGE null vs RAGE-expressing OVE26 simultaneously demonstrated improved renal function as shown by inulin clearance. This study showed that the diabetic RAGE null OVE26 kidneys had much lower MG levels than the RAGE-expressing control diabetic kidneys, even when hyperglycemia levels were the same. Our results showed, for the first time, that RAGE activity reduces kidney glyoxalase 1 levels, hence diminishing the anti-AGE benefits of the enzymeA RAGE-dependent pathway for the amplification of glycation and oxidative stress in the diabetic kidney may be provided by the RAGE-dependent regulation of glyoxalase 1, a crucial enzyme that detoxifies the primary AGE precursor MG, at least in this organ [52,58]. A different study on mice revealed that proinflammatory cytokines, including MIP-2 (macrophage-inflammatory protein 2), IL-1α, and TNF-α, were significantly decreased in TPA-induced cutaneous psoriasis lesions if RAGE was absent. However, because RAGE null mice had higher levels of IL-1Ra (interleukin 1 receptor antagonist), they showed an anti-

inflammatory effect, albeit only in vitro [53]. One of RAGE's ligands, EN-RAGE, is connected to the inflammatory cascade that contributes to leprosy development. Both RAGE and EN-RAGE levels indicate a marked rise in the multibacillary type of leprosy, particularly in the granuloma development and inflammatory process [54]. The highly conserved protein DJ-1/PARK7 is widely expressed, involved in many biological processes, and appears to be crucial in controlling how cells react to oxidative stress. According to several studies, cells that overexpressed DJ-1 showed greater resistance to oxidative insults, whereas cells that lacked DJ-1 were more vulnerable to cell death brought on by oxidative stress [55].

Approximately 70% of human diabetic individuals die from macrovascular disease, making it by far the most prevalent consequence. Using streptozotocin-induced diabetic apoE null mice, sRAGE therapy inhibited the development of accelerated aortic lesions in a way that was independent of both glucose and lipids. Following therapy, further evaluation of ligand levels showed that AGE and S100 levels were reduced in the tissue and plasma. To confirm these results, apoE null mice were given sRAGE or a placebo from 14 to 20 weeks after being rendered diabetic at 6 weeks. When compared to animals given a placebo, the mean lesion size and complexity were considerably lower after receiving sRAGE therapy. At the cellular level, the administration of sRAGE prevented smooth muscle cells (SMC) and mononuclear phagocytes from migrating and proliferating. Examining the underlying molecular pathways showed that sRAGE decreased S100 expression, CML-AGE accumulation, and RAGE expression [56].

5. RAGE IN BREAST CANCER

Multiple studies have shown that persistent inflammation contributes significantly to the growth of malignancies [57,58]. A pro-tumorigenic, inflammatory environment is created by activating several transcription factors, chiefly NF-κB, which regulates the production of cytokines that promote tumor growth and survival genes like Bcl-XL. In a positive feed-forward fashion, these soluble substances subsequently attract and activate immune cells of myeloid and lymphoid origin, setting off signaling pathways that create several pro-inflammatory mediators [59]. It has been related to the development of numerous malignancies and provides a key linkage across the accumulation of AGEs and cancer through its potential to activate NF-κB, RAGE signaling, and up-regulation [60,61]. The presence of AGEs in human cancers was initially demonstrated by immunohistochemical labeling in squamous cell carcinomas of the body parts such as colon and leiomyosarcomas, with significant heterogeneity among tumor types [62]. RAGE transcription in a panel of breast cancer cell lines was overanalyzed. Invasive TNBC cell lines showed increased RAGE expression, but weakly metastatic ERα+ breast cancer cell lines (MCF7, T47D, and BT474) showed little to no RAGE expression. According to these findings, the cell lines that express RAGE the most are those that are ERα- and highly metastatic breast cancers. Researchers examined RAGE expression in publicly available Gene Expression Omnibus (GEO) datasets to assess the relationship between RAGE and ERα-status. According to research on subtype-specific breast cancer, tumor specimens from individuals suffering from invasive breast cancer and basal type (mostly TNBC) breast cancer have much higher levels of RAGE expression than those from non-basal type (primarily ERα+ cancer) and normal breast cancer, respectively. Studies found that RAGE expression was higher in invasive breast cancer (IBC) than in normal. Along with relevant final result and other clinical information, we also examined RAGE expression in breast cancer TMAs using immunohistochemical. We discovered that RAGE expression was elevated in 92% of the samples in TNBC tissues. However, only 29% of HER2-positive TMAs expressed RAGE. We discovered that RAGE expression is often greater in metastatic tissue than in malignant tissue ($p<0.0001$) using a different TMA that included samples from both patients with metastatic disease and those with malignancy. Next, we looked at the RAGE expression clinical outcomes open-access dataset. We found that elevated RAGE expression was associated with a worse outcome. When combined, these findings demonstrate that TNBC and other highly aggressive and metastatic breast tumors are linked to RAGE expression [63,64]. The existence of an inflammatory microenvironment in solid tumors, particularly breast cancers, is now well-acknowledged. One of the cell surface proteins in the group of immunoglobulins is a receptor for advanced glycation end products (RAGE), which has been connected to chronic inflammation, which hastens the onset of several cancers [65]. Additionally, patient samples with distant metastases and lymph nodes showed high RAGE expression. Furthermore, we found that a worse prognosis for breast cancer was linked to increased RAGE expression [66,67]. It has been demonstrated that during carcinogen-induced mammary carcinogenesis, mS100a7a15 is up-regulated. Nevertheless, nothing is known about the direct functional involvement of mS100a7a15 in the development of illness. We have shown that the mammary glands of these transgenic mice became larger as a result of mS100a7a15 overexpression [74,75]. When RAGE is stimulated by its ligands, AGEs, HMGB1, and the S100 group of proteins, it activates many cellular signaling routes, which includes PI3K and, JAK/STAT, NF-ķB, Ras/MAPK, Rac1/cdc42, p44/p42, p38, and SAP/JNK MAPK, as well as transcription factors, such as NF-ķB, STAT3, HIF-1α, AP-1, and CREB [68,69]. Disease control is difficult due to the various yet linked signaling network of neoplasms, which presents unique potential for single gene targets unique to each molecular subtype of cancer. Given the state of onco-therapeutics today, research must concentrate on a particular molecular mechanism or pathway that contributes to various cancer stages and kinds, ranging from the oncogenic transformation of normal tissue flora to the survival and metastasis of cancer cells [70]. The dynamic transition from small, unchecked growths to aggressive malignancies is characterized by many molecular mechanisms that connect the shift from mitochondrial respiration to elevated glycolytic flux. The development and invasion of malignancies are caused by the signaling ligand axis, which is mediated by the receptor for advanced glycation end products (RAGE) [79, 80]. Interaction between AGEs, HMGB1, and the S100 proteins—which are mostly formed during pathological circumstances of glycation and inflammation—RAGE functions as a master regulator of tumor genesis, invasion, and

metastasis. The receptor-ligand combination is the main target for both prevention and successful treatment, regardless of the location of the cancer's genesis, genetic subtype, or stage of development. It gives medications that target RAGE and its ligands' preferential cytotoxicity; once these treatments are found, they may be employed in conjunction with traditional chemotherapy to effectively inhibit the growth and spread of malignancies while having no negative effects on healthy cells.

6. RAGE MEDIATED SIGNALING PATHWAY IN BREAST CANCER

6.1. NF–κB Signaling Pathway

One important transcription component that connects inflammation and cancer is NF-κB. It has been shown to have a reason to cancer carcinogenesis and endocrine treatment resistance. NF-κB is crucial for controlling inflammation, cell line survival, and proliferation [71–73]. Due to its several activities, Inflammatory TME is formed as a result of NF-κB stimulation. In solid tumors, NF-κB activation leads to the formation of an inflammatory tumor microenvironment [74]. IκB proteins start the CS route, while TNF-α, which reacts to UV light, cytokines, growth factors, bacteria, and mitogens, stimulates it [85]. When TNFα interacts with its receptor TNFR1, a series of proteins, including TRAF2, TRADD, and RIP, are recruited, initiating the cascade. The TRAF2 protein is one of these adaptor proteins; it binds to TNFR1 and activates IKKβ, which phosphorylates IκBα. It also recruits the complex IKKα, IKKβ, and NEMO [75,76]. NF-κB is constitutively active, meaning it is mis-regulated in a wide variety of human tumor types. Gene expression that maintains the cell growing and shields it from circumstances that might otherwise lead it to undergo apoptosis is activated by active NF-κB[77]. Chromosome translocations, deletions, and mutations linked to cancer can also affect genes that encode the NF-κB and IκB proteins. By dissociating NF-κB from the factor that regulates them, this may result in constitutive NF-κB activation [89,90].

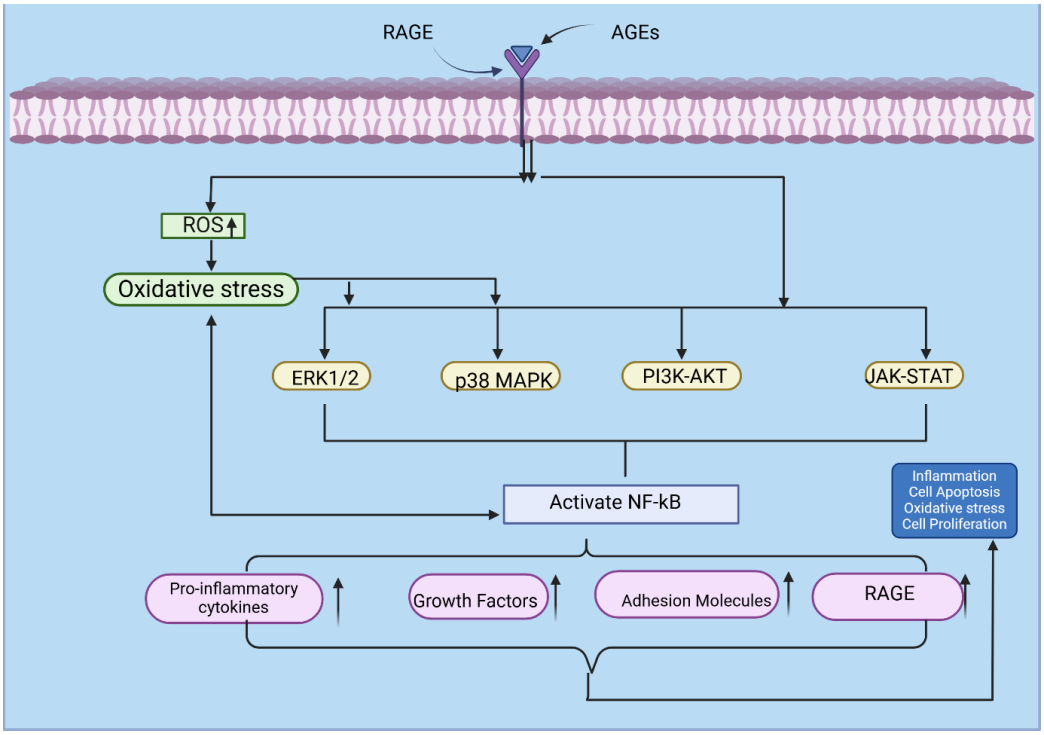

Fig. 2. Represent NF – kB Signaling Pathway

6.2 MAPK/ERK PATHWAY

Many pathophysiological alterations brought on by AGE have been linked to the MAPK pathway. Ho et al.. demonstrated that some MAPK inhibitors and NF-κB inhibitors might reduce AGE-induced apoptosis in HUVECs [78]. Breast cancers in humans that are generated from them may be classified as either steroid hormone dependent or independent of estradiol growth. The steroid hormone-independent subtypes frequently use growth factor or peptide hormone-mediated pathways where MAPK kinase activates the enzyme. MAP kinase pathways can also be used by estradiol-dependent tumor cells in at least one of three ways. We don't fully understand the exact processes underlying these impacts. It is crucial to take into account whether estrogen promotes the development of breast cancer by MAP kinase-independent pathways, MAP kinase-only pathways, or a mix of these two

mechanisms. A review of several data points to the possibility that progesterone and/or estrogen can promote proliferation via both MAP kinase-dependent and MAP kinase-independent mechanisms [79]. According to a survival study, people with primary breast tumors that had low ERK1/2 activity are more likely to survive without relapsing80Normal mammary epithelial cells that enhance upstream ERK1/2 modulators (including MEK1) undergo neoplastic transformation, underscoring about significance of the signaling network with breast cancer [81].

6.3 JAK/STAT PATHWAY

AGEs lead to the invasion and growth of numerous tumors, including colorectal and breast cancers, by activating RAGE and other transcription factors, including STAT-3 [82]. Our prior research found that AGE promotes the JAK2-STAT1/STAT3 pathway in NRK-49F cells. However, whether an AGE receptor, such as RAGE, is activated is yet unknown. JAK2 also adheres to STAT1 and STAT3. To show how RAGE and JAK2 are associated with AGE-induced STAT activation, antisense RAGE ODN and AG-490, a specific JAK2 inhibitor, were used.

6.4 PI3K/AKT PATHWAY

The 3′-OH group of phosphatidylinositol (PI) at intracellular membranes and plasma is phosphorylated by a type of lipid kinase called phosphoinositide 3-kinase (PI3K). Based on their structure, binding partners, and substrate specificity, they are divided into three groups. Only a few PI3K and mTOR inhibitors are currently authorized for the treatment of human cancers, although several small molecule inhibitors that target the PI3K/AKT/mTOR signaling pathway have been pre-clinically investigated. The most recent research on blocking the PI3K/AKT/mTOR signaling pathway in breast cancer is included in this article.

PI3K/AKT/mTOR pathway in breast cancer is often dysregulated by several pathways, resulting in the mutation of genes that suppress tumors, such as INPP4B and PTEN phosphatases, as well as increased PI3K activity and/or loss of PI3K inhibitory activities. One of the most often mutated PI3K genes is PIK3CA, which has mutations at two hotspot regions: a histidine residue (H1047) in the kinase domain and an acidic cluster (E542, E545, and Q546) in the helical domain. While mutations in the helical domain of p110α mostly depend on the loss of p85-dependent regulatory action, activating mutations in the catalytic subunit of p110α rapidly boost lipid kinase activity by permitting regulatory movements required for catalysis on membranes [83]. G protein-coupled receptors (GPCRs) may be the mechanism by which PI3KCB activation occurs in cancer. Additionally, in preclinical research, one of the main signs of acquired resistance to endocrine treatment is ligand-independent stimulation of the ER via its phosphorylation, which is mediated by the mTOR complex 1 (mTORC1)/S6K1 axis. One of the main causes of this phenomenon is increased activity of the PI3K/AKT/mTOR pathway.

7. RAGE-Dependent Crosstalk with ROS Signaling

In many clinical circumstances, such as diabetes, neurological diseases, and cancer, ROS signaling is essential for maintaining oxidative stress, persistent inflammation, and cellular dysfunction. The principal source of ROS generation in cells is triggered by the binding of RAGE ligands, including AGEs, S100 proteins, and HMGB1. The stimulation is brought on by the binding of internal adaptor molecules such as TIRAP and MyD [88], which then sets off the downstream activation of signaling cascades such as the PI3K/Akt, MAPK, and NF-κB pathways.

Hydrogen peroxide (H2O2) and superoxide (O2●−), which are frequent byproducts of several enzymes and metabolic activities, are the most common ROS. However, at the correct conditions, much more dangerous and reactive species are also created, including singlet dioxygen, the hydroxyl radical (●OH), and reactive nitrogenous species (RNS). Even in healthy mitochondria, the production of ROS is a collateral small activity that cannot be completely eradicated, in addition to water. It is a natural byproduct of using oxygen as an electron acceptor, ETC. Numerous oxidases and secondary metabolic activities produce H2O2, whereas the mitochondria and cytoplasm produce trace quantities of superoxide anion. SOD converts superoxide to hydrogen peroxide [84]. Although ROS are frequently associated with possibly adverse outcomes, it is a fallacy that all ROS are harmful to cells and that all antioxidants are beneficial. Since ROS are signal molecules required to control proper metabolism, cell development, differentiation, apoptosis, and autophagy, the production of minute quantities of ROS at physiological concentrations is a normal process. The activity of some enzymes that preserve the intracellular redox balance is intimately linked to the processes that control ROS levels. Pro-oxidant enzymes, which are often oxidases, and antioxidant enzymes, which scavenge reactive oxygen species, are the two main categories. Both groups contribute to the redox equilibrium, respond to different stimuli, and follow different roles; the imbalance in these activities brought on by the first group's preponderance is mostly to blame for the emergence of oxidative stress [85]. A healthy cell's ROS levels are balanced by a range of detoxification processes that are regulated by antioxidant enzymes. This helps maintain redox balance in healthy cells by maintaining ROS homeostasis. Other resources, include α-ketoglutarate dehydrogenase, monoamine oxidase, mitochondrial p66Shc, sirtuins, Nrf2, as well as forkhead box O3 (FOXO3), in addition to the underlying redox cycling processes, may also be important in increased ROS generation, Although ROS are thought to be primarily

produced by complex I and III of the mitochondrial respiratory chain with elevated membrane potential. Numerous clinical disorders may result from increased oxidative stress levels brought on by this increased generation of ROS or a malfunctioning defensive system. Peroxisomes, p450 metabolism, mitochondrial oxidative phosphorylation, and the activation of inflammatory cells like neutrophils and macrophages are a few examples of endogenous sources of ROS. It is believed that 1–2% of molecular oxygen undergoes one to three electron reductions throughout the respiratory process in the mitochondria, leading to the production of hydroxyl, hydrogen peroxide, superoxide, and peroxynitrite radicals [86].

8. Impact of RAGE mediated signaling on Tumor microenvironment

RAGE belongs to the immunoglobulin class and is a multi-ligand transmembrane surface receptorNumerous inflammatory illnesses, including sepsis, diabetes, and inflammatory bowel disease, have been linked to elevated expression of RAGE and its ligands. The increased expression and co-localization of RAGE and several of its ligands in a range of human malignancies, including colorectal tumors, suggest that the ligand-RAGE axis may also be essential for carcinogenesis and metastasis. RAGE ligands support cell invasion, immigration, and survival by engaging in intricate autocrine and paracrine interactions within the tumor's microenvironment [87]. Two of the RAGE ligands—S100 proteins and high-mobility group box 1 (HMGB1)—are extensively linked to carcinogenesis and metastasis. S100 proteins are tiny, calcium-binding molecules that can activate endothelial cells, macrophages, and lymphocytes in response to RAGE, hence promoting inflammation [88]. S100P expression has been discovered to be higher in human colorectal cancer, and in vitro investigations have shown that S100P stimulates the motility and proliferation of colon cancer cells. Numerous signaling cascades linked to tumor formation and metastasis are stimulated by ligand-RAGE interactions, such as the nuclear factor (NF)-κB, c-Jun N-terminal kinase (JNK), and the mitogen-activated protein kinase (MAPK).

According to epidemiological research, steroid sexual hormones are crucial for the development and spread of breast cancer. This disease is also linked to other risk factors, including diet, ethnicity, age, early menarche, not having children, becoming pregnant for the first time after turning 30, obesity, genetic mutations, smoking or drinking alcohol, and environmental pollutants, to name a few. Over a million women are thought to receive a breast cancer diagnosis each year [89,90].

Conclusion

An important molecular connection between diabetes and breast cancer is the AGE-RAGE axis, which promotes oxidative stress, chronic inflammation, and metabolic dysfunction—all of which aid in the development, spread, and metastasis of tumors. Diabetes-related insulin resistance and persistent hyperglycemia increase AGE buildup, which results in long-term RAGE activation and the stimulation of important carcinogenic pathways such PI3K/Akt, MAPK, JAK/STAT, and NF-κB. In addition to promoting angiogenesis, epithelial-to-mesenchymal transition (EMT), and cancer cell proliferation, these signaling cascades also alter the tumor microenvironment (TME) to facilitate immunological evasion and treatment resistance. Furthermore, by promoting cellular growth and survival processes, diabetes-induced metabolic changes such as hyperinsulinemia, elevated IGF-1 signaling, and the Warburg effect worsen the advancement of breast cancer.

RAGE signaling and ROS production interact to create a vicious cycle of oxidative damage and inflammation that increases genomic instability and creates an environment that is conducive to tumor growth. Targeting the AGE-RAGE axis appears to be a viable treatment approach in light of the mounting data that connects diabetes with breast cancer. RAGE antagonists, AGE inhibitors, and lifestyle changes that lower AGE buildup and RAGE activation are examples of potential therapies. The therapeutic uses of RAGE-targeted treatments and their effectiveness in severing the pathophysiological link between diabetes and breast cancer require more investigation. Future research may open the door to innovative treatment strategies that slow the advancement of cancer and metabolic diseases, thereby improving patient outcomes by clarifying the molecular complexities of the AGE-RAGE axis**.**

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