RECENT ADVANCES IN RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (RAGE) IN ORAL CARCINOGENESIS

G L Gokul[1], Dr. Palati Sinduja[2*], Dr. R. Priyadharshini[3]

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Abstract

The word 'glycation' refers to the non enzymatic reaction between the reducing sugar and a protein such as fructose or glucose that leads to the formation of a Receptor for Advanced Glycation End Products (RAGE). AGEs are a cohort of heterogeneous compounds that formed after the non enzymatic glycation of proteins, lipids and nucleic acids. The Receptor for Advanced Glycation End Products (RAGE) is a member of immunoglobulin. It is encoded in the Class iii region of the major histocompatibility complex. The enzyme RAGE which is expressed in the lung that readily measures levels easily at sites of inflammation, on inflammatory and epithelial cells. AGEs have a potent impact in tissues, stimulating processes that are linked to inflammation and its consequences. AGEs cause perturbation during a diverse group of diseases, like diabetes, inflammation, neurodegeneration, and aging. Thus, targeting the pathway may indicate a logical step within the prevention/treatment of these disorders. Ligation of RAGE on the cellular surface triggers a series of cellular signaling events, including the activation and translocation to the nucleus of transcription factor NF-kappaB, and results in the assembly of chemokines, pro-inflammatory cytokines, adhesion molecules and oxidative stress and causing inflammation. newer work has revealed the role of RAGE in inflammatory cell recruitment and extravasation of leukocytes across the endothelial barrier with further inflammatory events. RAGE is a crucial target to treat RAGE activation-associated diseases. The enzyme 'RAGE' is expressed by different cell types, which incorporates macrophages, neuronal, endothelial, lymphocytes and smooth muscle cells. In Advanced glycation end products (AGEs), RAGE binds with some of the enzymes like amyloid, amphoterin, S100/calgranulin, transthyretin, and a leukocyte integrin, Mac-1. Engagement of RAGE in intracellular signaling results in the activation of the proinflammatory transcription factor NF-kappaB to sustained cellular dysfunction and tissue destruction.

Keywords: End products, glycation, ligands, membrane bound, RAGE, Novel method

[1]Department of Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-77
[2*]Assistant Professor Department of Pathology Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-77
[3]Assistant Professor Department of Pathology Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-77

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1. Introduction

The process of glycation refers to the a non enzymatic reaction between the reducing sugar and the protein such as fructose or glucose which leads in the formation of Advanced Glycation End Products (AGEs)(1).The reaction of glycation is also called the Maillard reaction, which is named after the French chemist Louis Camille, 1912. A Receptor for Advanced Glycation End products was discovered in 1992. This receptor has the ability to bind the products of non-enzymatic glycation and oxidation of proteins and lipids (2). RAGE functions and highlights a new target for therapeutic interruption of RAGE signaling . In humans, prominent signals for RAGE activity include the presence and levels of two forms of soluble RAGE, sRAGE and endogenous secretory (es) RAGE. RAGE and the isoforms of RAGE play a pivotal role, regulating inflammation, metabolism and epithelial survival within the setting of inflammation is critically important in understanding the role of this receptor in tumor biology.

The Receptor 'Rage'

RAGE (Receptor for Advanced Glycation End Products) is also known as AGER (Advanced Glycation End Products Receptors). It is a transmembrane receptor. It belongs to the immunoglobulin superfamily and it has the ability to bind advanced glycation end products. RAGE interacts with multiple ligands, so it is called a multiple ligand receptor(3). It belongs to the member of immunoglobulin superfamily which is encoded by the class iii region of the major histocompatibility complex(4). Advanced Glycation Endproducts (AGEs) were indeed thought to be its main activating ligands but since then many other ligands of RAGE including damage - associated molecular patterns (DAMPs) have been identified. Activation and up regulation of Rage by its ligands leads to enhanced survival. RAGE is also considered as the pattern recognition receptor which has a wide variety of ligands. RAGE is expressed at low levels in a wide range of differentiated adult cells in a regulated manner but in mature lung type-1 pneumocytes it is expressed at substantially higher levels than in other resting cell types. RAGE is highly expressed and associated with many inflammations of body-related to pathological states such as vascular disease, cancer, neurodegeneration and diabetes(5). Due to the power of RAGE to acknowledge three-dimensional structures instead of specific amino alkanoic acid sequences, RAGE is capable of engaging a variety of ligands that lack sequence similarities. Due to this feature, this multiligand receptor can therefore be considered a pattern-recognition receptor (PRR) . Ligands that are found to be recognized by RAGE include AGEs, amyloid β-peptide , DNA binding protein high mobility group box-1 (HMGBl)/amphoterin , and S100/calgranulins(6). Advanced glycation endproducts (AGEs) are the various groups of macromolecules and which also have a minimum of 20 different specific AGEs are described so far .The main groups of AGEs are carboxymethyl lysine (CML), carboxyethyl lysine (CEL), methylglyoxal lysine dimer, pentosidine, glyoxal lysine dimer, glucosepane and glycolic acid lysine amide(7). The 'AGEs' enzyme can affect every tissue within the body virtually , whether through mediation of cellular damage via protein cross-linking or through their binding to cell surface receptors. Because various diseases are linked to AGEs, it's plausible that AGEs are often utilized as biomarkers, like for predilection to disease, state of disease activity, and/or response to therapeutic interventions(8). Our team has extensive knowledge and research experience that has translate into high quality publications (9–18))

Structure

The structure of RAGE exists in two forms. They are membrane bound form and soluble form. Membrane bound form refers to as mRAGE and soluble form refers to as sRAGE. mRAGE has three domains and sRAGE has an intracellular domain. It is the product of proteolytic cleavage of mRAGE. The cytosolic domain of mRAGE functions in single transduction, the transmembrane domain functions in anchoring the receptor and the variable domain binds RAGE ligands. The sRAGE includes the extracellular domain but lacks the transmembrane domain and cytoplasmic domain(19). RAGE is expressed as mRAGE and sRAGE. Membrane bound forms also called fl.RAGE. RAGE consists of one hydrophobic transmembrane-spanning domain, a highly charged cytosolic tail, and an extracellular region . This extracellular region consists of 1 N-terminal V-type immunoglobulin domain and two C-type (C1 and C2) immunoglobulin domains. a versatile linker separates the fully independent C2 domain from the integrated structural unit formed by the V-type and C1 domains . The V-type domain is taken into account because it is the principal site for interactions between RAGE and potential extracellular ligands(20).

Rage and Diabetes

In the microvessels, Cipollone and colleagues showed that enhanced RAGE expression in human diabetic sclerotic plaques co-localised with Cox-2, type 1/type 2 microsomal prostaglandin E2, and metalloproteinases, particularly in macrophages at the vulnerable regions of the artherosclerotic plaques (21).

Receptor for Advanced Glycation End Products (RAGE), which is present in human diabetes tissues targeting the dysfunction in chronic hyperglycemia. The principal site of RAGE expression in the

diabetic kidney was the podocyte (glomerular epithelial cell), with no expression of RAGE evident in the tubules or in the mesangium. Expression of the receptor was a contributing or consequence of vascular perturbation triggered by RAGE - independent pathways (22).

Rage and Arthritis

Arthritis may be a sort of joint disorder frequently amid arthralgia and stiffness of the affected joint. Osteoarthritis (OA) and atrophic arthritis (RA) are the 2 commonest types (23). RAGE has been detected in synovial tissue, macrophages, T cells and a few B cells within the affected joints of both OA and RA patients. These cells are implanted within the development of synovial inflammation in RA and OA, a task for RAGE in pathogenesis of both joint diseases, especially RA. Only the presence and up regulation of RAGE in focal degenerated cartilage of OA, also as in synovial tissue macrophages and infiltrating lymphocytes RA(24).

Rage and Sepsis

Sepsis may be a heterogeneous clinical syndrome defined as a systemic inflammatory response to infection. RAGE has been proposed to be involved within the pathogenesis of sepsis thanks to its role in transmitting signals form pathogen substrates to activate cells during the onset and perpetuation of inflammation, S100 calgranulins and HMGB-1 are elevated in septic patients and this further supports the role of RAGE within the pathogenesis of sepsis (25). But the actual thing is,The role of RAGE in sepsis still remains a mystery.

Rage and Inflammation

Increased expression of RAGE during a number of acute and chronic inflammatory diseases have suggested participation of RAGE and its downstream signaling pathways in perpetuating immune and inflammatory responses. Various mechanisms of RAGE in contributing to the inflammatory responses(26).

First, RAGE has been found on numerous immune cells that play key roles in perpetuating the immune reaction . These cells include neutrophils, T and B lymphocytes, monocytes and also dendritic cells. Second, many of the additional cellular ligands that trigger RAGE signalling are determined to be involved in acute and chronic immune responses (27). Third, RAGE expression has been found on endothelial cells, and this expressed RAGE can physically interact with the leukocyte Beta 2 integrity Mac-1. The craze Mac-1 interaction enables RAGE to function as an adhesion receptor for leukocytes. Fourth, pro-inflammatory transcription factor nuclear factor kappa B and its downstream target genes are activated following engagement of RAGE (28). Fifth, accumulation of RAGE ligands at site tissue injury and inflammation has been found to induce intracellular activation of nuclear factor kappa B. This sustained cellular response will initiate chronic tissue alterations (29).

2. Conclusion

This review highlighted the evidence connecting RAGE ligands axis to a number of pathological settings such as cardiovascular disease, neurodegeneration and inflammatory disease. To discuss the consequences of RAGE blockade in the pathological conditions, the soluble RAGE which may antagonize the RAGE-ligand interaction to competitively inhibit the activation of RAGE signaling.

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Conflict Of Interest

The authors would like to declare no conflict of interest in the present study.

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