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REVIEW

The RAGE gene crucial function in the etiology and consequences of type I diabetes

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Abstract

Type I diabetes (TID), among the 10 greatest causes of mortality worldwide, is estimated to afflict 642 million individuals by 2040. It is an autoimmune illness brought on by an association of environmental and genetic variables that cause T lymphocytes to destroy insulin-producing β-cells. Its prevalence continues to rise by 3−4% annually worldwide, enhancing the risk of mortality. So, the idea of diabetic kidney disease is widely established, and systemic treatment is essential. RAGEs are linked to inflammatory disorders that exist in a variety of TID-related cells; especially T cells. Variations in circulating RAGE concentrations have been linked to a higher chance of developing TID. Furthermore, T cells from at-risk individuals who develop TID have higher RAGE expression, which promotes T-cell cytokine generation.

Advanced glycation end products seemed to be the earliest RAGE ligands discovered, and they may suppressed by nutritional and medical interventions. Prediabetes had a higher concentration of advanced glycation end products, which is a good predictor of TID. It remains increased following TID diagnosis, and it is hypothesized that they are linked to the development and advancement of long-lasting problems, including retinopathy, nephropathy, and coronary heart disease. This review will provide a summary of RAGE's gene structure, describe the biological and pathophysiological activities, and give insight into how it contributes to the start, progression, and management of TID.

Keywords: Advanced glycation end products, Autoimmune disorders, RAGE, Type I diabetes

1. Introduction

Diabetes mellitus (DM) ranks among the leading causes of death globally as it represents 48% of all deaths in 2019 [1]. DM is characterized by a group of metabolic disorders that describe the abnormality of carbohydrate metabolism as a result of variable degrees of peripheral resistance to insulin action, along with a relative or absolute reduction in insulin production. Such diabetic complications arise from a wide range of disturbances in the regulatory systems for the storage and mobilization of metabolic fuels resulting from defective insulin secretion, insulin action, or both [2]. Annually, the diabetes-related organization re-evaluates the current diabetes diagnosis and screening recommendations based on new research and clinical practice findings [3].

2. Main text

2.1. Type I diabetes pathophysiology

Type I diabetes mellitus (TIDM) is a persistent autoimmune disorder distinguished by autoimmune damage in the pancreatic β-cells, mediated by

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CD4+, CD8+ T cells, and macrophages. Nowadays, TIDM is thought to be the result of complex interactions among genetics, abnormal metabolism, immune system, and other environmental factors that are different from case to case [4].

The clinical symptoms of TIDM are prefixed by a long-term prediabetic, marked by impaired insulin and anti-islet antibodies (ICA), among them, insulin antibody (IAA), and/or antiglutamic acid decarboxylase (GAD), anti-protein tyrosine phosphatase (anti-IA-2), and zinc-transporting protein antibody (ZnP8). These antibodies were found in the bloodstream at this time and are considered to be among the biomarkers for TIDM prediction [5].

The pathogenesis of TIDM was found to be the result of an interaction between pancreatic β-cells, adaptive, as well as innate immune systems, which is important in the disruption of pancreatic β-cells [4].

2.2. Genetic predisposition

The HLA system genes on chromosome 6 contain the majority of the genes linked to the onset of TIDM. Overexpression of HLA-I is characteristic of pancreatic sections from the affected donors with TIDM. This expression functions as a cytotoxic T cell's form of homing signal [6].

The onset of TIDM is believed to have started when the HLA-I molecule contacts the β-cell on antigen-presenting cells. These antigen-presenting cell-carrying self-antigens 12 reach the pancreas-related lymphatic vessels, and then spontaneously engage to CD4+ lymphocytes (T cells), and cause spontaneous CD8+ T-cell activation. Rapidly stimulated CD8+ T lymphocytes migrate toward the islet of the pancreas and destroy the β-cells with autoantigens presented on HLA-I surface molecules such as zinc transporter 8 (ZnT8), insulin-associated protein 2 (IA-2), and glutamic acid decarboxylase (GAD). The activated CD4+ T cells induce B-cell differentiation to plasma cells producing autoantibodies against proteins on the β-cells [7]. Attention must be impelled to the imbalance between the activity of the T-helper-1 and T-helper-2 cells. The autoreactive cells found on Th-1 cells release cytokines that promote inflammation, including interleukin (IL)-1, IL-6, IL-12, or tumor necrosis factor-α (TNF-α). In addition, they trigger natural killer cells, cytotoxic CD8+lymphocytes, and macrophages. Th-2 lymphocytes act as regulatory cells that inhibit Th-1 lymphocytes by releasing cytokines that are anti-inflammatory, such as IL-4, IL-10, or IL-13, to stimulate the immune defenses and lower the chance of developing diabetes [8]. IL-6, IL-1, TNF-α, C-reactive protein, and reactive oxygen species released by neutrophils, natural killer cells, and macrophages and other cytokines associated with inflammation trigger the immune system and worsen β-cell death. Deficiencies in regulatory T cells, a key component that breaks down autoimmunity, aggravate this process [7].

2.3. Environmental variables and risk of type I diabetes

As previously stated, TID is the outcome of a complicated illness in which genetic and environmental variables induce an autoimmune reaction that has not been fully explained yet [4]. However, certain key genetic predictors of TID have been found, such as HLA alleles, which only account for 40–50% of the familial cluster [6]. Conversely, 70% of twins who are monozygotic do not develop TID, suggesting that external factors could be involved, and the risk of TID is rising by 3–4% annually in developed countries, for unknown reasons [9]. Advanced glycation end products (AGEs) may be an environmental component of TID, as in the West, diets have an abundance of these nonenzymatic products that provide taste and color to meals (for instance, roasted meat or coffee). There has been growing evidence that long-term exposure to AGEs affects insulin secretion and induces β-cell dysfunction [10].

2.4. Advanced glycation end products/RAGE singling

AGEs binding to RAGE will initiate the inflammatory response, which will cause oxidative stress as well as β-cell damage through activating the inflammatory pathway of the transcription factors, which will increase the production of inflammatory mediators like IL-6 and TNF-α [11].

The AGER gene encodes RAGE, which is part of the immunoglobulin family. This receptor is thought to be proinflammatory and is expressed by a variety of cell types, including pancreatic β-cells and immune cells (dendritic cells, monocytes, macrophages, and subsets of T and B cells) [12].

Furthermore, growing evidence reveals an important link between RAGE and the pathophysiology of various human illnesses, including TIDM. These investigations showed that patients with TID reported greater levels of AGEs than did normal persons, indicating a considerable upregulation of RAGE signaling [11,13].

This review's objective is to give an overview of RAGE, its function in the onset as well as the

progression of TIDM, and how it might be utilized as the target of therapy. We conducted the RAGE and TIDM literature in great detail.

Fully assessed papers were used to discover the RAGE gene mechanism in TIDM. This review revolves around studies in English literature, papers/articles that did not meet the inclusion criteria were excluded from the review.

2.5. RAGE structure

The RAGE gene is found on chromosome 6p21.3 of the human genome, among the main histocompatibility complex, which also includes the most prevalent genes that confer inherited vulnerability to the onset of autoimmune diabetes [14]. It is an advanced glycation end-product receptor that is an irreversible product derived from the nonenzymatic interaction of glucose or other reducing sugars with proteins or lipids [15]. Smooth muscle cells, fibroblasts, macrophages, and T lymphocytes all contain this cell surface receptor, which belongs to the superfamily of immunoglobulin. Three components make up the structure intracellular, transmembrane, and extracellular. RAGE's extracellular part is the site of ligand binding and comprises three Ig domains: V-type, C1-type, and C2-type. These are followed by a transmembrane region and a brief but very active intracellular portion that is essentially linked to the gene signaling [14].

2.6. RAGE activity regulation

RAGE is considered a cell surface receptor with multiple ligand-binding capabilities that attract a variety of ligands, including AGEs and HMGB1, S100 calcium-binding proteins, and lipopolysaccharides [12]. The binding of this cell surface receptor, which is found on a variety of immune-related cells, including neutrophils, T lymphocytes, dendritic cells, and macrophages, is essential for RAGE signaling and the development of the RAGE-dependent response to inflammation [16]. AGEs are an especially interesting ligand since their exogenous entry into the body can expedite more quickly if processed meals high in AGEs are consumed. They can act as cytotoxic; as they trigger pathological inflammation, activate the renin–angiotensin–aldosterone system, initiate transforming growth factor-β signaling, and induce abnormal angiogenesis, genes that are associated with inflammation are expressed through these signaling cascades [10]. According the broad spectrum of pro-inflammatory ligands that may interact with RAGE indicates that chronic diseases other than diabetes, including other fibrotic diseases, have been linked to this receptor. It is recognized as an essential potential for regulating a wide range of fibrotic-related biological activities, including inflammation, cell proliferation, apoptosis, and angiogenesis [17].

2.7. Signaling pathways regulated by RAGE

Numerous cellular signaling pathways, including the JAK/STAT, GSK-3β, SAPK/JNK, Ras/MEK/ERK1/2, and NADPH oxidase pathways, are stimulated by the interaction of ligands with the RAGE receptor, then the activator protein 1, natural factor-kappa β, STAT3, and other transcription factors are stimulated, leading to a rise in the production and elimination of IL-1, IL-6, and TNF-α, including angiogenesis, oxidative stress, inflammation, proliferation, migration, and increased expression of RAGE [18]. This process then triggers further inflammatory molecules, resulting in a cycle of positive feedback that enhances the inflammation response (Fig. 1) [15].

2.8. Role of RAGE in type I diabetes mellitus

It has been observed that the RAGE receptor is present on T and B cells, neutrophils, dendritic cells, and macrophages, so it plays a specific role in the native and adaptive immune systems [19]. When RAGE–AGE interaction occurs in native immunity, macrophage development is triggered toward a pro-inflammatory state, resulting in the release of cytokines such as TNF-α and IL-6, while in the immune system's adaptive mechanism, RAGE is raised during stimulation of T cells, suggesting that RAGE may be involved in T-lymphocyte abnormalities that lead to autoimmune disorders like TIDM [18,20].

Several investigations have discovered that elevated RAGE expression is exclusively due to a condition known as hyperglycemia that promotes the production of proinflammatory RAGE ligands [21]. Similarly, RAGE polymorphism on T cells has been identified in those who are susceptible and eventually get TIDM, it suggests that alterations in T cells/RAGE activity are probably going to happen before clinical illness onset. As a result, RAGE may be both a trigger and an ongoing component for pancreatic islets and immune-cell failure, this comes to an end in TIDM at last [22].

2.9. Complications related to diabetes and RAGE

TIDM is a long-term metabolic condition that results in hyperglycemia, the elevated levels of sugar in the blood cause AGEs to develop and RAGE

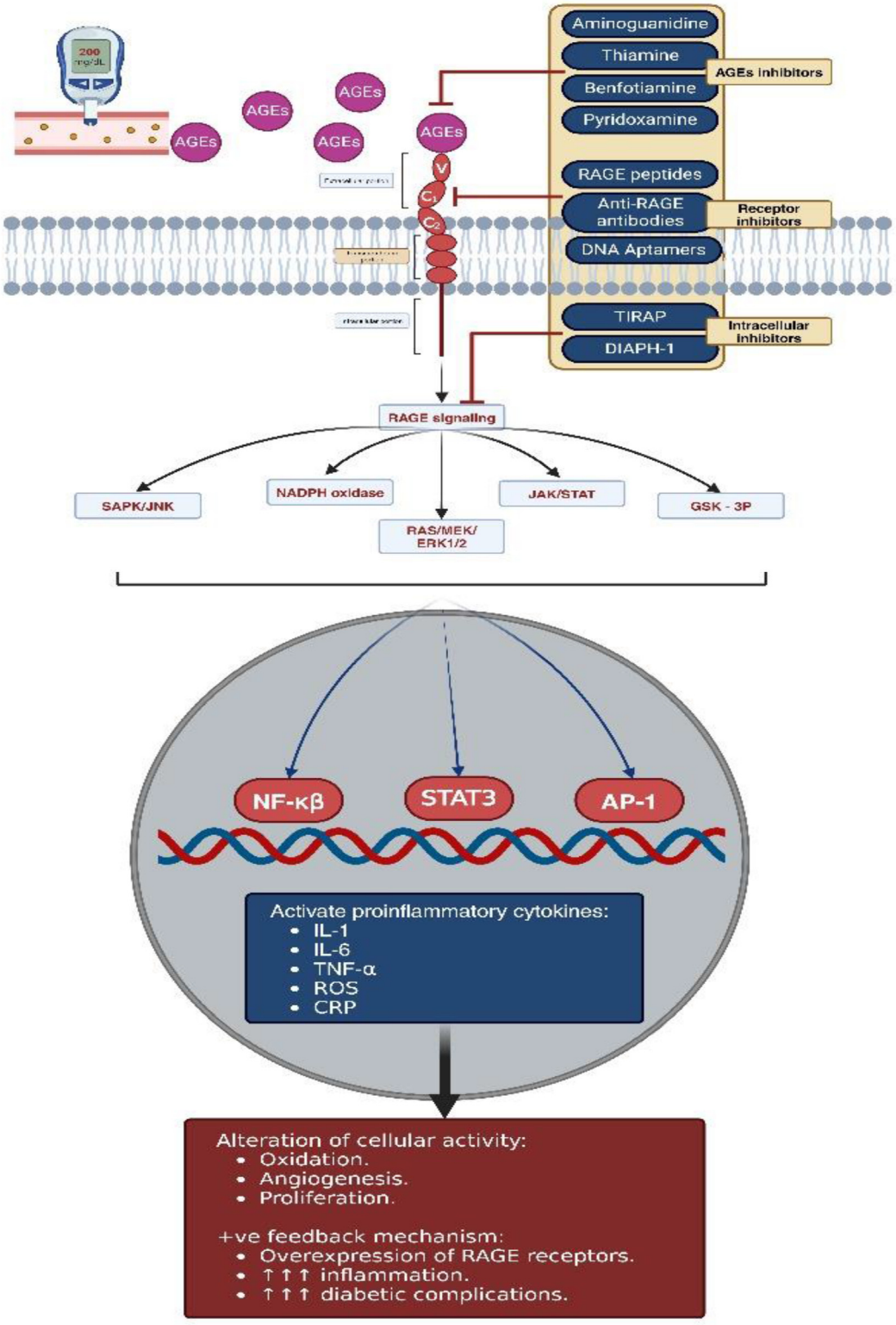

Fig. 1. Diagram showing the commonly recognized signaling pathways that are mediated by RAGE in TID and its regulation. AGEs, advanced glycation end products; AP-1, activator protein-1; CRP, C-reactive protein; GSK-3β, glycogen synthase kinase-3β; IL-1, interleukin-1; IL-6, interleukin-6; JAK/STAT, janus kinase/signal transducer and activator of transcription; NF-Kβ, natural factor-kappa β; Ras/MEK/ERK1/2, Ras/mitogen-activated protein kinase/ERK1/2; ROS, reactive oxygen species; SAPK/JNK, stress-activated protein kinase/c-Jun amino-terminal kinase; TID, type I diabetes; TNF-α, tumor necrosis factor-α.

expression to rise, which promotes the occurrence of diabetic vascular disorders [11,23].

2.10. RAGE and diabetic nephropathy

The diabetic nephropathy research suggests that the combination of RAGE and AGEs on the glomerulus activates the signaling route of natural factor-kappa β, and potentially disrupts the filtration barrier [24]. Compared to diabetic mice expressing RAGE-deficient diabetic species, they display a slower evolution of diabetes-related nephropathy, reduced production of fibrotic and inflammatory-related cytokines within kidney cells, and increased tolerance to kidney cell death [12].

2.11. RAGE and diabetic neuropathy

In diabetes-related neuropathy, electrical and morphological alterations in peripheral nerves are less significant in diabetes-related mice/deficient RAGE than in the normal species [12]. Furthermore, diabetic peripheral neuropathy is associated with elevated levels of both HMGB1 and RAGE, as HMGB1 binding to the RAGE receptor triggers the inflammatory response and destroys the nerves [25].

2.12. RAGE and diabetic retinopathy

Based on research on diabetes-related retinopathy, a proliferative retinal disease associated with diabetes (DRD) has been found with the interaction between RAGE and its associated ligands like HMGB1, AGEs, and S 100, respectively [12,26]. Moreover, the retina vascular membrane becomes demyelinated and undergoes a process of inflammation as a result of HMGB1's interaction with RAGE and the activation of transcription factor κB [27].

2.13. Controlling complications related to diabetes via RAGE-targeting therapy

Regulating RAGE activation may be useful even though RAGE affects the pathophysiology of many diseases [19,23]. It is now being studied as a disease-therapeutic target. RAGE small-molecule inhibitors are classified into two distinct groups: those that target the extracellular portion of the receptor using RAGE peptides, anti-RAGE antibodies, and DNA aptamers, while others target the inner cell region of the receptor using Toll/IL-1 receptor domain-containing adapter protein (TIRAP) and diaphanous-1 (DIAPH1) inhibitors [13,28]. An alternating approach is targeting RAGE ligands that might decrease signal transduction dependent on RAGE. In vitro, AGE inhibitors include aminoguanidine, thiamine, pyridoxamine, and benfotiamine, which have been therapeutically tested for relieving microvascular and macrovascular problems related to TID (Fig. 1) [13].

On the other hand, an antagonist of the soluble isoform of RAGE may directly inhibit RAGE activation [29], which is useful in several animal models of illnesses, such as diabetic atherosclerosis, diabetic nephropathy, and other vascular disorders [30]. Because the rise in autoantibodies coincides with the changes in sRAGE prediabetes, a period of therapy was proposed and then tested within the mice models. According to reports, supplying sRAGE to prediabetic mice provides long-term protection against the inheritance of diabetes, and the treatment with sRAGE leads to elevated levels of transforming growth factor-β1 and IL-10, two anti-inflammatory cytokines in the pancreatic cells of treated mice. sRAGE has also been investigated in an animal model that has diabetes as a prophylactic therapy for diabetic end-stage [13].

2.14. Conclusion

RAGE possesses biological activities that are linked to the development and prognosis of TID. Its expression is associated with the pathophysiology of TID through its functions in the immune system and pro-inflammatory cytokine pathways. Targeting RAGE seems to be a promising approach for regulating RAGE-mediated illnesses and secondary TID prevention, but more human clinical research is required to better comprehend both the positive and negative aspects of treating many RAGE-related disorders before developing potentially tailored RAGE therapeutic techniques.

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Conflicts of interest

There are no conflicts of interest.

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