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Review

Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases

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ABSTRACT

Historically, the receptor for advanced glycation end products (RAGE) was thought to exclusively play an important role under hyperglycemic conditions. However, more and more evidence suggests that RAGE in fact is an inflammation perpetuating multi-ligand receptor and participates actively in various vascular and inflammatory diseases even in normoglycaemic conditions. Various ligands include advanced glycation end products (AGEs), S100 proteins and amphoterins etc. Besides full-length RAGE, numerous truncated forms of the receptor have also been described including the well-characterized soluble RAGE (sRAGE). sRAGE has an ability to act as a decoy to avoid interaction of RAGE with its pro-inflammatory ligands. Ligand engagement of RAGE activates multiple signaling pathways and also forms a positive feedback loop for its own enhanced expression. This review will discuss the role of multi-ligand receptor i.e. RAGE in context to various vascular diseases, which have a pathophysiologically important inflammatory component in normoglycaemic conditions.

1. Introduction

Since its discovery in 1992, receptor for advanced glycation end products (RAGE) has been studied widely in different diseased conditions like diabetes, coronary artery disease, Alzheimer's disease etc [1–6]. RAGE is expressed on multiple cell types i.e. smooth muscle cells, macrophages, endothelial cells, cardiomyocytes, podocytes, epithelial cells etc [1,3]. Acting as a common receptor for a heterogeneous set of ligands, RAGE has been demonstrated to play an inevitable role in inflammation and vascular diseases [3,7–9]. RAGE has ability to recognize a diverse repertoire of endogenous ligands e.g advanced glycation end products (AGEs), amphoterins and S100 proteins/calgranulins, Mac-1 etc [3,6,10,11]. RAGE has been recognized as a key molecule in the development of severe chronic pathologies, including diabetic complications, atherosclerosis and its related manifestations, Takayasu's arteritis (TA), Kawasaki disease (KD), neurodegeneration and cancer [3,6,12–15]. Ligand engagement of RAGE activates multiple signaling pathways, depending on the availability and type of ligand, cell type and environment. In this article, we review the importance of RAGE-ligand axis in various vascular and inflammatory diseases under normoglycaemic conditions.

2. Structure and variants of RAGE

RAGE is an approximately 45 kDa protein, originally isolated from bovine lung endothelium on the basis of its ability to bind advanced glycation end products [1] and later has been characterized as a member of the immunoglobulin (Ig) superfamily of cell-surface molecules [2]. The entire mature receptor consists of 403 amino acids in man, rat, and mouse. The extracellular region of RAGE consists of one V-type (variable) immunoglobulin domain, followed by two C-type (constant) immunoglobulin domains stabilized by internal disulfide bridges between cysteine residues [16,17].

Besides full-length RAGE, numerous truncated forms of the receptor have been described [16–18] (Fig. 1). The existence of diverse RAGE isoforms from the same gene indicates that the pre-mRNA of RAGE undergoes alternative splicing. *In vitro* studies have shown that N-truncated isoform of RAGE is expressed on the cell surface in a way that is similar to full-length RAGE [19]. The V domain of RAGE has been shown to be critical for ligand binding; the N-truncated RAGE is unable to engage glycated end products. Nonetheless, it has been suggested that N-truncated RAGE could participate in the regulation of angiogenesis in a way that is independent from the classical RAGE activation pathway [20].

The C-truncated isoform, on the other hand, has received much more attention because of its potential significance in RAGE-mediated disorders. Soluble forms of RAGE are produced either by proteolytic cleavage of the full length RAGE by MMP-9 or ADAM10 metalloproteinases (sRAGE) or by alternative mRNA splicing, termed as endogenous secretory RAGE (esRAGE) [21–23]. They can act as decoy for RAGE ligands. These secreted variants, together, actually represent the total amount of

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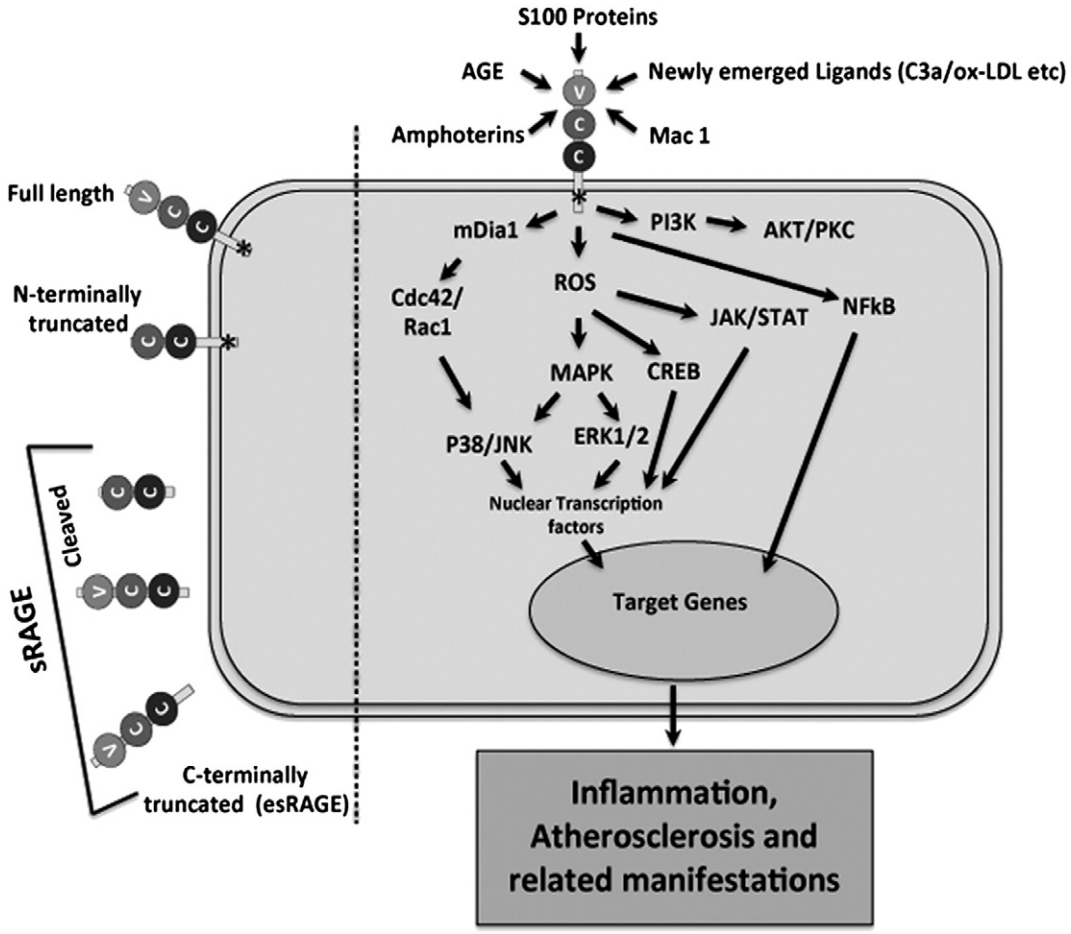

Fig. 1. Schematic representation of the different isoforms of the RAGE (left side) and key signaling events after RAGE-ligand interaction (right side). Left side: RAGE has three major isoforms i.e. full length, N-terminally truncated and C-terminally truncated. N-terminally truncated form lacks the ligand binding domain, where as C-terminally truncated forms lack the transmembrane to induce the cell signaling. C-terminally truncated forms majorly form a pool of soluble RAGE (sRAGE). sRAGE has the abilty to bind to the various RAGE ligands and therefore, it competes with full length RAGE for ligands and act as decoy molecule. Right side: Binding of RAGE to its ligands (AGEs, amphoterins, S100 proteins etc) leads to increase in reactive oxygen species (ROS), activation of various cell signaling pathways like MAPK, PI3K, JAK/STAT and NFkB. All these events finally lead to the promotion of inflammation and atherosclerosis.

soluble RAGE (sRAGE) that can be detected in the bloodstream. [6,24]. sRAGE may contribute to the removal/detoxification of a diverse repertoire of pro-inflammatory ligands that are implicated in human diseases. The potential significance of circulating sRAGE is being investigated in a variety of pathological conditions through clinical research studies. Thus, the decoy function of sRAGE suggests the presence of a regulatory negative feedback mechanism in which sRAGE can serve to prevent the activation of cell surface RAGE.

3. Vascular ligands of RAGE

Several pro-inflammatory ligands, which are implicated in vascular and inflammatory diseases i.e. advanced glycation end products (AGEs), amphoterins, S100 proteins and Mac-1 have been shown to activate RAGE [3,6,10,11] (Fig. 1).

3.1. Advanced glycation end products (AGEs)

Interaction of aldoses with proteins initiates a chain of non-enzymatic reactions leading to a covalent addition of advanced glycated end products (AGEs) to proteins. AGEs are heterogeneous in structure, exhibit characteristic yellow-brown pigmentation and fluorescence, and have a propensity to cross-link. AGEs are specifically recognized by cellular binding sites and are shown to accumulate in the course of ageing and at accelerated rates in diabetes and uremia [4,25]. Their deposition in several tissues (skin, kidney and vessel) has been linked to the activation of inflammatory cytokines and initiation of oxidative stress via generation of oxygen free radicals with subsequent development of atherosclerosis [26]. The reason for AGEs accumulation in these diseases is only partly understood and it is suggested that diminished renal clearance of AGEs may play a part in the process. AGEs have shown their effects on lipids, lipid metabolism and the development of atherosclerosis. AGEs are shown to co-localize in fatty streak, atherosclerotic lesions, lipid containing SMCs and macrophages [4,26].

The potential link between glycation and atherosclerosis and its underlying clinical manifestations has been recently investigated. AGE-modified ApoB have been found in the atherosclerotic plaques of euglycemic normolipidemic patients with atherosclerosis [27]. Moreover, AGEs have been found to be associated with coronary heart disease in both diabetic [28] and non diabetic subjects [29]. A number of potential mechanisms have been hypothesized to explain the link between glycation of lipoproteins and atherosclerosis and its clinical manifestations [30].

Activation of RAGE leads to the production of reactive oxygen (ROS) and nitrogen species (RNS) by a variety of mechanisms, which may have immediate deleterious effects in the vasculature associated with the onset of inflammation. In addition to being formed extracellularly and in the serum where they may bind RAGE, AGEs have been shown to form intracellularly in a ROS dependent manner. This may lead to accelerated deleterious effects such as amplified ROS generation and lipid oxidation causing retention of oxidized LDL (ox-LDL) in the vessel wall [5]. Sun et al. (2012) have recently shown that RAGE