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Soluble Receptor for Advanced Glycation End Products: A Biomarker for Microangiopathy in Type II Diabetes

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Introduction

The link between glycated proteins and vascular disease has been investigated for three decades. The first relationship was established in animal models, infusion of glycated proteins inducing nephropathy [**1**]. The receptor for Advanced Glycation End products (AGEs) RAGE has emerged as a key molecule playing pivotal roles in the pathogenic mechanisms of several major diseases, diabetic nephropathy, atherosclerosis, coronary artery disease, neurological complications of diabetes, including Alzheimer's disease [**2**].

Receptor for AGE

The receptor RAGE, firstly isolated from the bovine lung, is the main cell-surface molecule implicated in the toxicity of AGEs. RAGE gene is present on locus 6p21.3, next to the CHM class III protein family. RAGE can bind a wide range of endogenous molecules including AGEs [**3**], the high mobility group box-1 (HMGB-1) also called amphoterin c,amyloïd-β peptide and s100/calgranulins. RAGE is a member of the immunoglobulin (Ig) superfamily that contains three Ig-like domains one variable (V) and two constant (C1 and C2) in the extracellular part, a single transmembrane domain and one short cytosolic tail.

Different isoforms of RAGE

A publication summarizing the work of many laboratories showed that extensive splicing of RAGE transcripts led to as many as 20 splice variants [**4**]. In endothelial cells, only three isoforms of RAGE were detected at significant levels: N-truncated (Nt-RAGE), Full Length (FL-RAGE) and endogenous secretory (esRAGE).With the exception of lung tissues where constitutive expression of FL-RAGE is abundant, RAGE is expressed at low levels in most other tissues, including normal brain tissue.

An unexpected finding was that methylglyoxal human serum albumin (MG-HAS) and Nε-(carboxymethyl) lysine human serum albumin (CML-HAS), two major AGEs present in vivo and binding to the same receptor, differentially regulated the expression of RAGE isoform transcripts. MG-HSA stimulated expression of mRNA for all three isoforms of RAGE found in endothelial cells, whereas CML-HSA only stimulated transcripts for FL- and Nt-RAGE isoforms, without affecting esRAGE mRNA expression levels. In both cases, MG-HSA and CML-HSA stimulated RAGE expression by interacting with RAGE itself. However, MGHSA enhanced esRAGE expression, potentially implicating a negative feedback loop, because soluble RAGE thus generated may act as a decoy intercepting the interaction of ligands with cell surface RAGE and, thereby limiting RAGE-mediated cellular activation. Factors involved in the regulation of RAGE isoform expression could be important in rendering vascular bed more or less vulnerable to the effect of RAGE ligands [**5**]. FL-RAGE and ligand interaction sets up a positive mechanism that can accelerate disease progression. On the other hand soluble forms of RAGE provide significant inhibition to these positive feedback mechanisms, since these forms of RAGE contain functional ligand-binding domains but lack the cellular signaling domains.

In vitro studies

The binding of glycated proteins, plasmatic or cellular, to the endothelial RAGE was demonstrated in vitro. The activation of NADPH oxidase occurring after glycated protein binding to cellular RAGE resulted in NFκB activation which leads to gene expression (Figure 1). The proteins produced, facilitate leukocyte adhesion to endothelium (VCAM-1, ICAM-1 and MCP-1) or participate in inflammatory reaction such as Interleukin 6 [**6**].

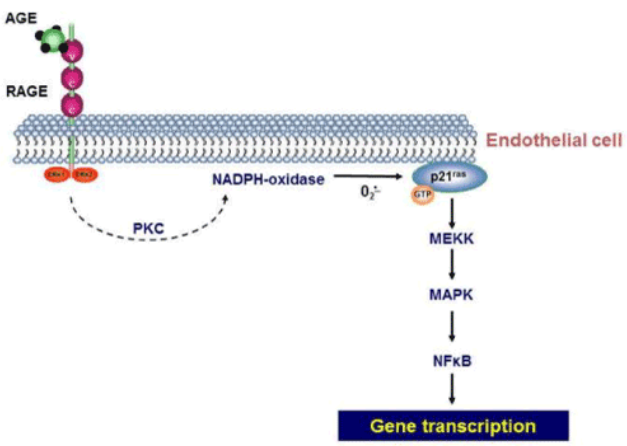

Figure 1: Intracellular activation, transduction and transcription mechanism following RAGE engagement by ligands.

PKC: Protein kinase C

MEKK: Mitogen-activated protein/Erk kinase kinase

MAPK: Mitogen-activated protein kinase

NFκB: Nuclear factor kappa B

NADPH oxidase: Nicotinamide adenine dinucleotide phosphate-oxidase

Animal Experiments

Since RAGE can be on cells as Full Length RAGE (FL-RAGE) or under soluble forms (esRAGE and sRAGE). The hypothesis that

soluble forms may have a protective effect in binding glycated proteins and inhibiting the link to cellular RAGE was supported by several experiments in animal models. In diabetic rats blockade of glycated protein binding to RAGE prevents increase in vascular permeability and oxidant stress [**7**]. Infusion of recombinant soluble RAGE in hyperlipidemic diabetic rats prevented from the development of accelerated atherosclerosis [**8**].

Soluble RAGE as a Biomarker

The level of s-RAGE is relatively constant in the same patients for three years [**9**]. However there is marked difference between sRAGE plasma level of different groups of population (Caucasian, African), which has to be taken into account for evaluating the predictive value of sRAGE. RAGE gene polymorphisms have been studied in human subjects for their potential relationship to sRAGE level modulation but few reports were conclusive. A short article reported that centenarians had a significantly higher level of circulating sRAGE than a group of young controls [**10**].

sRAGE can be measured in the plasma of patients suffering from vascular diseases. It was observed that type II diabetic patients with low plasmatic level of s-RAGE had a more sever microangiopathy associating retinopathy and nephropathy than those with a normal or high level of sRAGE [**11**]. The relationship between sRAGE level and macroangiopathy or cardiovascular mortality was also studied. The statistical significance of the correlation between low sRAGE and vascular risk was controversial. In a study including 1201 patients followed for 18 years the authors observed that the risk of diabetes (hazard ratio 1.64 [95% CI 1.10–2.44]), coronary heart disease (1.82 [1.17–2.84]), and mortality (1.72 [1.11–2.64]) but not ischemic stroke (0.78 [0.34–1.79]) was correlated to s-RAGE plasma level. They conclude that low levels of sRAGE were a marker of future chronic disease risk and mortality in the community and may represent an inflammatory state [**12**].

Most of the studies measuring plasmatic sRAGE did not differentiate esRAGE from sRAGE which may account for controversial results. In addition the ethnic variation of sRAGE level should be considered before concluding of the significance of low plasmatic sRAGE as a risk factor. Normal levels according to age, sex, geographical origin should be defined accurately. When these conditions will be fulfilled sRAGE may be considered as a reliable biological marker.

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