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RAGE, vascular tone and vascular disease

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ABSTRACT

Evidence provided by both clinical and pre-clinical studies regarding a central involvement of the receptor for advanced glycation endproducts (RAGE) in vascular disease continues to mount. RAGE is upregulated as a consequence of activation of the ubiquitous pro-inflammatory transcription factor NF-κB which is activated in response to diverse inflammatory stimuli including hyperglycaemia, oxidised low density lipoprotein (oxLDL) and reduced shear stress. RAGE may maintain and amplify inflammatory responses in the vasculature if ligand for the receptor is present. RAGE binding by circulating advanced glycation endproducts (AGEs) or S100 protein released by activated leukocytes results in the generation of reactive oxygen species (ROS) and further activation of NF-κB. This leads to upregulation of adhesion molecules for circulating monocytes as well as further upregulation of RAGE itself. In addition, these ROS may scavenge and reduce bioavailability of the labile vasodilator nitric oxide (NO), reducing its anti-inflammatory effects and possibly compromising control of vascular tone directly. In addition to atherosclerosis and vascular diseases associated with diabetes, recent data from studies in transgenic mice overexpressing the RAGE ligand S100A4/MTS1 suggest a role for RAGE in the pathogenesis of pulmonary arterial hypertension (PAH). RAGE antagonism also prevents proliferation and migration of pulmonary arterial smooth muscle cells in response to 5-HT, suggesting that S100–RAGE signalling may be of key importance in pulmonary vascular homeostasis and/or disease. Further study of the role of RAGE in inflammation seems likely to yield, not only promising therapeutics but key insights into the pathophysiology of vascular disease as well.

Contents

1. Introduction

The receptor for advanced glycation endproducts (RAGE) is a 35 kDa polypeptide of the immunogloblin superfamily (Neeper et al., 1992) that has recently been widely implicated as a mediator of both acute and chronic vascular inflammation in conditions such as atherosclerosis and in particular as a complication of diabetes (Schmidt et al., 1994; Hudson et al., 2003; Ramasamy et al., 2005; Basta, 2008). As shall be discussed, activation of RAGE may alter the response of vessels to mediators of tone by contributing to the phenotypical changes and remodelling associated with vascular disease and possibly due to altered bioavailability of the labile vasodilator nitric oxide (NO).

An early study demonstrated that RAGE is basally expressed in both smooth muscle and endothelial cells of the bovine systemic vasculature and in neurones innervating them in both large vessels (e.g. aorta) and the microvasculature (Brett et al., 1993). In the human peripheral vasculature, endothelial expression of RAGE is typically

Abbreviations: 5-HT, 5-hydroxytryptamine; AGEs, Advanced glycation endproducts; ApoE, Apolipoprotein E; DN-RAGE, Dominant-negative RAGE; NF-κB, Nuclear factor-κB; NO, Nitric oxide; NOS, Nitric oxide synthase; PAH, Pulmonary arterial hypertension; PRR, Pattern recognition receptor; PVD, Pulmonary vascular disease; RAGE, Receptor for advanced glycation endproducts; RVH, Right ventricular hypertrophy; SERT, Serotonin transporter; SMCs, Smooth muscle cells; sRAGE, Soluble RAGE; TLR, Toll-like receptor.

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diffuse and variable but is enhanced by risk factors for vascular disease such as hyperlipidaemia and in patients with symptomatic occlusive vascular disease. RAGE has also been found in early and end stage atherosclerotic lesions in the endothelium of human coronary artery (Ritthaler et al., 1995). Interestingly, this upregulation in disease states occurs in both the presence and the absence of hyperglycaemia associated with diabetes though both the severity of vascular perturbation and RAGE expression are enhanced by diabetes (Burke et al., 2004). These findings are corroborated by an observed upregulation of RAGE in the systemic vasculature of mice used as models of vascular inflammation in both euglycaemia and hyperglycaemia (Park et al., 1998; Kislinger et al., 2001; Bucciarelli et al., 2002; Harja et al., 2008).

In the course of this review, those properties of RAGE and its ligands that are relevant to vascular disease will be described and discussed in greater detail with emphasis on the immediate and chronic consequences of RAGE stimulation in the vasculature. Particular reference will be made to the role of RAGE in modulating vascular tone in atherosclerosis, diabetes and pulmonary hypertension, the latter being another disease involving chronic vascular inflammation. Promising drug targets will be explored as will the use of animal models contributing to current knowledge of RAGE.

2. Characteristics of receptor for advanced glycation endproducts

RAGE is able to bind a variety of structurally diverse ligands and sites of RAGE upregulation tend to show colocalisation with molecules thought to bind and activate the receptor. These include advanced glycation endproducts (AGEs), S100/calgranulin proteins, high mobility box group protein 1(HMGB1) and oxidised low density lipoprotein (oxLDL) (Hofmann et al., 1999; Basta et al., 2002; Harja et al., 2008; Sun et al., 2009). These sites also tend to display other markers of inflammation such as adhesion molecules for circulating inflammatory leukocytes (e.g. VCAM-1, ICAM-1 and E-selectin), matrix metalloproteinases (MMPs) and cyclooxygenase-2 (COX-2,) (Palinski et al., 1995; Basta et al., 2002; Harja et al., 2008). In addition to causing upregulation of adhesion molecules, RAGE is a counter-receptor for integrins on the surface of circulating leukocytes, specifically the β2-integrin macrophage-1 (Mac-1) (Chavakis et al., 2003), and participates directly in firm adhesion of leukocytes to the endothelium. A general summary of the primary RAGE ligands may be found in Table 1.

The ability of RAGE to recognise such a varied selection of ligands has led to the hypothesis that it is a pattern-recognition receptor (PRR) (Li et al., 2006). PRRs, such as the toll-like receptors (TLRs), are involved in innate immunity and depend upon recognition of three-dimensional structures rather than peptide sequences (Medzhitov & Janeway, 1997).

One of the best documented consequences of RAGE activation is the generation of reactive oxygen species (ROS) (Yan et al., 1994; Basta et al., 2002; Vincent et al., 2007). Increased ROS is also associated with formation of AGEs (Mullarkey et al., 1990) and formation of oxLDL (Steinbrecher et al., 1984). Thus, at sites of vascular inflammation there would be an expectation of increased ROS formation which would be enhanced further by activation of RAGE. ROS such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2) have direct effects on vascular tone (Rubanyi, 1988). In addition, O_2^- is able to react with NO to form peroxynitrite ($ONOO^-$); a reactive nitrogen species (RNS) and a vasodilator (Li et al., 2005; Szasz et al., 2007). $ONOO^-$ oxidises tetrahydrobiopterin (BH_4), an essential cofactor for the production of NO by nitric oxide synthase (NOS). This leads to the uncoupling of, and further generation of superoxide by NOS (Forstermann, 2006).

RAGE activation, in having the potential to produce ROS and RNS by a variety of mechanisms, may have immediate deleterious effects in the vasculature associated with the onset of inflammation, including alterations in vascular tone (Fig. 1).

RAGE binding also results in the activation and translocation of proinflammatory kinases and transcription factors including p21 ras, extracellular signal-related (ERK) and c-Jun N-terminal (JNK) mitogen-activated protein (MAP) kinases, and the ubiquitous proinflammatory transcription factor Nuclear Factor-κB (NF-κB) (Lander et al., 1997; Hofmann et al., 1999). Experimentally, this activation is prevented by the presence of ROS scavengers or dismutases and enhanced by glutathione depletion, though there is some evidence of a ROS independent component (Lander et al., 1997; Basta et al., 2005). NF-κB-DNA binding is associated with the expression of an altered cellular phenotype including the expression of adhesion molecules for circulating inflammatory cells such as VCAM-1 and ICAM-1 (Voraberger et al., 1991; Schmidt et al., 1995; Neish et al., 1992). Increased NF-κB activity has been

Table 1
Summary of the primary ligands of RAGE and their roles in the inflammatory process.

RAGE ligand	Location	Implicated inflammatory role	Ref.
AGEs	Serum Long-lived matrix protein Atherosclerotic plaques	Elevated in hyperglycaemia and in response to oxidative stress Activates RAGE Induces leukocyte chemotaxis (soluble AGEs) Dimerises with RAGE leading to enhanced biding to endothelial counterreceptors Directly scavenge NO	(Brownlee et al., 1984; Bucala et al., 1991; Schmidt et al., 1992; Vlassara et al., 1992; Schmidt et al., 1993; Palinski et al., 1995; Toure et al., 2008)
S100	Vascular SMCs Vascular ECs Activated leukocytes	Activates RAGE Secreted by activated leukocytes (S100A8/A9, S100A12) Augments interaction between the leukocyte Mac-1 and endothelial RAGE (S100B) Monocyte chemotaxis Evokes proliferatory/migratory responses in pulmonary SMCs	(Rammes et al., 1997; Hofmann et al., 1999; Yang et al., 2001; Chavakis et al., 2003; Lawrie et al., 2005; Heizmann et al., 2007)
HGMB-1	Vascular SMCs Vascular ECs Vascular macrophages	Activates RAGE and TLRs Causes neutrophil and SMC migration Upregulated by cytokine exposure Secreted by necrotic cells Causes cytokine secretion from endothelial, smooth muscle and immune cells Causes dimerisation of leukocyte RAGE and Mac-1 protein increasing affinity for endothelial ICAM-1	(Hori et al., 1995; Kalinina et al., 2004; Park et al., 2004; Li et al., 2006; Orlova et al., 2007)
Mac-1	Circulating leukocytes	Recognises and binds endothelial RAGE inducing firm adhesion Dimerises with RAGE leading to enhanced biding to endothelial counterreceptors	(Carlos & Harlan, 1994; Chavakis et al., 2003; Orlova et al., 2007)
oxLDL	Serum Atherosclerotic plaques	Elevated in hyperlipidaemia + hyperglycaemia Possesses AGE epitopes Activates LOX-1 receptor and RAGE	(Palinski et al., 1995; Imanaga et al., 2000; Harja et al., 2008; Sun et al., 2009)