The Emerging Role of RAGE in Sepsis

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Introduction

Sepsis and septic shock are the leading causes of death in intensive care units (ICUs) in developed countries despite recent advances in critical care medicine. Sepsis is the systemic inflammatory response to infection frequently associated with hypoperfusion followed by tissue injury and organ failure. Activation of monocytes/macrophages and neutrophils with consecutive release of proinflammatory mediators and activation of the coagulation cascade seem to play key roles in the pathogenesis of sepsis. This process is characterized by the massive release of proinflammatory mediators, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1/β, macrophage migration inhibitory factor (MIF), and high mobility group box-1 (HMGB-1) protein. In addition, neutrophil apoptosis is significantly delayed by these inflammatory mediators.

Promising new experimental treatment options are interference with MIF, HMGB-1, C5a or triggering receptor expressed on myeloid cells (TREM)-1 signal transduction pathways, and inhibition of apoptosis, which may improve prognosis of septic patients in the future. In addition, recent data suggest that the inflammation perpetuating receptor, RAGE (receptor for advanced glycation end-products) is critically involved in the immune response in sepsis. Furthermore, targeting RAGE signaling pathways is a potential new target for sepsis treatment [1, 2].

Receptor for Advanced Glycation End-products

RAGE is – like TREM-1 – a member of the immunoglobulin superfamily and was first identified in lung tissue, where it is located on the basolateral membranes of alveolar epithelial cells [3, 4]. The molecule is named RAGE because it was originally described as a receptor for advanced glycation end products (AGEs) [5]. AGEs are products of nonenzymatic glycation and oxidation of proteins, lipids and other macromolecules that appear especially in conditions with increased availability of reducing sugars and/or enhanced oxidative stress, particularly when molecules turnover slowly and aldoses are elevated [6].

RAGE expression is both constitutive and inducible depending on cell type and developmental stage. While RAGE is constitutively expressed during embryonal development, its expression is downregulated in adult life. Known exceptions are skin and lung, which constitutively express RAGE throughout life. Most of the other cells studied so far including monocytes/macrophages, endothelial cells, smooth muscle cells, fibroblasts, and neuronal cells do not express significant amounts of RAGE under
physiological conditions, but these cells can be induced to express RAGE in situations where inflammatory mediators and ligands accumulate [7, 8]. The activation of RAGE leads to the initiation of nuclear factor-kappa B (NF-κB) [9] and mitogen-activated protein kinase (MAPK) pathways [10]. In contrast to other receptors, RAGE-mediated cellular stimulation includes an increased expression of the receptor itself. This positive feedback loop, characterized by a ligand-receptor interaction followed by increased expression of the receptor itself, suggested the role of RAGE as a propagation and perpetuation factor and leads to the two-hit model of RAGE engagement [6].

## Localization and Structure of RAGE

The gene for RAGE is located on chromosome 6 near the major histocompatibility complex (MHC) III in humans and mice, in the proximity of genes encoding TNF, lymphotoxin and the homebox gene, HOX12 [11]. The extracellular domain of RAGE consists of one V-Type immunoglobulin domain followed by two C-type immunoglobulin domains. The V-Type domain, in particular, interacts with the potential extracellular ligands [12]. The C- and C'-domains probably have important roles in stabilizing the V-domain while docking with its ligands. The rest of the molecule is a single transmembrane spanning domain completed by a 43 amino acid highly charged cytosolic tail. This cytosolic tail lacks known signaling motifs such as phosphorylation sites, kinase domains, etc. Hofmann et al. [13] showed that the cytosolic tail is essential for signal transduction of RAGE, because a truncated form of RAGE with a deleted cytosolic tail is able to bind ligands as well as the wild-type receptor but does not mediate any cellular activation. In the rat lung, extracellular signal-regulated protein kinase-1 and -2 (ERK-1/2) were identified to bind directly to RAGE suggesting that ERK may play a role in RAGE signaling through interaction with RAGE [14]. The existence of truncated RAGE isoforms from the same gene implies that the pre-mRNA of RAGE in humans can be subjected to alternative splicing. In contrast, in mice these truncated isoforms seem to be produced by carboxyl-terminal truncation [6].

RAGE is expressed in normal tissues at low levels, aside from the lung and the skin, where RAGE is constitutively expressed. Although little is known about the physiological role of RAGE, it is possible that RAGE may fit the concept of pleiotropic antagonism [15]. This concept of an evolutionary basis for the development of age-related diseases postulates that genes that are beneficial during the reproductive phase of life may become deleterious. Interest initially focused mainly on the role of RAGE in chronic diseases. In particular, RAGE is upregulated in several chronic inflammatory settings, like rheumatoid arthritis, inflammatory kidney disease, arteriosclerosis, inflammatory bowel disease, and others [6, 13].

## RAGE Interactions with its Ligands in Acute Inflammation and Sepsis

RAGE is a multi-ligand receptor that interacts with different structures to path a signal into the cell and recognizes three-dimensional structures rather than specific amino acid sequences. Therefore, RAGE fulfills the requirements of a pattern recognition receptor (PRR). As a member of the Ig superfamily it interacts with a diverse class of ligands, including AGEs, S100/calgranulins, HMGB-1, amyloid β-peptide, amyloid A, leukocytes, prions, *Escherichia coli* curli operons, and β-sheet fibrils [6, 16].