RAGE-mediated inflammation, type 2 diabetes, and diabetic vascular complication

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Obesity is associated with inflammation and type 2 diabetes. Innate immune system comprised of cellular and molecular components plays an important role in the inflammatory reactions. Immune cells like macrophages and their cell surface pattern-recognition receptors (PRRs) are representative for innate immunity promoting inflammatory reactions. The receptor for advanced glycation end-products (RAGE) is a member of PRRs and a proinflammatory molecular device that mediates danger signals to the body. The expression of RAGE is observed in adipocytes as well as immune cells, endothelial cells, and pancreatic β cells under certain conditions. It has been reported that RAGE is implicated in adipocyte hypertrophy and insulin resistance. RAGE-mediated regulation of adiposity and inflammation may attribute to type 2 diabetes and diabetic vascular complications.

Keywords: rage, obesity, inflammation, toll-like receptors, pattern-recognition receptors
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RAGE, inflammation, and obesity

AGE-modified S100A8/A9 have been reported to strongly activate inflammatory responses via RAGE (16). S100A8/A9 was also shown to interact with TLR4 (17). Our groups have also shown that phosphatidylserine on the surface of apoptotic cells and LPS are also RAGE ligands (18, 19). Rapid removal of apoptotic cells by phagocytes is crucial for tissue development, homeostasis, resolution of inflammation, and prevention of autoimmune responses. RAGE was found to function as one of the PS receptors that recognize and initiate apoptotic cell clearance (18). LPS and the lipid A component responsible for LPS toxicity and known as endotoxin were found to directly interact with RAGE (19). LPS is also a well-known TLR ligand.

RAGE AND ADIPOSITY

Using RAGE and apoE double deficient mice, Ueno et al. demonstrated that absence of RAGE is associated with decreased epididymal fat weight and smaller adipocyte size, which are significantly associated with the decrease in atherosclerotic lesions (20). They also reported that circulating anti-inflammatory adiponectin levels in apoE−/−RAGE−/− were higher than apoE−/−RAGE+/+ mice, and their levels were significantly and inversely associated with aortic atherosclerosis. Very recently, Monden et al. demonstrated that RAGE directly regulated adipogenesis and hypertrophic process of adipocyte differentiation in vitro (21). Adenoviral overexpression of RAGE markedly increased generation of hypertrophic adipocytes and RAGE knockdown by using siRNA system significantly suppressed generation of hypertrophic adipocytes. Under high fat diet feeding in mice, RAGE deficiency is associated with less body weight, less epididymal fat weight, less adipocyte size, higher serum adiponectin, higher expressions of Glut4 and adiponectin in epididymal fat, and greater insulin sensitivity. It is now acceptable that direct role of RAGE in adipocyte hypertrophy and insulin resistance (Figure 1). However, RAGE ligands are still unknown to be involved in the RAGE-dependent adiposity. Further studies are required to characterize the interplays among a variety of RAGE ligands and inflammatory reactions in obesity and type 2 diabetes.

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RAGE POLYMORPHISMS, OBESITY, AND INFLAMMATION

Several functional single nucleotide polymorphisms have been identified in human RAGE gene. The G82S occurs in the ligand-binding V domain of RAGE and affects ligand affinity, resulting in the enhancement of proinflammatory reactions and immune/inflammatory diseases (22, 23). In obese subjects, S/S carriers showed significantly higher concentrations of AGE and C reactive protein than G allele carrier and lower concentration of soluble RAGE, a decoy receptor (24). S allele at RAGE G82S polymorphism may be more closely associated with proinflammatory reactions under obese conditions rather than non-obese status, thus linking to the development of obesity-associated complications. We very recently reported that the induction of RAGE expression in pancreatic β-cell by insufficient leptin action under obesity conditions could trigger β-cell failure in type 2 diabetes (25). It is thus considered that RAGE could be a potential targeting receptor for the prevention and treatment of the development of obesity, β-cell failure, vascular complications, and inflammation in type 2 diabetes (Figure 1).

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