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Review

AGE-RAGE axis blockade in diabetic nephropathy: Current status and future directions

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ABSTRACT

Diabetic nephropathy is one of the most frequent micro-vascular complications both in type 1 and type 2 diabetic patients and is the leading cause of end-stage renal disease worldwide. Although disparate mechanisms give rise to the development of diabetic nephropathy, prevailing evidence accentuates that hyperglycemia-associated generation of advanced glycation end products (AGEs) plays a central role in the disease pathophysiology. Engagement of the receptor for AGE (RAGE) with its ligands provokes oxidative stress and chronic inflammation in renal tissues, ending up with losses in kidney function. Moreover, RAGE activation evokes the activation of different intracellular signaling pathways like PI3K/Akt, MAPK/ERK, and NF-κB; and therefore, its blockade seems to be an attractive therapeutic target in these group of patients. By recognizing the contribution of AGE-RAGE axis to the pathogenesis of diabetic nephropathy, agents that block AGEs formation have been at the heart of investigations for several years, yielding encouraging improvements in experimental models of diabetic nephropathy. Even so, recent studies have evaluated the effects of specific RAGE inhibition with FPS-ZM1 and RAGE-aptamers as novel therapeutic strategies. Despite all these promising outcomes in experimental models of diabetic nephropathy, no thorough clinical trial have ever examined the end results of AGE-RAGE axis blockade in patients of diabetic nephropathy. As most of the AGE lowering or RAGE inhibiting compounds have emerged to be non-toxic, devising novel clinical trials appears to be inevitable. Here, the current potential treatment options for diabetic nephropathy by AGE-RAGE inhibitory modalities have been reviewed.

1. Background

Diabetic nephropathy is identified as the leading cause of end-stage renal disease (ESRD) across the world, imposing heavy health care costs associated with dialysis and transplantation. A considerable proportion (20–40%) of all diabetic patients including type 1 and type 2 develop diabetic nephropathy in their disease course (Gheith et al., 2016; Narres et al., 2016); Indeed, the incidence of diabetes related ESRD continues to expand (Burrows et al., 2017). Pathologically, diabetic nephropathy is reflected by the glomerular basement membrane thickening, glomerular mesangial matrix expansion, glomerular nodular sclerosis (Kimmelstiel-Wilson lesion) which culminate in overt glomerulosclerosis in the advanced stages (Qi et al., 2017). From a clinical perspective, diabetic nephropathy is chiefly manifested by increased urinary albumin excretions and progressive deteriorations in renal function as reflected by reduced glomerular filtration rate; both signs indicating relentless kidney damage. Moreover, hypertension is almost an indispensable feature of diabetic nephropathy (Ritz et al., 2011; Van Buren and Toto, 2011). Currently, strict glycemic and blood pressure control constitute the mainstay of management for diabetic nephropathy; however, a significant proportion of diabetic patients still progress to ESRD, eventually requiring dialysis which underlines the urgent demand for developing novel management or treatment strategies (Ahmad, 2015).

2. AGE

The first report regarding non-enzymatic reaction between reducing sugars and proteins dates back to 1912 by Maillard, during which process brown-colored substances were produced (Newton, 2011). This interaction starts with chemical binding of the carbonyl groups to the amino groups on proteins, generating Schiff bases and later Amadori compounds. Then, these substances are condensed and cross-linked to form the melanoidin (Yamamoto et al., 2007). However, it lasted until 1981 to document that Maillard reaction happens inside human bodies and these terminal organic substances were designated as “AGE”

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(Monnier and Cerami, 1981). The generation and build-up of AGE is highly facilitated under diabetic states as glucose provides the main source of carbonyl groups for glycation reactions. Additionally, the principal AGEs in vivo include pyrraline, N-carboxymethyl lysine (CML), methylglyoxal/glyoxal lysine amide, and pentosidine (Saremi et al., 2017).

The most salient mechanisms that give rise to the elimination of AGEs include proteolysis outside the cells and receptor mediated uptake followed by intracellular degradation. Macrophages and Kupffer cells actively participate in AGEs endocytosis, generating low molecular weight soluble peptides that are excreted into the urine by the kidneys (Stirban et al., 2014).

Stable AGE-protein crosslinks, however, can be formed and accumulated in the tissue as they are very resistant to the proteolytic degradation (Thomas et al., 2005). Therefore, in addition to receptor-mediated mechanisms, AGEs confer their effects via directly changing the proteins' structure and perturbing their cellular function (Coughlan et al., 2007). Moreover, formation of AGE-related crosslinks on the proteins not only facilitate their tissue accumulation, but also disrupt matrix-matrix and matrix-cell interactions extracellulary leading to impairments in organ function (Kranstuber et al., 2012).

Methylglyoxal is a glucose-derived compound that contributes to the formation of AGEs by modulating proteins (Karachalias et al., 2003). This prevailing compound in diabetic tissues is metabolized by the glyoxalase 1, a rate-limiting enzyme that is highly expressed under hyperglycemic states (Rabbani and Thornalley, 2017). The striking role of glyoxalase 1 was detailed when glyoxalase 1 knockout mice exhibited signs of diabetic nephropathy after a 6 month period; instead, mice overexpressing this enzyme were guarded against detrimental consequences of hyperglycemia, displaying minimal renal alterations in comparison with their wild-type counterparts (Giacco et al., 2014).

3. RAGE

First characterized in 1992, the receptor for advanced glycation end products, a multi-ligand transmembrane receptor, belongs to the superfamily of immunoglobulins with principal roles in chronic inflammatory responses as well as immune functions (Mulrennan et al., 2015; Neeper et al., 1992). High-mobility group protein (B)1 (HMGB1), S-100 calcium-binding protein, amyloid-β-protein, Mac-1, and phosphatidylserine along with AGEs are among the most recognized ligands of RAGE (Lee and Park, 2013). Although this membrane receptor has a relatively wide tissue distribution; it is expressed mainly on the vascular and neural tissues (Brett et al., 1993). Almost all cell types in the kidneys express RAGE –from endothelial and mesangial cells to podocytes and tubular epithelial cells; it has, however, been claimed that RAGE is expressed more on the podocytes rather than the endothelial and mesangial cells of the glomeruli (Tang et al., 2011; Wendt et al., 2003).

4. RAGE and diabetic kidney disease

Highly abundant AGEs in diabetic milieu of the kidneys up-regulate RAGE expression (Tanji et al., 2000). RAGE activation by AGEs leads to the generation of reactive oxygen species (ROS) and amplifies inflammation so that aids in the establishment of chronic inflammatory state in the kidneys culminating in gradual loss of kidney architecture and function (Ramasamy et al., 2005). In addition to reducing antioxidant enzymes and cellular glutathione levels, RAGE activation results in the up-regulation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), nitric oxide synthase (NOS), and cyclooxygenase (COX); the events that exacerbate and intensify the inflammation (Kim et al., 2010). Indeed, it has been shown that AGE mediated RAGE activation on cultured murine podocytes creates endoplasmic reticulum (ER) stress as well as elevation of intracellular calcium levels and thereby gives rise to the increased apoptosis rates (Chen et al., 2008). More importantly, RAGE-deficient diabetic mice

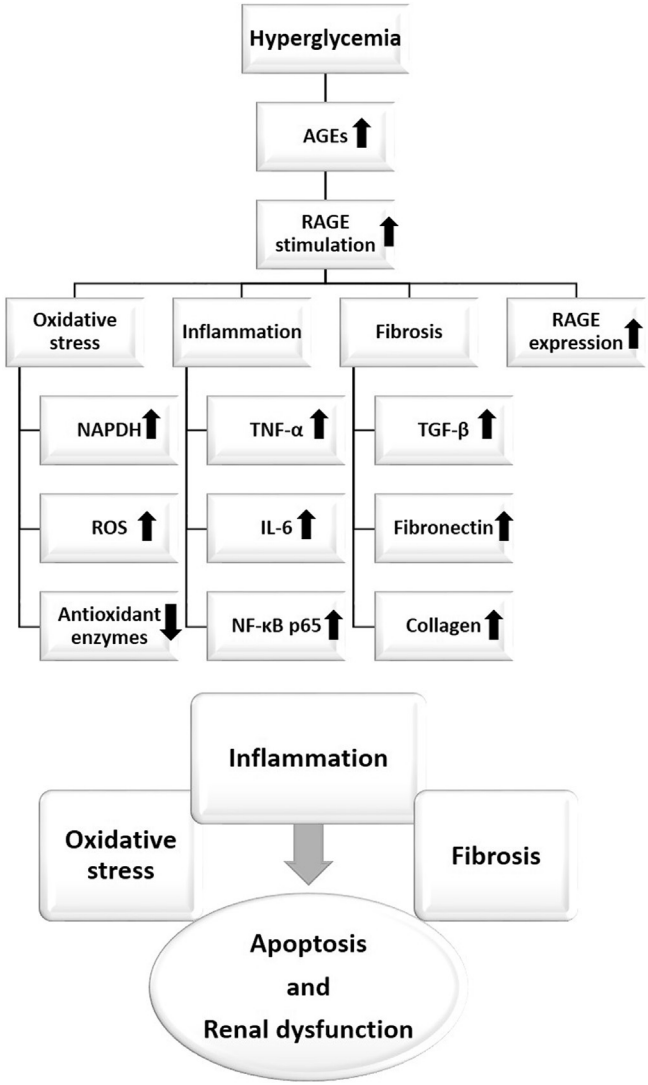

Fig. 1. Event highlights in AGE-RAGE axis activation in the time of diabetic nephropathy. Sustained hyperglycemia due to diabetes facilitates increased productions of AGEs that stimulate their cell surface receptors, RAGEs. Intensified triad of oxidative stress (increased activities of NADPH and ROS levels as well as reduced antioxidant enzymes activities), inflammation (increased activities of the central proinflammatory pathway, NF-κB with resultant elevations in proinflammatory cytokines line TNF-α and IL-6), and fibrosis (increased production of profibrotic cytokine, TGF-β; and extracellular fibrotic fibers, fibronectin and collagen) leads to renal architectural and functional perturbations in diabetics. AGEs, advanced glycation end products; RAGEs, receptors for advanced glycation end products; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; IL-6 interleukin-6; TGF-β, transforming growth factor-beta.

demonstrate delayed development of diabetic kidney disease, express less inflammatory and fibrotic mediators in renal tissues, and become more resistant against renal cell apoptosis as compared to the wild-type animals; the finding that highlights the salient contributory role of AGE-RAGE axis in the pathogenesis of diabetic nephropathy (Hagiwara et al., 2018; Myint et al., 2006). Additionally, RAGE activation on glomerular podocytes promotes the secretion of heparanase. Heparin sulfate is an integral part of glomerular basement membrane (GBM), degradation of which by heparanase disintegrates the filtration barrier (An et al., 2017). RAGE overexpressing mice, conversely, develop more severe forms of nephropathy after induction of diabetes (Yamamoto et al., 2001).