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Editorial

Advanced Glycation End Products (AGEs) and Cardiorenal Disorders

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A non-enzymatic reaction between ketones or aldehydes and the amino groups of proteins, lipids and nucleic acids contributes to the aging of macromolecules [1,2]. This process begins with the conversion of reversible Schiff base adducts, and then to more stable, covalently-bound Amadori rearrangement products [1,2]. Over a course of days to weeks, these early glycation products undergo further reactions and rearrangements to become irreversibly crossed-linked, fluorescent protein derivatives termed advanced glycation end products (AGEs) [1,2]. Under hyperglycemic or oxidative stress conditions such as diabetes, formation and accumulation of AGEs have been known to progress at an accelerated rate [1,2]. There is a growing body of evidence that AGEs play a role in the pathogenesis of chronic kidney disease (CKD) and cardiovascular disease (CVD) [3-7]. In this short communication, I briefly review the pathological role of AGEs in cardiorenal disorders and its therapeutic intervention by DNA aptamer.

AGEs and CVD

Arterial stiffness is associated with the prevalence of CVD and could predict future cardiovascular events in healthy subjects or patients with CVD [8]. Quantitative and qualitative alterations of collagen and elastin fibers by AGE modification contribute to decreased elastic properties of the vessels, thereby being involved in arterial stiffness [9].

Engagement of receptor for AGEs (RAGE) with the ligand, AGEs elicits oxidative stress generation via NADPH oxidase and subsequently activates the redox-sensitive transcription factor NF-kB, which could promote inflammatory, proliferative, and thrombogenic reactions in vessels, contributing to accelerated atherosclerosis [3-6].

Bone marrow-derived circulating endothelial progenitor cells (EPCs) are critical to vascular repair [10]. Diabetes is associated with endothelial dysfunction, decreased EPC function and mobilization, which could accelerate atherosclerosis and increase the risk for CVD in diabetic patients [10]. The AGE-RAGE interaction has impaired vascular repair not only by inducing apoptotic cell death of EPCs, but also by inhibiting the EPC adhesion, spreading and migration [9]. Serum levels of AGEs are inversely associated with the number and migratory activity of circulating EPCs in apparently healthy subjects, further supporting the clinical relevance of AGEs in impaired endothelial cell repair [11].

Vascular calcification is a common problem among the elderly and the patients with diabetes and CKD, and might be associated with increased morbidity and mortality of CVD [12,13]. We have previously shown that AGEs or RAGE activation induces osteoblastic differentiation of microvascular pericytes or aortic smooth muscle cells, respectively, which would play a role in atherosclerotic plaque calcification in diabetes and CKD.

HDL and its major protein constituent, apolipoprotein AI, promote reverse cholesterol transport, thereby preventing foam cell formation in atherosclerotic lesions by stimulating cholesterol efflux from macrophages [14]. AGEs have been shown to decrease mRNA levels of adenosine triphosphate-binding membrane cassette transporter A1 (ABCA1) and ABCG1 in THP-1 cells, crucial factors in macrophage cholesterol efflux and reverse cholesterol transport, thus implicated in accelerated atherosclerosis in diabetes [14]. Further, we have recently found that AGE-RAGE interaction significantly reduces gene expression of silent mating type information regulator 2 homolog 1 (SIRT1) in THP-1 macrophages, a highly conserved NAD^+-dependent protein deacetylase, which could play a protective role against CVD [15]. Given that monocytic SIRT1 expression is decreased in patients with stable coronary artery disease and acute coronary syndromes compared with healthy subjects [16], the pathological crosstalk between AGEs and anti-aging molecules, SIRT could contribute to the development and progression of atherosclerotic CVD as well.

AGEs and CKD

Diabetic nephropathy is a leading cause of end-stage renal disease, and accounts for disabilities and the high mortality rates in patients with diabetes [7]. Diabetic nephropathy is characterized by functional and structural changes in the glomerulus, such as glomerular hyperfiltration, thickening of glomerular basement membranes and an expansion of extracellular matrix in mesangial areas [7]. It ultimately progresses to glomerular sclerosis, which is associated with increased albumin excretion and renal dysfunction.

Interaction of AGEs with RAGE has evoked inflammatory reactions, thereby causing progressive alteration in renal architecture and loss of renal function in diabetes [17-19]. RAGE-overexpressing diabetic mice have shown progressive glomerulosclerosis with renal dysfunction, compared with diabetic littermates lacking the RAGE transgene [17]. Diabetic homozygous RAGE null mice failed to develop significantly increased mesangial matrix expansion or thickening of the glomerular basement membrane [18]. Moreover,

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deletion of RAGE prevented diabetic nephropathy in the OVE26 type 1 mouse, a model of progressive glomerulosclerosis and decline of renal function [19].

DNA aptamer directed against AGEs (AGE-aptamer)

Aptamers are short, single-stranded DNA or RNA molecules that can bind with high affinity and specificity to a wide range of target proteins [20]. Numerous aptamers have been developed and used in the clinical fields as a tool for modulating the function of various proteins [21].

We have found that high-affinity AGE-aptamer inhibits glomerular hypertrophy and extracellular matrix protein accumulation, decreases urinary excretion levels of albumin, and prevents renal dysfunction in type 2 diabetic animals [22]. In this study, AGE-aptamer directly bound to AGEs and resultantly blocked the binding of AGEs to RAGE, and continuous infusion of AGEs-aptamer dramatically decreased AGE levels in the glomeruli of diabetic mice [22]. So, it is conceivable that AGE-aptamer might decrease the glomerular accumulation of AGEs via the blockade of RAGE-induced, oxidative stress-mediated AGE formation in the kidney. In addition, since turnover rate of aptamer-bound AGEs by THP-1 macrophages was increased, AGE-aptamer could enhance the elimination of AGEs from the body through the increased turnover by macrophages.

We have very recently found that AGE-aptamer not only inhibits neointima formation after balloon angioplasty, but also reduces the expression levels of AGEs, RAGE and an oxidative stress marker, 8-hydroxy-2'-deoxyguanosine in balloon-injured arteries [23]. Further, compared with control-aptamer, AGE-aptamer significantly suppressed smooth muscle cell proliferation, macrophage infiltration, and platelet-derived growth factor-BB (PDGF-BB) expression in balloon-injured carotid arteries [23]. These findings suggests that AGE-aptamer might prevent balloon injury-induced neointimal hyperplasia by reducing PDGF-BB and macrophage infiltration via suppression of the AGE-RAGE-mediated oxidative stress generation. Taken together, the observations suggest that blockade of the AGE-RAGE axis by AGE-aptamer might be a novel therapeutic target for preventing CVD and CKD in diabetes.

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