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EDITORIAL

Albumin turns on a vicious spiral of oxidative stress in renal proximal tubules

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Albumin, the major component of proteinuria, is well recognized as a marker of renal diseases, particularly glomerular diseases. It is also known that the microalbuminuria, which reflects the endothelial disorder, predicts prognosis of the cardiovascular diseases. However, the albuminuria is not merely a sign of glomerular disease, but it causes proximal tubular cell injury.

Albumin uptake activates various signal transduction cascades in proximal tubule cells (Fig. 1). The activation of the intracellular signaling can be initiated by albumin endocytosis. In this process, activation of PI3 kinase may play important role in membrane traffic [1, 2]. It is less clear how the lysosome compartment holding albumin activates NADPH oxidase. However, activation of protein kinase C is implicated [3, 4]. Activated PKC, by which p47phox and p67phox, components of NAPDH oxidase, localized in cytosole as inactive forms, are translocated to membrane [5], activates NADPH oxidase and generates superoxide (O_2^-).

Akt-dependent p47phox activation in NADPH oxidase is also reported in leukocytes [6]. NADPH oxidase is abundantly localized in proximal convoluted tubule cells in kidney [7]. Superoxide is converted to hydrogen peroxide (H_2O_2) by SOD. H_2O_2 induces variety of intracellular signaling, such as MAP kinases (ERK1/ERK2, JNK, p38), PI3 kinase, AKT, JAK-STAT, AP-1, and NF-κB.

MAP kinase plays a critical role in determination of cell growth and death. H_2O_2 activates apoptosis signal-regulating kinase 1 (ASK1) by enhancing dimerization [8]. ASK1 promotes p38 and JNK phosphorylation. p38 activation, in particular, leads to apoptosis by activating caspases. Meanwhile, it is reported that H_2O_2 activates PI3K and Akt, which inhibits ASK1 activity in human embryonic kidney 293 cells [9]. Both signals are transduced in the cell in response to ROS; however, the net impact to determine the cell survival and death seems to depend on the strength of oxidative stress.

Key words: oxidative stress, glia maturation factor, angiotensin II, hydrogen peroxide, proximal tubule, proteinuria.

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In protein overload model mouse, glia maturation factor-B (GMF-B) is induced in three weeks in proximal tubule cells, which may turn on the vicious cycle for ROS generation in proximal tubule [10]. GMF-B, a 17-kD intracellular protein, regulates the life/death signaling by activating p38 [11]. Kaimori et al [10] found that the overexpression of GMF-B causes augumented reorganization of F-actin, as well as vulnerability to oxidative stress, making cells more susceptible to apoptosis under oxidative stress. The reason for the susceptibility to cell death is that the H_2O_2 stimulation persists in GMF-B overexpressing cells, in which H_2O_2-generation enzyme, CuZn-SOD, is up-regulated, and the H_2O_2-reducing enzymes, glutathione peroxidase and catalase are down-regulated [10]. Recently, this phenomenon has been reconfirmed by astrocytes from GMF-B null mouse, which is resistant to death by H_2O_2 stimulation by decreasing CuZn-SOD [12].

Other major downstream signaling molecules from H_2O_2 stimulation are inflammation-related signaling molecules, such as NF-κB [3, 4] and JAK-STAT [13]. Numerous reports showed that albumin induced variety of effecter molecules through NF-κB, including MCP-1, RANTES, IL-8, PDGF, TGF-β, endothelin, and fractalkine [3, 4, 14]. IFN-γ–inducible genes, including interferon regulatory factor-1, MHC-I, MHC-II, and MCP-1 are up-regulated in albumin-overloaded proximal tubule without direct activation by IFN-γ [15]. Nakajima et al [13] revealed that the H_2O_2 generation by albumin uptake causes Jak2 activation and subsequent Stat1 and Stat5 phosphorylation in proximal tubular cells in culture. Overall, the net results of exposure of proximal tubule cells to albumin results in production of cocktail of cytokines and growth factors, which act in autocrine and paracrine manner.

In this issue of *Kidney International*, Wolf et al [16] have added new information to the complex albumin signaling cascade in proximal tubule. They demonstrated that the proximal tubule cells up-regulated TGF-β type II receptor by albumin. The promoter of the TGF-β type II receptor is regulated by AP1, which is induced by H_2O_2 stimulation. However, this induction was completely

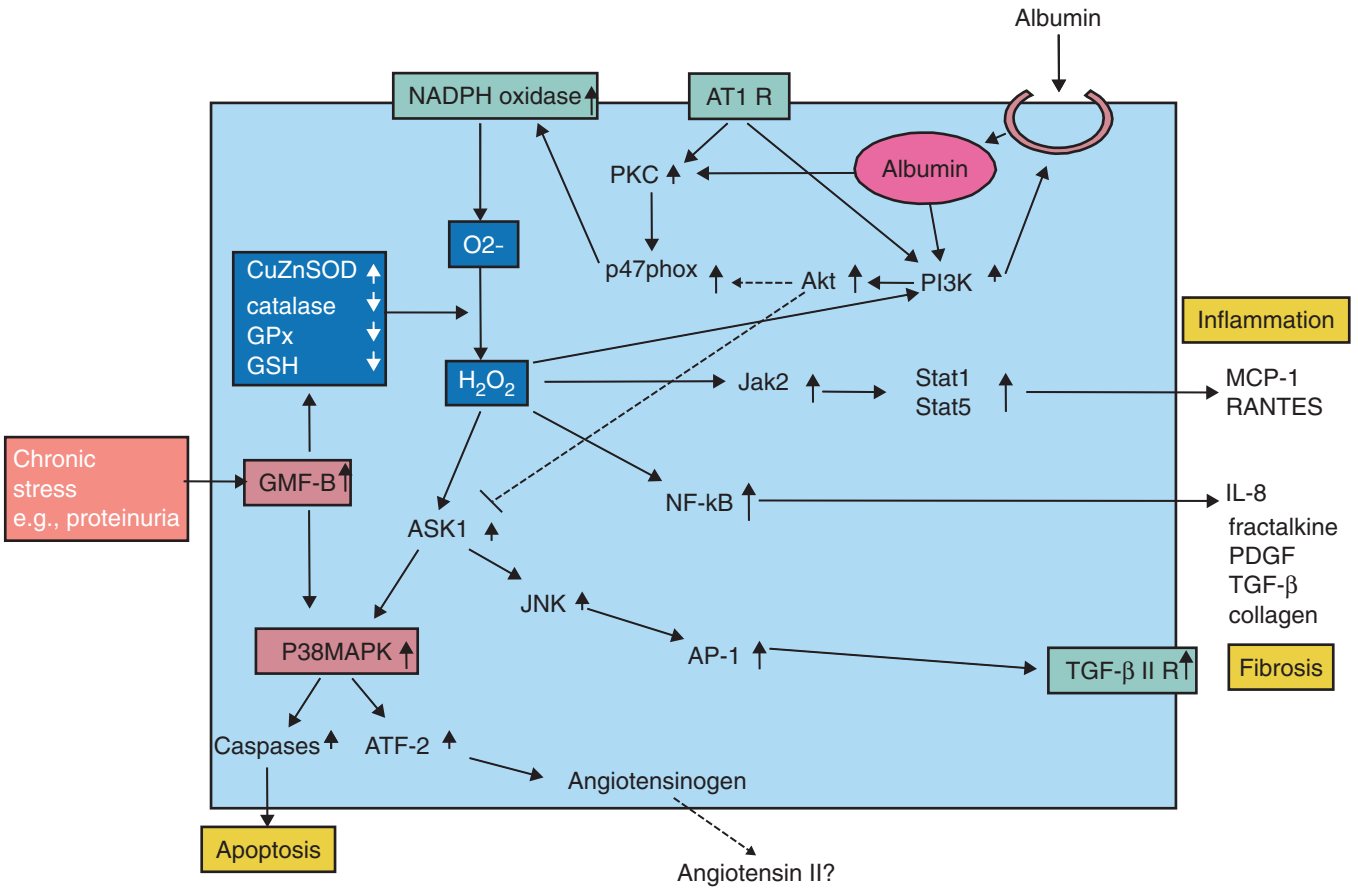

Fig. 1. Hypothetical signal transduction cascade of proximal tubule cells in response to protein overload. Arrows mean positive stimulation confirmed in tubular cells, and arrows with dot line means positive stimulation confirmed in another cells. Abbreviations: Akt, protein kinase B; AP-1, activator protein-1; ASK-1, apoptosis signal-regulating kinase-1; AT1 R, angiotensin type 1 receptor; ATF-2, activating transcription factor-2; CuZnSOD, cupper zinc superoxide dismutase; GMF-B, glia maturation factor; GPx, glutathione peroxidase; GSH, glutathione; Jak, Janus protein kinase; JNK, c-JUN N-terminal kinase; MCP-1, macrophage chemoattractant protein-1; NF-κB, nuclear factor κB; p47phox, 47 kD subunit of the phagocyte oxidase; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PKC, protein kinase C; RANTES, regulated on activation, normally T cell–expressed and –secreted; Stat, signal transducers and activators of transcription; TGF-β, transforming growth factor-β; TGF-β II R, transforming growth factor-β type II receptor.

abolished by angiotensin II (Ang II) type 1 receptor antagonist, suggesting Ang II–mediated TGF-β type II receptor induction. They speculated that albumin leads to tubular synthesis of Ang II, although they did not show the activation of local Ang II generation in proximal tubule cells. How can we reconcile the new finding of involvement of Ang II in proximal tubule activation by albumin? Hsieh et al [17] reported that ROS induced angiotensinogen in proximal tubule cells exposed to high glucose. They showed that p38 is involved the angiotensinogen gene up-regulation by ROS stimulation. They speculated that the phosphorylation of the nuclear activating transcription factor-2 (TFA-2) via p38 may activate the angiotensinogen gene transcription by binding of ATF-2 and CREB heterodimer to the cAMP-responsive element of the promoter. These results imply the potential that another vicious cycle can be turned on by activation of local Ang II generation by albumin overload.

How can we clinically apply the identification of the signaling effects of albumin in proximal tubule? The complex signal cascade provides the possibility of the multiple means of intervention and modulation against inflammation, fibrosis, and apoptosis.

Given that local Ang II generation is enhanced and, consequently, oxidative stress is exaggerated, AT1 antagonist, which also hemodynamically reduces proteinuria, can cut off the vicious cycle for ROS generation due to autocrine Ang II generation in tubular cells. Moreover, some angiotensin receptor antagonists may directly reduce the oxidative injury by antioxidative action of lowering the formation of carbon-central radicals and hydroxyl-radicals [18]. In contrast, the mechanism of the other vicious cycle generated by GMF-B activation is largely unknown. Potential involvement of protein kinase A in the activation of GMF-B was shown in C6 cells [11]; however, no report has been published concerning

the mechanism of GMF-B induction except for albumin overload in proximal tubule. The elucidation of GMF-B activation in proximal tubule may provide a new avenue of the therapy for chronic proteinuric nephropathy.

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