Editorial

Interleukin-6 signaling in podocyte hypertrophy

Diabetic kidney disease is characterized by increased albuminuria associated with structural changes, such as thickening of the glomerular basement membrane, mesangial expansion, and podocyte depletion followed by glomerulosclerosis. Glomerulosclerosis is preceded by early hypertrophic changes in the glomerulus [1]. Among the many characteristic glomerular pathologic changes, a decrease in the number of podocytes has been considered the strongest predictor of diabetic kidney disease progression. Because mature podocytes are incapable of replication, podocyte depletion can contribute to the development of hypertrophy in the remaining podocytes. Although podocyte hypertrophy has been considered to play an important pathophysiological role in the development of the early stages of diabetic kidney disease, the mechanisms driving podocyte hypertrophy remain poorly characterized.

Unlike mesangial cells and tubular epithelial cells, podocytes cannot actively synthesize DNA or proliferate because of their high cyclin-dependent kinase activity. However, podocytes can undergo hypertrophic changes through activation of extracellular signal-regulated kinases 1 and 2 or protein kinase B in response to high glucose, angiotensin II, or shear stress [2]. In addition, activation of the mammalian target of rapamycin complex 1 pathway can also induce a sustained hypertrophic stimulus, eventually leading to podocyte depletion and development of glomerulosclerosis [3].

Hypertrophy and hyperplasia are representative cellular responses to compensate for cellular stress or cell injury. These responses are accompanied by cell cycle changes; specifically, quiescent cells reenter the G1 phase to increase the synthesis of organelles and proteins. Although other glomerular cells such as endothelial and mesangial cells can easily proliferate, podocytes undergo hypertrophy instead of hyperplasia, thereby producing additional foot processes to compensate for remnant basement membranes due to podocytopenia [4]. Why do podocytes undergo hypertrophy instead of hyperplasia? The cell cycle can be arrested in the G1 and G2 phases, both of which prevent progression to mitosis. These checkpoints in the cell cycle are important for cell hypertrophy to prevent aberrant mitosis of cells with significant DNA damage. Because mitosis of cells with defective DNA leads to cell death, podocytes with mitotic changes are especially susceptible to detachment or death.

In many glomerular diseases, interleukin-6 (IL-6) has been shown to be an important mediator of glomerular inflammation [5]. IL-6 is mainly produced by leukocytes but is also synthesized and secreted from mesangial cells in response to angiotensin II and from podocytes after lipopolysaccharide stimulation [6]. Signal transducer and activator of transcription 3 (STAT3) is the major downstream effector of the IL-6 family signaling pathway. Recently, deletion of STAT3 from podocytes was reported to have beneficial effects in an animal model of nephrotoxic serum nephritis [7]. Although many experimental data have suggested a role for IL-6 in inflammation of mesangial cells and tubule cells, few studies have focused on IL-6 signaling in glomerular podocytes *in vivo*. Recently, Nagayama et al [8] reported that podocytes express glycoprotein 130 (gp130), the most common signal-transducing receptor subunit of the IL-6 family of cytokines. gp130 mediates signaling mainly through the Janus kinase (JAK)/STAT3 pathway, although it also mediates signaling through the mitogen-activated protein kinase and phosphoinositide 3-kinase pathways. Nagayama et al found that podocyte IL-6 signaling, including downstream STAT3 phosphorylation, was activated after systemic IL-6 administration or lipopolysaccharide injection in mice. However, the role of IL-6 signaling in podocyte hypertrophy was not investigated.

Because podocyte alterations and dysfunction play pivotal roles in the initiation and progression of diabetic kidney disease, it is important to understand the signaling abnormalities that lead to podocyte hypertrophy. In this issue of *Kidney Research and Clinical Practice*, Jo et al [9] report that the IL-6 level was significantly increased in the media and lysates of podocytes cultured in the presence of high glucose. In addition, Jo et al observed that STAT3 was activated by high-glucose stimulation and IL-6 administration, whereas this effect was attenuated by anti-IL-6 neutralizing antibodies. Immunoprecipitation analysis revealed increased phospho-JAK2 recruitment to gp130 when cells were stimulated with high glucose and IL-6, whereas the addition of anti-IL-6 neutralizing antibodies abrogated these changes. Furthermore, Jo et al found that podocyte hypertrophy was significantly increased after stimulation with high glucose and IL-6, whereas it was diminished by the addition of anti-IL-6 neutralizing antibodies. Based on these findings, Jo et al conclude that IL-6 plays a prominent role in the local activation of JAK2/STAT3 in podocyte hypertrophy under diabetic conditions. It is worth bearing in mind that this study was performed entirely *in vitro* and that the IL-6 signaling pathway was examined at only 1 time point instead of investigating serial changes of IL-6 signaling after high-glucose stimulation. Further *in vivo* studies are needed to

validate the findings of this *in vitro* study, specifically ones that focus on the role of IL-6/JAK2/STAT3 signaling in podocyte hypertrophy. Identification of the mechanism of podocyte hypertrophy will potentially lead to the development of new therapeutic targets for diabetic kidney disease.

Conflicts of interest

The author has no conflicts of interest to declare.

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