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Role of Activating Transcription Factor 3 (ATF3) in diabetic nephropathy

Ho Lee¹, Jin Cha¹, Jung Ghee¹, Ji Yoo¹, Young Kang¹, Hye Min², Ji Lee², Jee Han³, Dae Cha¹

¹Department of Internal Medicine-Nephrology, Korea University Ansan Hospital, Korea, Republic of

²Department of Internal Medicine-Nephrology, Wonkwang University Sanbon Hospital, Korea, Republic of

³Department of Pathology, Inha University Hospital, Korea, Republic of

Objectives: Activating Transcription Factor 3 (ATF3) is a transcriptional factor in response to stress, and reported that its expression is activated by ER stress and oxidative stress. Recent reports suggest that ATF3 involves in the development of diabetes through modulation of glucose regulatory molecules such as GSK. Therefore, persistent ATF3 expression induced by excessive ROS or ER stress likely has detrimental effects, overwhelming its initial compensatory role. Nonetheless, the exact functional role of ATF3 as a target molecule responsible for oxidative stress-mediated diabetic kidney injury is largely unknown. Hence, the aim of this study was to investigate the role of ATF3 in diabetic nephropathy.

Methods: To investigate the chronological changes of ATF3 in kidney in accordance with the progression of diabetic nephropathy, 6 week old db/m and db/db mice were sacrificed at 8, 12, 16 and 20weeks. Plasma and urinary levels of ATF3 protein levels were measured as well as the changes in renal morphological and functional changes. In addition, we examined the effects of high glucose and angiotensin-II on the synthesis of ATF3 in cultured podocytes and PTCs.

Results: Although plasma ATF3 concentrations did not show significant differences between diabetic and control mice, Urinary levels of ATF3 were significantly higher in the diabetic mice than in the controls. Interestingly, urinary excretion of ATF3 persistently increased during the course of diabetic nephropathy in diabetic mice. In renal tissues, ATF3 expression was significantly increased in the diabetic kidney even in the early stage of diabetic nephropathy. Interestingly, increased ATF3 expression was associated with activation of NOX1, NOX4 and Smad 2/3 and NF- κ B. In cultured podocytes and PTCs, high glucose, angiotensin II stimuli markedly increased ATF3 synthesis and secretion.

Conclusions: These findings suggest that ATF3 is activated in early stage of diabetic environment, may be an important pathogenic role in diabetic nephropathy.