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ATF-3 in diabetic nephropathy

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Objectives: Activating Transcription Factor 3 (ATF3) is a stress-adaptive transcription factor, which has been suggested to be involved in maintaining glucose homeostasis. ATF3 respond rapidly to various stimuli like high glucose, fatty acids and oxidative stress, and is observed to either protective or detrimental effects in diabetic condition. Therefore to elucidate the exact role in diabetic nephropathy of ATF3, we investigated the role of ATF3 by examining the ATF3 expressions in cultured renal cells and by inhibition with Raf-inhibitor GW5047 on diabetic mice model.

Methods: ATF3 level was examined in the mouse podocytes and NRK cells with either overexpression or downregulation with ATF3. 8 week db/m and db/db mice as the model of diabetic mice were examined for the expression of ATF3 and were treated with GW5074, a Raf1 kinase inhibitor targeting the ATF3 at a dose of 0.5mg/kg for 12 weeks.

Results: In cultured mouse podocytes and NRK cells, high glucose and angiotensin II markedly increased ATF3 expression. Gene Expressions of NOX4, MCP-1 and NF-kB were augmented by ATF3, and were attenuated by ATF3 siRNA. Interestingly, ATF3 overexpression and suppression resulted in modulation of nephrin in podocytes. In db/db mice, plasma ATF3 level was not different from control db/m, however the urinary ATF3 excretion was significantly higher. Treatment of GW5074 decreased urinary ATF3 excretion. Urinary excretion of albumin and nephrin were significantly attenuated in GW5074 treated db/db mice. Overall lipid profile or HOMA-IR, HbA1c level was not different from each group, but the GW5074 significantly improved systemic oxidative stress. Trend of increase in gene expression of JNK, p-38, smad2, ERK was noted in diabetic mice, which was downregulated by GW5074 treatment.

Conclusions: These findings suggest that in diabetic condition, the activation of ATF3 is associated pathogenesis of diabetic nephropathy and targeting ATF3 may have a protective role in the disease progression.