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High glucose induces membrane-bound transcription factor peptidase site1 via carbohydrate response element binding protein to modulate ER stress in mesangial cells

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Background and aims: High glucose (HG) evokes a variety of gene expressions in mesangial cells (MC) that alter cellular functions responsible for the development of diabetic glomerulopathy. We previously reported that HG activates hypoxia-inducible factor-1α and its target genes expression in MC, leading to an extracellular matrix expansion in diabetic glomeruli. A glucose responsive transcription factor, carbohydrate response element binding protein (ChREBP), plays a pivotal role in such derangement of gene regulation. To provide more insight into glucose-mediated gene regulation at genome-wide level, we performed chromatin immunoprecipitation with anti-ChREBP antibodies followed by DNA microarray analysis (ChIP-chip) and identified membrane-bound transcription factor peptidase site1 (MBTPS1) as a novel target gene of ChREBP in MC. MBTPS1 proteolytically activates a class of transmembrane transcription factors at the endoplasmic reticulum (ER) and participates in the regulation of cellular events such as response to ER stress; however the role of MBTPS1 in MC under diabetic circumstances is largely unknown. In the present study, we examined the mechanism by which MBTPS1 is induced by HG in MC, and the role of MBTPS1 in the regulation of cellular function.
Materials and methods: Cultured human MC were incubated in HG (25 mM glucose) and normal glucose (NG; 5.6 mM glucose), and the gene and protein expression were analyzed. Gene expressions in the kidney of diabetic model mice were determined by real time PCR.
Results: ChIP-chip assay revealed binding of ChREBP to MBTPS1 gene at 2.5kb in 3'-flanking region. In validation analyses, exposure to HG for 24h enhanced MBTPS1 mRNA expression in cultured MC (2.4±0.43 fold, compared to NG). Knock-down of ChREBP abrogated this induction response. MBTPS1 is known for the proteolytic activation of activating transcription factor-6 (ATF6), which is involved in the adoptive response to ER stress. In support of these issues, HG induced the activation of ATF6 in MC and the inhibitor of MBTPS1 cancelled this activation. Interestingly, the target genes of ATF6 were not universally induced by HG; C/EBP homologous protein, a critical determinant of ER stress-induced apoptosis, was induced by 4.8±1.1 fold ($p<0.05$), whereas X-box-binding protein 1 was induced by 1.8±0.2 fold ($p<0.05$) of and glucose-regulated protein-78 was not induced, indicating that MBTPS1 may participate in the control of the fate of MC exposed to HG. Moreover, the expression of MBTPS-1 mRNA was upregulated in the kidney of streptozotocin-induced diabetic model mice compared to control mice (1.36 fold).
Conclusion: HG-mediated induction of MBTPS1 via ChREBP operates in response to ER stress in MC, which may provide novel insights into the pathogenesis and therapeutic intervention of diabetic nephropathy.
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