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A Potential Therapeutic Target for Diabetic Nephropathy

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Lysophosphatidic acid (LPA) is known to regulate various biological responses by binding to LPA receptors (LPARs). Previously, it was reported that serum level of LPA are elevated in the diabetic conditions, but the involvement of LPA in development of diabetes and its complications remains unknown. We investigated the role of LPA signaling in diabetic nephropathy and the molecular mechanisms involved. The mRNA level of LPAR1 was significantly increased in both LPA-treated mouse renal mesangial cells (SV40 MES 13) and the kidney cortex of diabetic db/db mice. Increased albuminuria, glomerular tuft area and glomerular volume were observed in db/db mice; this was reduced by ki16425 (LPAR1/3 antagonist) treatment. TGFβ expression was upregulated in SV40 MES13 cells by LPA stimulation or in the kidney cortex of db/db mice, but which were blocked by ki16425 treatment. In addition, TGFb expression was regulated by LPAR1 expression. LPA treatment increased phosphorylated GSK3β at ser9 and induced translocation of SREBP1 into the nucleus, contributing to the induction of TGFβ expression in SV40 MES13 cells. Phosphorylated GSK3β and nuclear SREBP1 accumulation were increased in kidney cortex of db/db mice, and ki16425 treatment reduced these pathways. These results suggest that LPAR1 signaling increased TGFβ expression via GSK3β phosphorylation and SREBP1 activation, contributing to the development of diabetic nephropathy.
Mesangial cell proliferation has been considered as a major factor contributing to glomerulosclerosis, which is a typical symptom of diabetic nephropathy (DN). Treatment with LPA increased the proliferation of SV40 MES13 cells concomitant with the increased expression of cyclin D1 and CDK4. On the other hand, the expression of $p27^{Kip1}$ was decreased. The expression of Krüppel-like factor 5 (KLF5) was upregulated in kidney cortex of db/db mice and LPA-treated SV40 MES13 cells. The activation of mitogen-activated protein kinases (MAPKs) and subsequent enhanced expression of early growth response 1 (Egr1) were observed in LPA-treated SV40 MES13 cells and the kidney cortex of db/db mice. Moreover, LPA significantly increased the activity of Ras-related C3 botulinum toxin substrate (Rac1) GTPase in SV40 MES13 cells, and LPA-induced hyperproliferation was regulated by Rac1 activity. These results demonstrated that the Rac1/MAPK/KLF5 signaling pathway was one of the mechanisms involved in LPA-induced mesangial cell proliferation in DN.
We also investigated the effects of a specific pharmacological inhibitor of LPAR1, AM095, on DN in streptozotocin (STZ)-induced diabetic mice to exclude a possible contribution of LPAR3 inhibition. AM095 treatment significantly reduced albuminuria and the albumin to creatinine ratio and significantly decreased the glomerular volume and tuft area in the treated group compared with the STZ-vehicle group. In the kidney of STZ-induced diabetic mice, the expression of LPAR1 mRNA and protein was positively correlated with oxidative stress. AM095 treatment inhibited LPA-induced reactive oxygen species production and NADPH oxidase expression as well as LPA-induced toll like receptor 4 (TLR4) expression in mesangial cells and in the kidney of STZ-induced diabetic mice. In addition, AM095 treatment suppressed LPA-induced pro-inflammatory cytokines and fibrotic factors expression through downregulation of phosphorylated NFκBp65 and c-Jun N-terminal kinases (JNK) in vitro and in the kidney of STZ-induced diabetic mice. In conclusion, AM095 is effective in preventing the pathogenesis of DN by inhibiting TLR4/NF-κB and the NADPH oxidase system, consequently inhibiting the inflammatory signaling cascade in renal tissue of diabetic mice, suggesting that LPAR1 antagonism might provide a potential therapeutic target for DN.