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Targeting N-acetyltransferase 10 with remodelin ameliorates renal oxidative stress and fibrosis in diabetic mice

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Objectives : N-terminal (Nt) acetylation is known to be a highly abundant co-translational protein modification, but can also be added post-translationally. Recent advances highlight Nt-acetylation as a key factor in many biological pathways and remodelin, a small molecule inhibitor of N-acetyltransferase 10, can reverse the cancerous conditions such as epithelial to mesenchymal transition and hypoxia. This study examined the potential renoprotective effect of remodelin in type 2 diabetic mice.
Methods : Four groups of male C57BLKS/J db/m and db/db mice were used. Diabetic and non-diabetic mice were intraperitoneally injected with 1 mg/kg body weight remodelin weekly for 12 weeks, starting at 8 weeks of age.
Results : Remodelin treatment significantly reduced albuminuria in db/db mice compared to the control group. While the body weight of remodelin-treated db/db mice was lower at 12 weeks, there were no significant differences in serum glucose levels or HbA1c between the two groups. Histological analysis revealed that remodelin improved glomerular matrix expansion and inflammation, while also reversing diabetes-induced renal apoptosis and oxidative stress. Masson's trichrome and α-smooth muscle actin staining further demonstrated that tubulointerstitial fibrosis and inflammation were attenuated by remodelin treatment. At the molecular level, remodelin administration increased renal mRNA expression of TNF-α, MMP9, E-cadherin, α-SMA, fibronectin, TGF-β1, and CCN5 in diabetic mice. Additionally, Western blot analysis showed that Remodelin suppressed Nrf2 protein levels while increasing HO-1, Keap1, and NQO1, suggesting an atypical modulation of the Nrf2 signaling pathway. Bax2 levels were also reduced, indicating an anti-apoptotic effect.
Conclusions : These findings suggest that remodelin exerts renoprotective effects in diabetic nephropathy by inhibiting inflammatory and fibrotic pathways while modulating oxidative stress responses through Keap1-Nrf2 signaling.