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Genetic deletion or pharmacologic intervention of p300/CBP-associated factor attenuates renal injury by suppressing cell apoptosis in diabetes

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Objectives: As a member of the GNAT family of histone acetyltransferase, p300/CBP-associated factor (PCAF) is involved in the regulation of cell transcription, progression, and differentiation. In addition, PCAF has been known to bridge transcriptional factors to the transcriptional complex to provide appropriate levels of gene activities in cells in response to extracellular stimuli. The objective of this study was to evaluate whether PCAF might be involved in the pathogenesis of diabetic kidney disease by observing results from genetically deletion or pharmacologic inhibition of PCAF.

Methods: We examined renal effects of the PCAF inhibitor, garcinol, in *db/db* or *db/dm* mice, and this pharmacologic intervention experiment was complemented by the genetic deletion study that compares renal injury in streptozotoicn-indued PCAF KO mice (B6.Cg-Kat2b^{tm1Nkt}/Orl) and wild-type mice.

Results: Treatment with garcinol decreased albuminuria and positive areas of trichrome and α-smooth muscle actin in kidneys of *db/db* mice although it did not affect most of renal mRNA levels relating to inflammation, epithelial-mesenchymal transition and profibrotic factors. Furthermore, renal protein levels of antioxidants such as NQO1, catalase, SOD1 and SOD2 were not different between garcinol-treated and vehicle-treated *db/db* mice. However, TUNEL-positive cells and ratio of Bax to Bcl-2 were decreased by garcinol treatment in *db/db* mice. Consistent with these findings, induction of diabetes in PCAF KO mice resulted in reduced albuminuria and attenuated renal interstitial fibrosis and cellular apoptosis without any significant effect on renal expression of inflammatory and profibrotic markers and antioxidants.

Conclusions: These data suggest that renoprotection observed with pharmacologic PCAF inhibition and genetically deletion of PCAF in diabetic kidneys is associated with reduced cellular apoptosis. Epigenetic control by modulating PCAF activity might be a novel therapeutic strategy that could modulate complicated and complex pathways in the pathogenesis of diabetic kidney disease.