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Role of epigenetic histone modifications in pro-fibrotic gene regulation by 12-Lipoxygenase in Diabetic Nephropathy

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Background: Epigenetic chromatin histone modifications such as H3-lysine methylation (H3KMe) and acetylation (H3KAc) at gene promoters have profound effects on gene expression. Increased expression and activity of TGF-β1 (TGFB) and 12/15-Lipoxygenase (LO) as well cross-talk between them play important roles in the upregulation of profibrotic genes (Collagen1a1, PAI-1 and CTGF) in Diabetic Nephropathy. We previously demonstrated the key role of H3KMe in profibrotic gene expression induced by high glucose and TGFB in renal mesangial cells (MC).In this study, we evaluated potential role of the LO-TGFB cross-talk in the regulation of histone modifications and expression of a key H3K4-methytransferase (HMT) Set7/9 in MC and renal cortex from diabetic mice.

Methods: We determined gene expression by QRT-PCR and histone modifications by Chromatin immunoprecipitation (ChIP) assays in rat MC treated with 12(S)-HETE (an LO- product) as well as in MC derived from wild type (WT) or LO-knockout (LOKO) mice after TGFB stimulation. In vivo relevance was tested using renal cortex from streptozotocin induced diabetic LOKO mice, and WT diabetic mice treated with LO siRNAs.

Results: Results showed that 12(S)-HETE increased the expression of profibrotic genes and SET7/9, and also altered H3K9Ac/H3K4Me1/H3K4Me3 levels at profibrotic gene promoters in rat MC. Interestingly, TGFB induced Set7/9 and profibrotic gene expression as well as H3K9Ac at their promoters was significantly ameliorated in MC from LOKO mice. Furthermore, SET7/9 and profibrotic gene expression were increased in diabetic WT mice and these were significantly attenuated in diabetic LOKO mice, as well as in diabetic WT mice treated in vivo with LO siRNAs.

Conclusion: These results demonstrate that oxidized lipids of the LO pathway can regulate key HMTs and histone modifications under diabetic conditions and also play important roles in TGFB induced epigenetic mechanisms involved in profibrotic gene expression. This in turn can augment extracellular matrix deposition and fibrosis linked to diabetic nephropathy.

Keywords: 12-lipoxygenase, diabetic nephropathy, fibrotic gene, histone modification