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Renoprotective Effect of COMP-angiopoietin-1 in *db/db* Mice with Type 2 Diabetes

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Background : Inflammatory processes have been recently seen as underlying the pathogenesis of diabetic nephropathy. Angiopoietin-1 (Ang1) is known to be a ligand acting on endothelial cells via the Tie2 tyrosine kinase receptor. Ang1 plays essential roles in regulating vascular growth, development, maturation, permeability, and inflammation. We have developed a soluble, stable, and potent Ang1 variant, cartilage oligomeric matrix protein (COMP)-Ang1. Here, we investigate the protective effects of this factor on the renal injury in diabetic *db/db* mice.

Methods : *db/db* mice were treated with recombinant adenovirus expressing either COMP-Ang1 or LacZ. Histology, inflammatory and fibrotic parameters, and signaling pathway were evaluated.

Results : COMP-Ang1 reduced albuminuria and decreased mesangial expansion, thickening of the glomerular basement membrane, and podocyte foot process broadening and effacement. COMP-Ang1 suppressed both renal expression of intercellular adhesion molecule-1 and monocyte chemoattractant protein-1 and monocyte/macrophage infiltration in diabetic *db/db* mice. COMP-Ang1 also reduced renal tissue levels of transforming growth factor-β1 (TGF-β1), α-smooth muscle actin, fibronectin, as well as Smad 2/3 expression, but increased Smad 7 expression. In human umbilical vein endothelial cells (HUVECs) grown in high glucose concentrations of glucose, recombinant COMP-Ang1 protein (Ang1rp) decreased nuclear factor-κB (NF-κB) expression. Ang1rp-mediated inhibition of increased NF-κB-DNA binding in nuclear extracts from HUVECs grown in high glucose was significantly blocked by soluble Tie2 receptor-Fc.

Conclusion : We conclude that COMP-Ang1 has an anti-inflammatory effect by inhibiting the Tie2/NF-κB pathway, which may lead to decreased activation of TGF-β/Smad 2/3 pathway and renal fibrosis in *db/db* mice.