C16

Role of PAI-1 in ECM Remodeling in Diabetic Kidney

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Diabetic nephropathy is the leading cause of ESRD and is characterized by excessive deposition of ECM in the kidney. The amount of ECM deposited depends upon the balance of synthesis and degradation. PAI-1 is known to play a role in ECM remodeling in the kidney through suppression of plasmin generation and MMP activation. We utilized PAI-1 deficient mice, glomerular mesangial cells isolated from PAI-1 deficient mice, and normal rat tubular epithelial cells subjected to PAI-1 gene silencing through transient transfection with PAI-1 siRNA to elucidate the contribution of PAI-1 in ECM remodeling in diabetic kidney. PAI-1 gene deficiency and gene silencing increased plasmin and MMP activity and at the same time decreased the expression of TGF-beta 1, fibronectin, and collagen I mRNAs and proteins in response to high glucose and/or TGF-beta 1. In PAI-1 deficient mesangial cells, recombinant PAI-1 upregulated TGF-beta 1 and collagen I mRNA expression in response to high glucose and TGF-beta 1. The effect of recombinant PAI-1 on collagen expression was abrogated by anti-TGF-beta 1 antibody and TGF-beta 1 receptor inhibitor suggesting that the effect of recombinant PAI-1 is mediated by TGF-beta 1. PAI-1 plays an important role in ECM remodeling in diabetic kidney through both suppression of protease activity and upregulation of TGF- beta 1 mRNA expression.