

GLOMERULOSCLEROSIS IN THE *COL1A2*-DEFICIENT MOUSE MODEL: HOMOTRIMER PATHOGENESIS AND MMP EXPRESSION

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ABSTRACT

The *Colla2*-deficient (*oim*) mouse model exclusively synthesizes homotrimeric type I collagen due to the lack of functional $\text{pro}\alpha 2(\text{I})$ collagen chains. The mouse develops a type I collagen glomerulopathy that has previously been shown to initiate postnatally and progress in a gene dose-dependent manner, accumulating type I collagen within the renal mesangium, resulting in podocyte foot effacement and proteinuria. In this study we examine the pre- and post-translational expression of type I collagen and MMPs -2, -3, and -9 in wildtype, heterozygous and *Colla2*-deficient glomeruli to determine whether the pathogenic collagen is homotrimeric in nature, and whether alterations in MMP expression play a role in disease progression. Analysis of whole kidney and isolated glomeruli by immunohistochemistry and CNBr peptide mapping suggest that homotrimer is the accumulating type I collagen isotype in sclerotic glomeruli of both affected and heterozygous mice. Steady state MMPs-2, and -3 mRNA levels exhibited significant increases by three months of age, with corresponding protein increases compared to age-matched wildtype mice. Steady state MMP-9 mRNA levels significantly increased by three months of age, but MMP-9 protein expression was significantly decreased. Our findings suggest that upregulation of MMPs-2 and -3 expression is not sufficient to prevent homotrimeric type I collagen deposition and that their induction does not appear to be an initiating event, but may represent a secondary wound response.