Public Abstract

First Name:Anna

Middle Name:

Last Name:Roberts-Pilgrim

Adviser's First Name:Charlotte

Adviser's Last Name:Phillips

Co-Adviser's First Name:

Co-Adviser's Last Name:

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

Type I collagen, normally synthesized as a heterotrimeric molecule comprised of two alpha1 chains and one alpha2 chain, is the most abundant structural protein synthesized by the body. Mutations in this molecule cause dramatic phenotypic effects as seen in persons with Osteogenesis Imperfecta (OI) and Ehlers Danlos syndrome. The COL1A2-deficient mouse model that we study synthesizes a type I collagen molecule that only contains three alpha1 chains a homotrimeric molecule that does not include the alpha2 chain. Along with severely brittle bones seen in Type III OI patients, these mice also show accumulation of homotrimeric collagen in the glomeruli of their kidneys that subsequently impair their renal filtering. Our lab has previously proven that these mice develop glomerulosclerosis in a gene dose-dependent manner and that the whole kidney steady state mRNA of the alpha1 chain of type I collagen is up-regulated in mice that are homozygous for the mutation in the COL1A2 allele. My research has been focused on examining the degradation of homotrimeric type I collagen within these affected glomeruli and, combined with the over-synthesis of the collagen alpha1 chain, determining whether there is a correlative effect on the severity of the disease. The major contributors to degradation within the glomeruli are matrix metalloproteinases (MMPs) which break down type I collagen as well as other extracellular matrices that are localized between cells. Presently, I have discovered that homozygous mice at one month of age show an increase in MMPs -2 and -3 mRNA steady state levels and a subsequent increase in the fore-mentioned MMPs protein levels at 3 months of age. This data suggests that as homotrimer is being synthesized, the glomeruli are responding by increasing the amount of degradative enzymes to remove it. However, the effort to maintain the integrity of the glomeruli has been unsuccessful. This homotrimer accumulation then leads to podocyte foot effacement that subsequently results in impaired filtration of blood. Logically, the next question would be " why is the increase in enzymes not preventing the accumulation of homotrimer? " Although the alpha1 and alpha2 chains of type I collagen are 97% homologous and have been for the past 50 million years, the absence of the alpha2 chain may remove a key site of recognition needed by the MMPs to efficiently degrade the collagen molecule. We are presently collaborating with other labs to determine whether select MMPs cleave homotrimeric type I collagen at the same rate as heterotrimeric type I collagen, and have preliminary data that suggests it doesnâ€™t. This fascinating development has also been found along side our recent data that suggests sclerotic glomeruli in heterozygous oim mice, who are capable of synthesizing both normal and homotrimeric type I collagen, only accumulate homotrimer in diseased glomeruli. Taken together, my research implies that in the COL1A2-deficient mouse model homotrimeric type I collagen is being synthesized by mesangial cells in the glomeruli, but due to retarded degradation by MMPs, is unable to be removed at an appreciable rate, leading to accumulation and glomerulosclerosis. This exciting new information may xtend to several types of glomerulopathies and may help elucidate the disease mechanisms and possibly provide new avenues for therapeutics.