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Mitochondrial dysfunction in renal inflammation and fibrosis

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Mitochondria plays important role in maintaining cellular integrity by regulating various cellular processes. Kidney fibrosis is characterized by marked mitochondrial loss in the kidney tubules and a marked proinflammatory gene expression. The mechanism of immune activation and its relationship to the metabolic defect is poorly understood. By analyzing kidneys of patients and animal models with fibrosis we observed a significant mitochondrial defect, including the loss of the mitochondrial transcription factor A (TFAM) in kidney tubule cells. We generated mice with tubule-specific deletion of TFAM (*Ksp-Cre/Tfam* $^{flox/flox}$). These mice developed severe mitochondrial loss and energetic deficit (ATP level decline) by 6 weeks of age, kidney fibrosis, immune cell infiltration and progressive azotemia causing death was observed around 12 weeks of age. Mechanistic studies demonstrated that in the TFAM KO mice aberrant packaging of the mitochondrial DNA (mtDNA) resulted in escape of the mtDNA into the cytosol of the renal cells, activation of the cytosolic cGAS-STING (Stimulator of interferon genes) DNA sensing pathway, and thus cytokine expression and immune cell recruitment. Genetic deletion or pharmacological inhibition of STING ameliorated kidney fibrosis in mouse models of chronic kidney disease, demonstrating that in addition to its essential role in metabolism TFAM sequesters mtDNA to prevent the activation of innate immune pathways and fibrosis.