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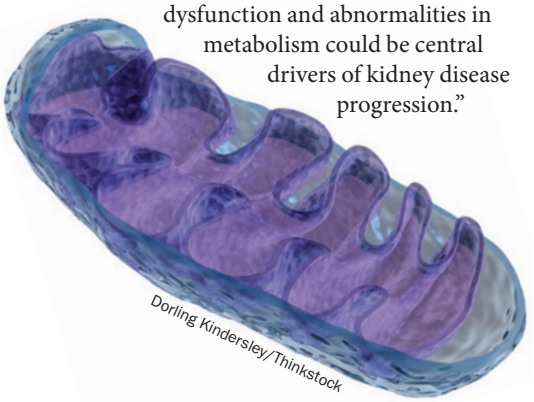
GLOMERULAR DISEASE

# Autophagy failure and mitochondrial dysfunction in FSGS

Researchers report that failure of autophagy may be a central mechanism in the pathogenesis of focal segmental glomerulosclerosis (FSGS). Jeremy Duffield and colleagues showed that abrogation of autophagic pathways in murine nephrons is sufficient to recreate many of the characteristic features of the human disease.

"We performed our study because autophagy is important in cellular metabolic and mitochondrial homeostasis," explains Duffield. "We hypothesized that mitochondrial dysfunction and abnormalities in metabolism could be central drivers of kidney disease progression."



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To disrupt normal autophagic pathways in murine nephrons, the researchers mutated the *Atg5* gene—which has a critical role in the formation of autophagosomes—using a Cre–*loxP* system. "We are fortunate to have a mouse in which the Cre enzyme is expressed only in the embryonic progenitor cells that form the nephron of the kidney. Using this mouse we very efficiently caused DNA recombination and, therefore, mutation of *Atg5* in the kidney epithelium," says Duffield.

At 2 months of age the mutant mice showed albuminuria and tertiary podocyte foot-process effacement but normal kidney function. They had severe albuminuria, tubulointerstitial disease and glomerular changes at 4 months, and died from kidney failure by 6 months.

Analysis of podocytes and tubular cells from the mutant mice revealed vacuolization, abnormal mitochondria, increased production of reactive oxygen species (ROS) and evidence of endoplasmic reticulum (ER) stress. Similar ultrastructural changes were seen in biopsy samples from patients with idiopathic FSGS.

"Autophagy failure leads to very early generation of high levels of ROS from the nephron in advance of any histological pathology. The major source of the ROS appears to be dysfunctioning mitochondria, which might arise as a result of impaired turnover of mitochondria and mitochondrial proteins in podocytes and tubule cells," says Duffield. He concludes that these findings—together with data from genome-wide association studies, human mutation studies and studies of diabetic nephropathy—suggest that mitochondrial dysfunction and ER stress as a result of impaired autophagic organelle turnover could be central drivers of FSGS development.

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**Original article** Kawakami, T. *et al*. Deficient autophagy results in mitochondrial dysfunction and FSGS. *J. Am. Soc. Nephrol*. doi:10.1681/ASN.2013111202