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Mitochondrial Dysfunction in Podocytes Caused by CRIF1 Deficiency Leads to Progressive Albuminuria and Glomerular Sclerosis in Mice

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Objectives: Recent studies have implicated mitochondrial disruption in podocyte dysfunction, which is a characteristic feature of primary and diabetic glomerular diseases. However, the mechanisms by which primary mitochondrial dysfunction in podocytes affects glomerular renal diseases are currently unknown.

Methods: To investigate the role of mitochondrial oxidative phosphorylation (OxPhos) in podocyte dysfunction, glomerular function was examined in mice carrying a loss of function mutation of the gene encoding CR6-interacting factor-1 (CRIF1), which is essential for intramitochondrial production and the subsequent insertion of OxPhos polypeptides into the inner mitochondrial membrane.

Results: Homozygotic deficiency of CRIF1 in podocytes resulted in profound and progressive albuminuria from 3 weeks of age; the CRIF1-deficient mice also developed glomerular and tubulointerstitial lesions by 10 weeks of age. Furthermore, marked glomerular sclerosis and interstitial fibrosis were observed in homozygous CRIF1-deficient mice at 20 weeks of age. In cultured mouse podocytes, loss of CRIF1 resulted in OxPhos dysfunction and marked loss or abnormal aggregation of F-actin. These findings indicate that the OxPhos status determines the integrity of podocytes and their ability to maintain a tight barrier and control albuminuria.

Conclusions: Analyses of the glomerular function of the podocyte-specific primary OxPhos dysfunction model mice demonstrate a link between podocyte mitochondrial dysfunction, progressive glomerular sclerosis, and tubulointerstitial diseases.