PATHOLOGY

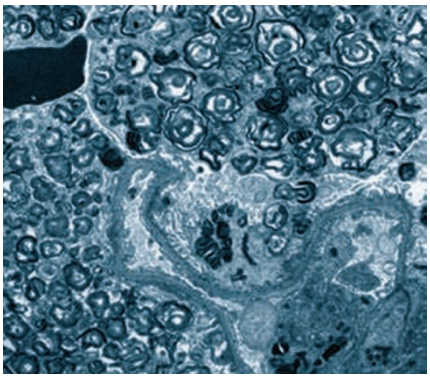
Electron microscopy illuminates the pathology of Fabry nephropathy

Enzyme-replacement therapy (ERT) can slow the decline of renal function in patients with Fabry disease, but once proteinuria develops, responsiveness to ERT is limited. Fresh research has discovered early changes in podocytes that correlate with the markers of progression of Fabry nephropathy. "Fabry nephropathy is a very heterogeneous disease," notes Behzad Najafian, the paper's lead author. Thus, standardized dosing of ERT is unlikely to suit all patients. "These biomarkers can potentially be used to guide clinical decisions for when to start ERT and how to adjust the dosage," he points out.

Najafian *et al.* used quantitative stereological electron microscopy to assess the relationship between glomerular structure and renal function in young patients with Fabry disease who had little or no proteinuria. Kidney biopsy specimens were obtained from 14 such patients, who had not yet received primary ERT, and compared with biopsy samples from nine healthy, living kidney donors.

Fabry disease was associated with significantly increased podocyte foot process width and significantly decreased endothelial cell fenestrations in glomeruli. Inclusion bodies containing globotriaosylceramide (GL-3, which accumulates in patients with Fabry disease owing to the absence of α-galactosidase) occurred in podocyte, endothelial and mesangial cells from the patients, but were most abundant in the cytoplasm of podocytes. The fractional volume of podocytes occupied by GL-3 inclusion bodies increased with patient age, and correlated closely with the amount of proteinuria ($r = 0.68$) and with the width of foot processes ($r = 0.81$). The accumulation of GL-3 in podocytes is thought to induce cellular injury that manifests as proteinuria.

Najafian's team is now researching the effect of ERT on structural glomerular changes in adults and children with Fabry disease. "Structural parameters that can closely predict renal function … could be used as diagnostic or prognostic biomarkers, or can be used as primary end points in clinical trials," he suggests. These biomarkers might also help to identify patients at high risk of progression.



Fabry disease. Permission obtained from Nature Publishing Group © Fischer *et al*. *Mod. Pathol.* **19**, 1295–1301 (2006).

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Original article Najafian, B. *et al.* Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. *Kidney Int.* doi:10.1038/ki.2010.484