Identifying the causes and cellular effects of Focal segmental glomerulosclerosis (FSGS).

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A major factor in morbidity and mortality worldwide is end stage renal disease (ESRD). At least 10% of ESRD is caused by focal and segmental glomerulosclerosis (FSGS), a form of steroid resistant nephrotic syndrome. This is devastating disease, that is typically associated with oedema, proteinuria, hypertension, microscopic haematuria, and renal insufficiency, which usually leads to end stage renal failure despite the use of prolonged and toxic immunosuppression. A particularly difficult aspect of FSGS is that in up to 60% of cases, it will recur following kidney transplantation(1-3).The incidence of FSGS, which is particularly common in children, has increased markedly recently with the latest epidemiological study showing a dramatic increase in FSGS as a proportion of primary glomerulopathy from 17 to 59% beween 1992 and 2002(4).

The aetiology of FSGS is still unknown although a major recent advance has been the identification of the podocyte as the target cell in this disease. Podocytes are part of the glomerular capillary wall of the kidney which is responsible for plasma ultrafiltration during primary urine formation and dysfunction of this process results in extensive leakage of plasma proteins – the nephrotic syndrome. Podocytes are terminally differentiated epithelial cells critical in preventing protein passage across the filtration barrier. This is achieved via a highly regulated and dynamic cytoskeleton, leading to maintenance of unique foot processes. Defects in podocytes play a major role in the pathogenesis of FSGS. Notably mutations in a number of cytoskeleton-regulating genes cause FSGS (5). We have developed a number of conditionally–immortalised human podocyte cell lines from both normal and diseased glomeruli from patients with known nephrotic syndrome disease causing mutations (6). We wish to use these unique resources and state of the art proteomic, cell biology and cell imaging techniques (both light and electron microscopy) to understand how mutations in podocyte proteins lead to disease.

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