Podocyte actin in health, disease and treatment*

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Brief review of the field

Focal segmental glomerulosclerosis (FSGS) is a common and important cause of nephrotic syndrome. It is now generally accepted that the predominant glomerular lesion in FSGS is injury to podocytes (visceral glomerular epithelial cells). Podocytes have a complex cellular architecture with interdigitating processes maintained by a precise organization of actin filaments in the cellular cytoplasm. Electron microscopic analysis of the glomerular capillary wall shows that, on the urinary side, the foot processes of the podocytes are organized in a precise manner with slits between them through which filtration occurs (Figure 1A). It has been known for decades that a cardinal feature of the glomerular capillary wall in proteinuric states is flattening or effacement of the foot processes so that this precise organization has been disrupted: it is clear from examination of the podocyte cytoplasm that this effacement is associated with flattening of the actin filaments (Figure 1B). Doubts have been expressed about the specificity of this finding, including by this author [1] citing, for example, that similar changes are seen in children with severe protein malnutrition in kwashiorkor [2]. This observation is still unexplained, but in recent years, it has become ever clearer that the precise organization and regulation of the actin cytoskeleton in the podocyte is essential for the maintenance of its normal structure and function, and that disruption thereof is a feature of podocyte diseases and is associated with proteinuria, and perhaps most importantly of all that therapeutic agents which have beneficial effects in nephrotic syndrome are capable of restoring the podocyte actin cytoskeleton.

Early work that supports this line of thought came from the same group, led by Martin Pollak, responsible for the paper under discussion here. Firstly, they reported that mutations in the gene encoding alpha-actinin IV, which plays an important role in actin polymerization, were associated with autosomal dominant late-onset familial FSGS [3]. Next, they showed that the mutant form of the protein binds more avidly to actin and affects the mechanical properties of actin gels, providing an explanation for its effect on podocyte structure [4]. Another group then showed that podocyte-specific transgenic expression of the mutant alpha-actinin IV gene in mice leads to FSGS [5], demonstrating that it is the effects of the gene in the podocyte rather than any other cell that is responsible for the disease. The final proof of the causative role of the mutation came in experiments in which the group of Pollak showed that, when the mutant gene was ‘knocked-in’ in mice, the animals developed FSGS, showing that this gene defect alone is capable of causing the disease [6]. The mechanisms underlying the effects of the mutant protein have now been demonstrated in detail [7]. Most recently, the group of Pollak provided further evidence that the physicochemical characteristics of actin fibres formed with the mutant alpha-actinin IV show altered flexibility that can explain the effects on the podocyte [8]. Other groups have reported different gene mutations which affect the actin cytoskeleton and also cause FSGS: for instance, in the gene encoding CD2-associated protein which encodes a protein that is important in linking to actin fibres [9].

However, nephrologists have inevitably asked whether these rare familial forms of FSGS are analogous to the much more common sporadic forms of the disease. Shared mechanisms are likely to exist, but does the actin cytoskeleton play a similar role in idiopathic FSGS? We do not yet know for sure, but recent observations on the mechanisms of action of drugs which are effective in FSGS have caused real excitement and shown the way to more specific forms of treatment. Calcineurin inhibitors, especially cyclosporin, are widely used in the treatment of proteinuric diseases including FSGS; their use originally being based on the assumption that the diseases are immune-mediated and the immunosuppressive effects of such drugs are likely to be helpful. Faul et al. [10] made the novel observation that the anti-proteinuric effects of cyclosporin can be explained by direct effects on the podocyte actin cytoskeleton (and therefore the cell's shape) and are independent of its effects on T lymphocytes. The mechanism involves synaptopodin, a key stabilizer of the actin cytoskeleton in podocytes. When synaptopodin is phosphorylated, it is protected from degradation. Calcineurin (which is blocked by cyclosporin) dephosphorylates synaptopodin and allows its degradation. Thus, cyclosporin prevents degradation of
sions about transplantation for those who reach end-stage renal disease: recurrence in a transplanted kidney is much less likely in patients whose original disease was genetic.

The basic science around podocyte diseases, their genetic and cellular basis, and the modes of action of therapeutic agents have made remarkable progress in recent years. This is already yielding benefits in the clinic, and patients afflicted by FSGS, together with the nephrologists caring for them, can take real encouragement from the speed of the advance of knowledge and the way in which it is guiding the design of better and safer forms of treatment.

**Take-home message**

Gene mutations which affect actin in podocytes predispose to FSGS; this adds to the evidence that an improved therapy for this disease requires agents which target the podocyte and protect its actin cytoskeleton.

**Conflict of interest statement.** None declared.

**References**


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