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Review Article

Current concepts of the podocyte in nephrotic syndrome

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ABSTRACT

Nephrotic syndrome is a disorder of the glomerular filtration barrier, and central to the filtration mechanism of the glomerular filtration barrier is the podocyte. We are starting to better understand how this cell, with its unique architectural features, fulfils its exact filtration properties. The multiprotein complex between adjacent podocyte foot processes, the slit diaphragm, is essential to the control of the actin cytoskeleton and cell morphology. Many of the proteins within the slit diaphragm, including nephrin, podocin, transient receptor potential-6 channel, and α-actinin-4, have been identified via genetic studies of inherited nephrotic syndromes. Signaling from slit diaphragm proteins to the actin cytoskeleton is mediated via the Rho GTPases. These are thought to be involved in the control of podocyte motility, which has been postulated as a focus of proteinuric pathways. Nephrotic syndrome is currently treated with immunosuppressive therapy, with significant adverse effects. These therapies may work in nephrotic syndrome due to specific effects on the podocytes. This review aims to describe our current understanding of the cellular pathways and molecules within the podocyte relevant to nephrotic syndrome and its treatment. With our current knowledge of the cellular biology of the podocyte, there is much hope for targeted therapies for nephrotic syndromes.

Introduction

The nephrotic syndrome (NS) describes a triad of hypoalbuminemia, edema, and proteinuria. It is the most common glomerular disease of childhood and has an incidence of approximately 2:100,000 [1].

NS may be classified by response to steroids—steroid responsive and steroid resistant. It is possible that a different pathophysiology underlies these different subgroups; however, this does not explain those who are initially responsive but later become resistant. Minimal-change nephropathy is reported as the most common cause of NS in children (approximately 80% of cases) according to the International Study of Kidney Disease in Children (1967–1974). Most of these will be steroid responsive. Approximately 20% of NS will be clinically steroid resistant [steroid-resistant NS (SRNS)]. and about 60% of these will have focal segmental glomerulosclerosis (FSGS) on biopsy. Those with FSGS may progress to end-stage renal failure requiring renal transplant. One of the greatest challenges in managing FSGS is the recurrence risk of 30–50% after the first transplant and higher for subsequent grafts [2].

The glomerular filtration barrier (GFB) is composed of two cell types, the capillary endothelial cells and the podocytes, separated by a specialized glomerular basement membrane. In addition, mesangial cells support the structure of the glomerulus, and parietal epithelial cells line the capsule encircling the glomerular capillaries (Fig. 1). The cell–cell

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junction between adjacent podocyte foot processes is known as the slit diaphragm and is a highly sophisticated complex of proteins that orchestrates signaling to the interior of the cell.

Much has been discovered about the genetics of NS since the discovery of the gene encoding nephrin in 1998 [3]. Nephrin, along with other proteins in the slit diaphragm, is now known to be essential to the filtration mechanism of the GFB. Mutations in genes encoding slit diaphragm proteins have led to proteinuria and renal failure in animal models, and have also been identified in humans with NS. The discovery of these slit diaphragm proteins has led to subsequent studies on podocytes identifying both downstream pathways with effects on actin cytoskeleton remodeling within foot processes, as well as upstream factors involved in the pathogenesis of NS. In this review, we will discuss the slit diaphragm proteins, the cellular pathways in the podocyte, the control of the podocyte actin cytoskeleton, podocyte motility, and the effects of current therapies for NS on the podocyte. Finally, we will elucidate some of the current breakthroughs that are helping us to understand the nature of circulating factors in the pathogenesis of SRNS.

Podocyte physiology

The tri-layer GFB comprises of the fenestrated capillary endothelial cells, the glomerular basement membrane, and the podocyte. The podocyte has many unique properties that are key to its role in ultrafiltration.

The podocyte consists of a cell body, major processes, secondary processes, and finely interdigitating foot processes. The slit diaphragm membrane, which links the foot processes, controls the ultrafiltration of molecules by signaling to the actin cytoskeleton within the foot processes. In addition to the actin cytoskeleton within the foot processes, other important structural components of the podocyte include vimentin-rich intermediate filaments and microtubules. These components all contribute towards cell shape and rigidity. Microtubules regulate cell motility, vesicular transport, cell polarity, and organization and positioning of the membrane organelles. Crosstalk between actin and microtubules enables changes at the slit diaphragm to be transmitted to the nuclei via microtubule-associated proteins, and enables the podocyte to respond to signals from the foot processes [4].

Under the cell body and its major processes lies the subpodocyte space. This is estimated to cover 60% of the GFB, and the level of resistance within this space (which is controlled by tight exit pores) contributes significantly to the overall permeability of the GFB [5].

It is interesting that the podocyte, traditionally described as an epithelial cell, shows several features of smooth muscle cells when fully differentiated. It expresses smooth muscle cell markers such a smoothelin and calponin [6], and is thought to have a contractile function [7]. It has been speculated that, instead of it being the mesangial cell, the podocyte might have the role of supporting capillary pressures, preventing capillary expansion and maintaining ultrafiltration [6].

Regulation of the actin cytoskeleton

A universal pathological feature of NS is podocyte foot process effacement, as seen by electron microscopy. The dynamic control of the actin cytoskeleton is essential in maintaining the shape and movement of the foot processes, as well as in maintaining cell–cell contacts. More than a hundred proteins are involved in the regulation of actin, enabling processes such polymerization and depolymerization [9]. When arranged linearly as a central core of filament bundles, actin can provide significant tensile strength [8]. Actin branching in the form of filopodia or lamellipodia is likely to drive cell motility, as has been seen in the growth cones of neurons. Actin monomers can self-assemble, but this is kinetically unfavorable. The two important catalysts for rapid actin assembly are formins, which enable actin filaments to elongate at a rapid rate [10], and the actin-related protein 2/3 (Arp2/3) complex,

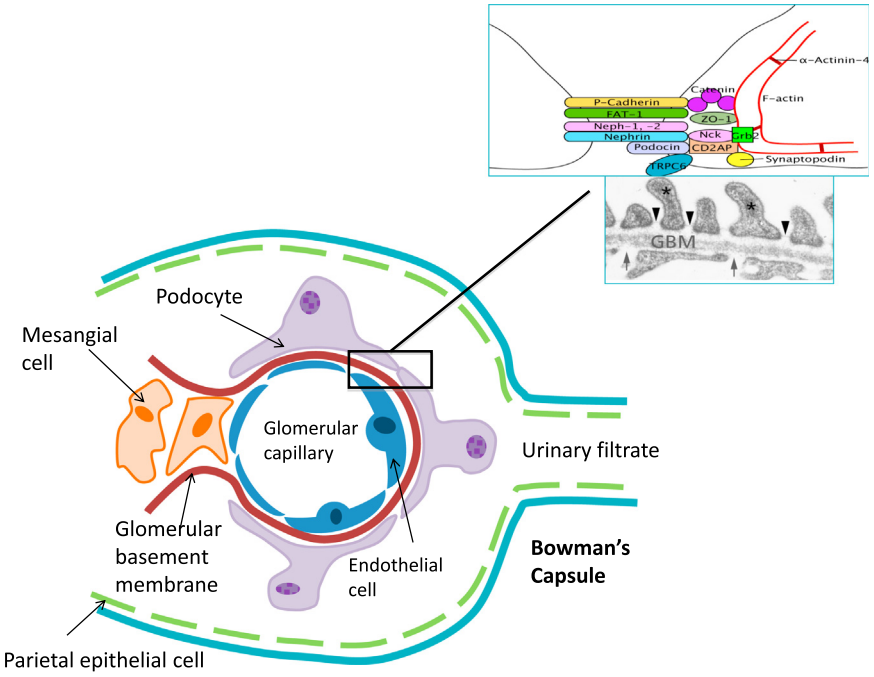

Figure 1. Diagram of a glomerular capillary, showing the three cell types, as well as the parietal cells of Bowman's capsule, and their interrelationship in supporting the glomerulus and forming the filtration barrier.