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Review

Mechanism of podocyte detachment: Targeting transmembrane molecules between podocytes and glomerular basement membrane

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ABSTRACT

The glomerular filtration barrier is highly size and charge selective, both podocyte and glomerular basement membrane are essential for permeability. In disease state, with the normal filtration structure broken down, podocytes detach from the glomerular basement membrane. The total number of podocytes decreasing followed by proteinuria. Although the mechanism of podocytes loss is still being debated, adhesion dysfunction is thought to contribute to the decrease in podocyte density. Others have given much attention to podocyte foot process fusion, podocyte apoptosis, and podocyte proliferation disability in the pathological state. This review focuses on the interaction of podocytes with glomerular basement membrane, and the molecules contributing to podocyte detachment. Here we illustrate biology character of the transmembrane matrix receptors integrin $\alpha_3\beta_1$, α-/β-dystroglycan, and tetraspanin CD151, we interpret cellular and extracellular transmembrane matrix receptor interrelated proteins. And we summarize the previous research achievement to reveal the internal connections of those proteins and to know how they work together preventing podocyte detachment and then sustaining the normal shape of glomerular filtration barrier.

1. Introduction

The glomeruli in the kidneys of an adult human produce 130–180 L of ultrafiltrate everyday, and the process occurs through the capillary wall of the glomerulus. The filtration barrier in these highly specialized units is composed of three layers: the fenestrated endothelial cell layer, the glomerular basement membrane (GBM), and the epithelial cells (podocytes) [1]. Proteinuria, resulting from defects in glomerular filtration is an early pathologic feature of many conforms of chronic kidney diseases, including minimal change disease, focal segmental glomerulosclerosis, membranous glomerulopathy, and lupus nephritis [2]. Podocytes line the outer aspect of the GBM, form the final barrier to protein loss, associated directly to the marked proteinuria [3]. In response to injurious stimuli, podocytes often undergo a range of adaptive changes, including hypertrophy, dedifferentiation, detachment, and apoptosis [4]. Once a critical proportion of the total podocyte population is lost, the remaining cells are unable to compensate, the change is irreversible, both apoptosis and detachment contribute to the development of glomerulosclerosis and renal failure progression together [5].

Based on recent progress in the molecular pathology of podocytes, four causes of podocyte foot process effacement and proteinuria can be identified:

- abnormalities of proteins of the slit diaphragm complex and its associated lipid rafts;
- abnormalities in the GBM or the adhesive interaction between the podocytes and the GBM;
- abnormalities of the actin cytoskeleton;
- alterations in the apical membrane domain of podocytes [6].

Of those points, focus on the slit diaphragm and actin cytoskeleton has been detailed once again. In this article, we will focus on the GBM and podocytes adhesive interaction, and reveal the in-depth molecular mechanism of podocyte detachment. Integrin $\alpha_3\beta_1$ and dystroglycan are two transmembrane molecules that mediate the binding of podocytes to the glomerular basement membrane. In fact, in addition to play as adhesion protein, they also work together with other associated proteins to make up receptor complex, translate outside–inside signaling to sustain the integrity of the kidney filtration barrier [7].

2. Podocyte and glomerular basement membrane

2.1. Podocyte

Podocytes are highly specialized and differentiated epithelial cells, in terms of their cytoarchitecture, podocyte may be divided into three structurally and functionally different segments: cell body, major processes and actin-rich secondary foot processes (Fig. 1). The cell body is at the center of podocyte, and essentially lies

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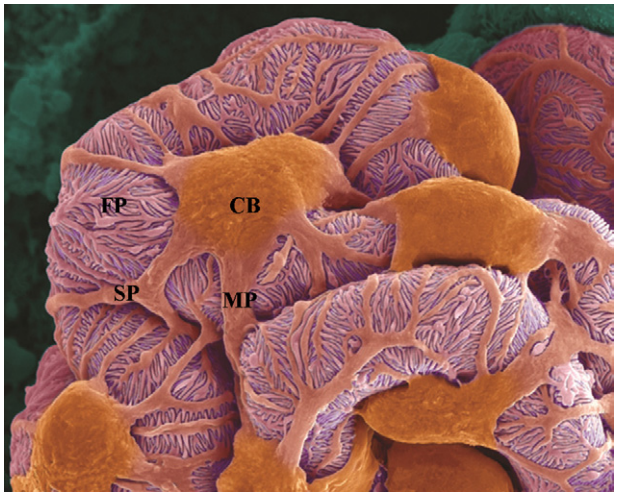

Fig. 1. Scanning electron micrograph of normal rat glomerular capillaries. The kidney glomerulus consists of a tightly coiled network of capillaries. The urinary side of the capillary wall is covered by the highly branched podocytes. The large cell body (CB) sends out thick primary major processes (MP) that further ramify secondary foot processes (SP) that form specialized interdigitate adjacent cell–cell junction architecture. Under the foot processes (FP) is the glomerular basement membrane that surrounds the glomerular capillary. Below the surface, blood flows through the coiled is the core of a glomerulus. (Not visible in this view). ©Dennis Kunkel Microscopy, Inc.

in the urinary space [8]. The foot processes embed into the glomerular basement membrane affixed by cell surface adhesion proteins, such as $\alpha_3\beta_1$-integrin and α-/β-dystroglycans, to guarantee the stability of the podocytes. Adjacent podocyte foot processes form a specialized interdigitate cell–cell junction architecture, the zipper-like architecture is called slit diaphragm [9]. Tiny pinholes on the slit diaphragm form the basis of the size-selectivity of podocytes, they are freely permeable to water and small solutes but relatively impermeable to plasma proteins [10]. The slit diaphragm is composed of numerous proteins that are not generally found elsewhere in the body, such as nephrin, podocin and CD2-associated protein [11]. These "podocyte-specific" proteins make the slit diaphragm specialized for carrying out the renal ultrafiltration function. In proteinuric diseases, foot process effacement and podocytes detach into the urine are often observed, but how these processes occurred in the development of proteinuria, the specific mechanisms are not well understood.

2.2. Glomerular basement membrane

As the structural foundation of the glomerular capillary, the glomerular basement membrane provides support for endothelial and podocyte anchoring on both sides. Similarly to all basement membranes, the main components of the GBM include type IV collagen, nidogens, laminin, heparan sulfate proteoglycan, proteoglycans and agrin [12]. The GBM contributes importantly to the kidney's filtration barrier, it both acts as a physical filter and charge barrier. Jarad et al. demonstrated that proteinuria coincided with GBM defected timely, provides the key evidence of GBM is a selective molecular sieve [13]. And as a charge barrier, while a decrease in negatively charged occurs, proteinuria can result from either primary podocyte or primary GBM defects. Mutation of GBM proteins encoding genes caused proteinuria, nephrotic syndrome, and progressive renal failure [14]. Knockout studies in mice and genetic findings in humans show that the laminin and type IV collagen components are particularly important for GBM structure and function. Study on gene mutation of the mouse laminin α5 results in a variety of developmental defects, including broken down of the glomerular basement membrane and failed of glomerular vascularization [15]. Alport syndrome is an inherited nephropathy characterized by alterations of the glomerular basement membrane because of mutations in type IV collagen genes [16]. These results highlight the importance of the GBM for establishing and maintaining the properly functioning glomerular filtration barrier.

2.3. Connection of podocytes and glomerular basement membrane

The preservation of appropriate podocytes adherence to the underlying GBM is critical for maintaining normal glomerular filtration. These adhesions are integrated with the cytoskeleton to participate in functional maintenance of cellular and extracellular structures [17]. Glomerular development and function are dependent on cell-matrix interaction. This interaction is mediated by binding receptors to extracellular matrix proteins and is modulated by both intrinsic podocyte proteins and extracellular matrix constituents of the GBM [18]. Previous studies have confirmed that transmembrane cell receptors such as $\alpha_3\beta_1$-integrin, α-/β-dystroglycans and tetraspanin CD151 served as bridge proteins between matrix and podocytes [19]. They play as primary adhesion receptors that band to their ligands located on the GBM. In addition to their structural roles in the FP adhesion, integrin and dystroglycan are also transducers of extracellular signals in an "outside-in" fashion to regulate intracellular actin dynamics [20].

3. Transmembrane matrix receptors

3.1. Integrin

Integrins are heterodimeric transmembrane receptors composed of α and β subunit. The predominant integrin expressed in podocyte is $\alpha_3\beta_1$ integrin, the molecule is composed of large extracellular domains (β subunit) and relatively small cytoplasmic domains (α subunit) [21]. Integrin β_1, the most abundantly expressed integrin subunit, binds at least 12 α subunits, forming dimmers which are critical for cellular and extracellular matrix interaction [22]. Moreover, integrin $\alpha_1\beta_1$ and $\alpha_8\beta_1$, both highly expressed in the kidney, play a minor role in glomerular development [23]. Integrins regulate cell functions, including adhesion, migration, cell cycle regulation, and differentiation. They serve as physical attachment sites for the actin filaments and form focal adhesions to recruitment of intracellular cytoskeletal proteins. The actin dynamics in response to extracellular stimuli are regulated at the integrin adhesion site, by focal adhesion kinase, integrin-linked kinase (ILK) and the actin polymerization complex Arp2/3 [24]. These findings suggest that the integrin-binding status in podocytes might influence the cytoskeletal organization and thereby contribute to determining the foot process shape. The cell–matrix integrin signaling is indispensable for maintaining the delicate architecture of the glomerular filtration barrier. Decreased expression of $\alpha_3\beta_1$ integrin is closely related to podocyte depletion, consistent with this, mice that lack α_3-integrin are born without podocyte foot processes formation [25]. In podocytes, $\alpha_3\beta_1$-integrin serves as the podocyte cell-matrix adhesion modulator rather than as an adhesion receptor. Lack of α_3-integrin does not impair adhesion of podocytes but rather increases adhesion and protects against puromycin aminonucleoside induced podocyte detachment [26]. Mice with podocyte-specific deletion of integrin β_1 are born normal but cannot complete postnatal renal development. They exhibit detectable proteinuria on day 1 and die within a week [27]. Thus, expression of integrin by the podocyte is critical for maintaining the structural integrity of the glomerulus.