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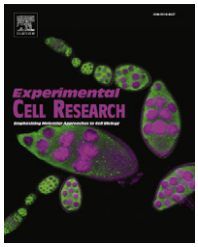

Review Article

Podocytes: Gaining a foothold

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ABSTRACT

In an attempt to understand the basis of glomerular disease, significant progress has been made in understanding the mechanisms that determine podocyte development and the maintenance of podocyte health. This review examines recent advances in this area focusing on the podocyte intercellular junction, actin cytoskeletal dynamics, and determinants of podocyte cell polarity, autophagy and mTOR biology.

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Introduction

The human kidney contains approximately a million individual filtering units called glomeruli composed of specialized capillaries that are surrounded by a basement membrane and glomerular epithelial cells or podocytes. These capillary tufts are structurally supported by modified smooth muscle-like cells called mesangial cells. Though all glomerular components are important for proper glomerular development and function, the podocyte has recently been the focus of numerous investigations. Over the past decade, identification of human diseases with podocyte-specific gene mutations and observations from animal models and cell culture studies have led to intense scientific interest in the role of podocytes in glomerular diseases (Table 2). Although investigation of the mechanisms of glomerular disease during this period has focused largely on this cell, there is growing evidence to support the importance of the inter-dependence between all components of the glomerulus.

Study of podocyte biology can be broadly divided into investigation of mechanisms and physiology that define podocyte development, the maintenance of mature podocyte health, and the response of podocytes to injury. Podocyte development involves the metamorphosis of a cuboidal epithelial cell sitting on the glomerular basement membrane into a cell with octopus-like primary, secondary, and tertiary (or foot) processes that interdigitate to form unique intercellular junctions called the slit diaphragm. Podocyte maintenance in maturity requires cell signaling-dependent structural changes to maintain filter integrity and to maintain glomerular health. In most glomerular disease states the podocyte undergoes dramatic morphological change best seen by scanning electron microscopy involving spreading and shortening of its finger-like tertiary processes, a process termed "foot process effacement". While the morphological appearance of podocytes found in many glomerular diseases might be indistinguishable, it is likely that the underlying molecular disease mechanisms that cause these changes in morphology are distinct. Understanding the unique molecular mechanisms that are responsible for these differences will ultimately aid us in designing specific therapies for individual disease conditions. In the following discussion, we will review recent progress in understanding mechanisms inherent in podocyte development and in the maintenance of podocyte health.

Podocyte development

Podocyte precursor cells are polarized cuboidal epithelial cells that undergo differentiation with emergence of octopus-like processes that ultimately extend to surround glomerular capillaries. These processes possess a highly organized three-dimensional structure with three levels of branching. Primary processes arise from the podocyte cell body and divide further to form secondary processes. Both the primary and secondary processes are primarily microtubule and intermediate filament-based structures. Additional processes arising from secondary processes form finger-like actin-based tertiary or foot processes that interdigitate in the plane of the basement membrane. The molecular mechanisms that determine the metamorphosis from podocyte precursors to differentiated podocytes remain poorly understood.

Podocyte polarity

*Cellular p*olarity or asymmetric distribution of cellular constituents including membrane proteins and organelles is a fundamental property that determines cell structure and function. Cell plasma membranes are polarized in the axis perpendicular to its basement membrane into apical and basolateral domains demarcated by a cell–cell junction. Morphological examination of early podocyte development revealed migration of the podocyte cell–cell junction from an apico-lateral to basolateral position prior to emergence of nascent primary processes that extend along the glomerular basement membrane [1,2]. It is remarkable that beyond the emergence of these initial podocyte processes, studies have not been performed that image the morphogenesis of secondary and tertiary podocyte processes. Therefore, it is not surprising that we have only a rudimentary understanding of the molecular mechanisms that provide the cues that initiate podocyte differentiation and ultimately define podocyte architecture.

Evolutionarily conserved protein complexes that conspire to specify polarity in a variety of other polarized cell types also appear to play a role in establishing polarity in podocytes [3,4]. Among the established polarity complexes known, the Par3–Par6–aPKC complex is necessary for establishing and maintaining polarity in polarized epithelia and neurons. In polarized epithelial cells, the par3/par6/aPKC complex facilitates asymmetric targeting of proteins that maintain the functional differences between the apical and basolateral domain [5,6]. In podocyte precursors, the par3/par6/aPKC polarity complex is initially targeted to the apicolaterally-placed adherens junction. With cellular differentiation, this polarity complex moves with this cell junction toward the basement membrane before apparently taking up a position with the forming tertiary process intercellular junction. While mice engineered to obtain podocyte-specific deletion of aPKC lambda/iota (activated protein kinase C) exhibited normal podocyte development at birth [4], these animals ultimately exhibited abnormal podocyte morphology, proteinuria and glomerulosclerosis post-gestation, suggesting that there is an ongoing role of par3/par6/aPKC complex proteins in maintenance of podocyte morphology in maturity.

The molecular mechanisms that define podocyte process patterning are of interest because determinates of these patterns might be disordered in podocyte disease or might be employed following podocyte injury to restore normal morphology. In addition to apicolateral polarity podocytes also exhibit polarity in the plane of the tissue defined by the unique pattern assumed by their interdigitating processes. To obtain this unique patterning, these cells appear to employ molecular mechanisms similar to those used in axonal path finding or in patterning of other complex tissues. For example, Nephrin and Neph1 are cell adhesion molecules of the Ig superfamily that are specifically targeted to podocyte intercellular junctions. When deleted in human inherited disease or in mouse genetic mutant models, absence of Nephrin or Neph1 results in a developmental phenotype in which podocyte tertiary process formation and podocyte intercellular junction is dramatically disrupted, suggesting that these proteins are required for normal podocyte patterning [7,8]. The hypothesis that Nephrin and Neph1 participate in tissue patterning is supported by evidence of the function of their homologs *hibris* and *roughest* in developing *Drosophila* compound eyes [9,10]. The fly eye is a complex tissue assembled from