How to Build a Tight but Permeable Glomerular Junction

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The filtering glomerulus is a highly specialized capillary bed that simultaneously provides maximal permeability for low molecular weight solutes and highly efficient retention of plasma macromolecules under a decreasing gradient of arteriolar pressure. Fenestrated endothelia, glomerular basement membrane, and interdigitating foot processes from podocytes are the primary structural elements of the filtration barrier. Slit diaphragms establish cell–cell contact between foot processes as the final element of the filtration barrier and are a decisive factor in modulating size selectivity.[1] In the past decade, the discovery of genes mutated in inherited forms of nephrotic syndrome has expanded our understanding of the molecular composition of the slit diaphragm.[2] The discovery of these framework molecules were quickly followed by identification of a series of associated intracellular signaling and adaptor proteins[3,4] (for reviews, see references[5,6]).

The molecular mechanisms of cell–cell interaction among podocytes and their associated signaling events demonstrate several unique features. Podocytes during glomerulogenesis evolve from primordial columnar epithelial cells linked together by apical junction complexes containing classical elements of tight and adherens junctions. These intercellular junctions migrate basally during the capillary loop stage to initiate glomerular slit diaphragm formation.[7] In the mature slit diaphragm, tight junction–associated proteins include zonula occludens 1 (ZO-1), membrane-associated guanylate kinase 1/2, and calcium/calmodulin-dependent serine protein kinase.[7,8] The mature glomerular slit diaphragm demonstrates a functionality usually associated with tight junctions in other cells: Its main role is to provide a barrier function[9] with selective permeability,[10] it defines domains with distinct cell membrane properties and cell polarity,[11] and it offers an array of cell–cell signaling functions.[5] The intercellular filtration slit is 25 to 45 nm wide[12] and somewhat resembles other adherens junctions that show similarly sized intercellular gaps.[13] Typical adherens junction proteins, such as P-cadherin and α-, β-, and γ-cathenin, are found in the vicinity of the slit diaphragm and co-localize with tight junction–associated ZO-1.[14]

The study published in this issue of *JASN* by Fukasawa *et al.*[15] provides additional evidence to support a slit diaphragm model of a *modified* adherens and a *modified* tight junction, with the tight junction proteins more closely associated with slit diaphragm–specific molecules. This is the latest update on five decades of research by Dr. Farquhar and her group to define better the junctional complexes of the glomerular slit diaphragm. This longitudinal effort reflects a remarkable expansion of knowledge starting from pioneering work on the ultrastructural definition of the slit using sophisticated cell biologic approaches and now integrating and combining cell biology with a systems biology approach.

In this study, cell fractionation, immunofluorescence, and immunoelectron microscopy help to define the association of typical tight junction proteins with the slit diaphragm; in particular, junctional adhesion molecule A (JAM-A), occludin, and cingulin are found in the slit diaphragm and co-localize with nephrin in intact glomeruli. Tight junctions in the slit diaphragm network with signaling cascades (aPKC, Rab3b, and Rab13) and complexes responsible for maintaining cell polarity (PAR-3, PAR-6, and Crumbs). In a puromycin model of heavy proteinuria, these proteins, together with ZO-1, increase, whereas the "core" slit diaphragm proteins, nephrin and podocin, decrease. The authors speculate that slit diaphragm–specific proteins interact with classical tight junction proteins to facilitate maturation of the slit diaphragms from classical tight junctions in glomerular development followed by the reversal of these mature arrangements during puromycin nephrosis. The concept that developmental processes are reawakened in disease states is widely known in cancer research.[16] Finally, Fukasawa's work suggests the relationship between slit diaphragms, tight junction proteins, and the actin cytoskeleton in podocytes is a critical connecter for renal diseases associated with foot process effacement.

By contrasting our knowledge from traditional epithelial tight junctions with the unique situation in podocytes,[17] Farquhar's group establishes a model for linking junctional physiology with podocyte cell biology, leading to a better understanding of what makes this junction so unique. Their data support an emerging picture of the slit diaphragm as being not simply a static scaffold for the filtration barrier but rather a highly dynamic and vulnerable process involving complex signaling cascades.

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Several challenges to this concept remain, mostly why the transition from slit diaphragm to tight junction in nephrosis produces an increase and not, as one would predict, a decrease in permeability for macromolecules. For nephrologists, understanding these events and their associated signaling cascades is clinically relevant, because novel approaches and innovative treatment strategies for glomerular failure may be deduced from this knowledge. Five decades after the first work by Dr. Farquhar and her colleagues, the podocyte slit diaphragm remains a fascinating and promising area of research.

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DISCLOSURES

None.

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See related article, "Slit Diaphragms Contain Tight Junction Proteins," on pages 1491–1503.

Type II Calcimimetics and Polycystic Kidney Disease: Unanswered Questions

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The proteins involved in polycystic kidney disease (PKD) detect extracellular cues at primary cilia, cell–cell and cell–matrix contacts, and affect signaling pathways essential to the three-dimensional structure of tubular epithelium. Reduction in one of these proteins below a critical threshold results in a phenotypic switch characterized by defects in planar cell polarity, increased rates of proliferation and apoptosis, expression of a secretory phenotype, remodeling of the extracellular matrix, and cyst development.[1,2] Evidence in the past decade strongly suggests that alterations in two major interacting second messengers, intracellular calcium and cyclic adenosine monophosphate (cAMP), play a central role in the pathogenesis of increased cell proliferation and fluid secretion.[3,4]

Polycystin-1 and -2, the proteins encoded by the genes mutated in autosomal dominant PKD (ADPKD), constitute a family (TRPP) of transient receptor potential (TRP) channels.[5] Polycystin-2 (TRPP2) exhibits characteristic structural features of a TRP channel. Polycystin-1 (TRPP1) is a distant TRP homologue with possible polycystin-2–independent channel activity. Polycystin-1 directly interacts and fibrocystin-polyductin (the protein encoded by the gene mutated in autosomal recessive PKD [ARPKD]) indirectly interacts with polycystin-2

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