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Review

Polycystins, focal adhesions and extracellular matrix interactions ☆

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ABSTRACT

Polycystic kidney disease is the most common heritable disease in humans. In addition to epithelial cysts in the kidney, liver and pancreas, patients with autosomal dominant polycystic kidney disease (ADPKD) also suffer from abdominal hernia, intracranial aneurysm, gastrointestinal cysts, and cardiac valvular defects, conditions often associated with altered extracellular matrix production or integrity. Despite more than a decade of work on the principal ADPKD genes, PKD1 and PKD2, questions remain about the basis of cystic disease and the role of extracellular matrix in ADPKD pathology. This review explores the links between polycystins, focal adhesions, and extracellular matrix gene expression. These relationships suggest roles for polycystins in cell–matrix mechanosensory signaling that control matrix production and morphogenesis. This article is part of a Special Issue entitled: Polycystic Kidney Disease.

1. Introduction

Mutations in the polycystin genes PKD1 and PKD2 are responsible for autosomal dominant polycystic kidney disease (ADPKD), the most common heritable human disease [1]. The proteins encoded by PKD1 and PKD2 function together as a mechanosensory ion channel complex [2,3] that controls calcium influx in response to fluid flow [4] or calcium release from intracellular calcium stores [5]. Polycystin-1 is required for polycystin-2-dependent calcium transients and is thought to stimulate polycystin-2 channel activity [4]. While the identification of the PKD1 and PKD2 genes as mechanosensors provided important leads in determining the basis of cystic disease [6,7], the cellular mechanisms maintaining normal tissue architecture that are controlled by polycystins remain unclear. Most recent studies have focused on a role for polycystins as mechanosensors in primary cilia with good reason. Nearly every cystic disease protein identified in the past 10 years, including polycystin-1 and polycystin-2, has been shown to localize to the cilium and in some cases directly affect ciliogenesis [8]. The cilia hypothesis of cystic disease in its original form posited that cilia, via the activity of polycystin mechanosensory channels, sense tubule lumen fluid flow; loss of cilia mechanosensory signals due to polycystin mutation uncouples fluid flow from regulation of epithelial cell proliferation or cell orientation and leads directly to tubule lumen distension and cyst formation [4]. The elegant simplicity of this model has been challenged on several fronts in recent years. The unexpected finding that conditional knockout of polycystins and other cilia associated genes after postnatal day 14 results in very delayed and in some cases non-uniform cyst formation argues against an acute effect of impaired flow sensing [9–11]. The requirement for injury or stress to the kidney for cyst formation in these models has shifted attention to how mutations in cyst genes predispose tubule cells to failed regeneration and tubule repair [10,11]. It is also perhaps surprising that polycystin-1-deficient embryonic kidneys do not form cysts when explanted and grown in culture despite the lack of tubule flow and lack of the postulated flow sensor polycystin-1 [12]. Thus while the genetic evidence for a central role of the primary cilium in cystic disease remains strong, the model of polycystins as a flow sensors in the cilium may not be sufficient to fully explain polycystin loss of function phenotypes. This point is made clear by the observation that the consequences of polycystin-1 loss of function in the kidney are much more severe than the phenotype of kidney "cilia-null" animals. In conditional, kidney-specific Kif3a knockout mice, kidney tubule cells lack cilia and cystic pathology (fusiform dilatations) first appears at postnatal day 5 (P5), with full involvement of the kidney at P35 [13]. In contrast, kidney-specific knockout of Pkd1 using the same Ksp-Cre line produces cystic kidneys at birth with full involvement of the kidney at P12 followed by death between P14 and P17 [14]. These results as well as studies dating back to the 1980s linking renal and extrarenal ADPKD pathology to alterations in the extracellular matrix, invite a re-examination of polycystin function.

2. ADPKD and integrity of the extracellular matrix

The idea that matrix defects or altered cell adhesion contribute to ADPKD pathology arose in the 1980s with the findings that the extracellular matrix of cystic tissue or cells derived from cysts was dramatically different from normal kidney tubules [15,16].

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Overproduction of ECM proteins has been observed in several studies of ADPKD cells [15,17] and in ADPKD animal models [18–20]. Epithelial cells from cysts also show increased adhesiveness to type I and type IV collagen and decreased migration in response to growth factors [21,22]. Altered expression of integrin cell adhesion receptor subtypes has also been reported in ADPKD cells [21,23]. In addition, genes encoding extracellular matrix proteins or cellular proteins involved in adhesion figure prominently in the lists of upregulated mRNAs in expression profiling studies of human cystic tissue and cystic animal models [23–27]. In some cases, changes in matrix adhesion gene expression precede changes in proliferation-associated genes [27].

Direct evidence that mutations in cell adhesion and extracellular matrix genes are sufficient to cause kidney cyst formation can be found in mouse knockout studies. A hypomorphic mouse laminin-5 mutant develops cortical and medullary kidney cysts with persistence of immature laminins (laminin 332) and basement membrane thickening around cystic tubules [28]. Mutations in the focal adhesion complex protein tensin result in a slowly progressive kidney cystic pathology, indicating that weakening of focal adhesions is sufficient to cause cysts [29].

While these findings suggest that polycystins regulate cell adhesion or matrix composition and that mutations affecting cell adhesion can cause kidney cysts, it has been difficult to assign a primary role for polycystins in regulating cell–matrix interactions since altered extracellular matrix synthesis is a well known response to tubule distension and tissue inflammation [30], both of which occur in the course of cyst development [31]. To separate polycystin-associated cyst initiation events from disease progression and consequences of cyst formation requires a more comprehensive analysis of the data.

3. Extrarenal manifestations of ADPKD and the extracellular matrix

Extrarenal manifestations of ADPKD more directly suggest a link between polycystin function and extracellular matrix production. ADPKD is strongly associated with intracranial and aortic aneurysm [32,33]. It is estimated that 8% of all ADPKD patients also have aneurysm, a significantly higher frequency than that in the general population [34]. Aneurysm is a weakening of the blood vessel wall, commonly caused by mutations in extracellular matrix proteins, for example collagen III and fibrillin [35]. The elasticity and adaptation of the aortic wall to pulsatile blood pressure relies on mechanosensitive responses of vascular smooth muscle cells interposed between layers of elastin matrix that confer recoil properties on the vessel wall [36]. Aneurysmal pathology is characterized by increased production and accumulation of matrix proteins between elastin layers, increased proliferation of vascular smooth muscle cells, elastin fragmentation, and ultimately wall thinning leading to rupture and hemorrhage [36]. Significantly, vascular fragility and aneurysm have been modeled in mouse Pkd1 knockout and hypomorphic mutants [37,38]. In Pkd1 hypomorphs, thickening of the vessel wall media by increased deposition of proteoglycans and fibronectin is the earliest pathology associated with dissecting aneurysm [37]. Hassane et al. propose that loss of polycystin-1 alters smooth muscle interaction with matrix allowing them to revert to a synthetic phenotype, resulting in overproduction of matrix proteins. This phenotype, as well as earlier work showing persistence of embryonic gene expression in ADPKD cells [39], introduces the idea that polycystins may normally act as negative feedback regulators that promote cell differentiation and downregulate matrix synthesis. Recent studies of polycystin-deficient vascular smooth muscle cells (VSMC) have implicated polycystin-1 and polycystin-2 in mechanosensation of stretch or vessel pressure [40]. In normal VSMCs, increased lumenal pressure activates stretch-activated ion channels in VSMCs resulting in calcium influx, smooth muscle contraction and a strengthening of the vessel wall that resists further vessel dilation, a response known as the Bayliss effect [41]. Loss of polycystin-1 or overexpression of polycystin-2 in smooth muscle inhibits activation of stretch-activated ion channels that mediate myogenic tone. The implication of this work is that the balance of polycystin-1 and polycystin-2 expression can alter the sensitivity of smooth muscle cells to mechanosensory signaling, either by direct interactions with stretch-activated channels or indirectly by effects on the cytoskeleton [40]. By modifying how cells respond to stretch [42], mutations in polycystins are likely to have a broad impact on cellular mechanisms regulating synthesis and degradation of vessel wall extracellular matrix [43].

Other less well studied extrarenal pathology associated with ADPKD also suggests a role for polycystins in cell–matrix interactions. ADPKD is associated with increased occurrence of abdominal wall hernia [44]. Structural weakness of the abdominal wall may be associated with residual effects of developmental abnormalities such as failed ventral closure (omphalocoel) or, more commonly in adults, to altered body wall collagen composition [45]. Other extrarenal manifestations of ADPKD that may involve matrix defects include gastrointestinal cysts, cardiac valve defects and pericardial effusion [46,47].

Overproduction of matrix collagen has also been observed in zebrafish models of polycystin-1 and polycystin-2 deficiency [18]. Polycystin knockdown or mutation in zebrafish causes dorsal axis curvature which is linked to overexpression collagen mRNAs and protein expression in the notochord. Reducing matrix gene expression by *col2a1* knockdown rescues axis curvature defects, suggesting that abnormalities in matrix composition or amount are developmental defects linked directly to polycystin function and not secondary consequences of tissue damage or inflammation [18]. Persistent expression of notochord collagen genes in polycystin-deficient embryos further emphasizes a potential role for polycystins in negative feedback regulation of matrix synthesis that signal completion of morphogenesis. This view of polycystins as sensors of mature extracellular matrix may be analogous to “outside-in” integrin signaling [48].

4. Association of polycystins with focal adhesions and extracellular matrix proteins

Biochemical and immunolocalization studies have placed polycystin-1 in multiple cell adhesion structures including focal adhesions, the principal cellular structure mediating cell–matrix adhesion [21,49–52]. Focal adhesions form when cell–matrix attachment induces clustering of integrin receptors, recruiting multiple structural and signaling molecules to the integrin intracellular C-terminus [53]. Focal adhesion structural proteins include talin, tensin, vinculin and alpha-actinin and signaling proteins include focal adhesion kinase, c-Src, p130cas and paxillin [53]. Focal adhesions also anchor intracellular actin filaments and support assembly of actin stress fibers, key cellular structures mediating not only cell adhesion but also active matrix sensing. Cells actively probe their local environment by both ligation-induced signaling, which depends on cell–matrix biochemical interactions, as well as by traction-induced signaling which depends on cellular force generation between points of cell–matrix contact and mediates cell responses to the rigidity of the extracellular matrix [48,54]. Focal adhesions also provide a direct path for external forces to generate cell responses to mechanical perturbation. For example, force applied directly to focal adhesion-anchored actin filaments is sufficient to open mechanosensitive stretch-activated ion channels and initiate calcium signaling responses that strengthen local cytoskeletal structure [55]. Several lines of evidence point to a role for polycystin-1 as an active component of focal adhesions.

Polycystin-1 is localized to focal complexes in both smooth muscle and epithelial cells [52,56]. In epithelial cells, polycystin-1 is

associated with multiple focal adhesion components including talin, vinculin, p130Cas, FAK, alpha-actinin, paxillin and pp60c-src and is posttranslationally modified by tyrosine phosphorylation, suggesting that polycystin-1 may regulate or be regulated by cell–matrix interactions [56,57]. Expression of the polycystin-1 C-terminus in spreading inner medullary collecting duct cells stimulates phosphorylation of the focal adhesion components focal adhesion kinase and paxillin, and promotes FAK-paxillin association [58]. Conversely, polycystin-1-deficient cells show reduced spreading and altered migration [21,58].

In addition to being associated in focal adhesions with matrix-binding integrin receptors, the large N-terminal extracellular domain of polycystin-1 contains multiple motifs predicted to participate directly in cell adhesion [6]. These include the N-terminal leucine rich repeats (LRR), a C-type lectin domain, and the PKD repeats [6]. An isolated polycystin-1 LRR domain fusion protein has been shown to bind directly to the matrix proteins collagen I, fibronectin, and laminin, confirming initial structural predictions [59]. C-type lectin protein domains are commonly involved in calcium-dependent carbohydrate binding [60]. The polycystin-1 C-type lectin domain binds to collagen I and collagen IV in a calcium-dependent fashion, suggesting a potential role for polycystin-1 matrix binding in vivo [61]. The PKD repeats of polycystin-1 are structurally related to Ig domains found in other cell adhesion receptors but comprise a distinct domain family [62]. While the function of the polycystin-1 PKD domain is not known, related PKD domains are present in collagenolytic proteases where they function as binding domains for insoluble collagen [63,64]. Taken together, the results indicate a role for polycystin-1 as a matrix-binding component of focal adhesion complexes. If so then how might polycystin-1 differ from integrins and why might polycystins have a unique and essential role in cell–matrix adhesion?

A unique role for polycystin-1 in focal adhesion complexes most likely relates to its role as a mechanosensory protein. A characteristic feature of many mechanosensory and matrix proteins is a structure based on tandem domain repeats that have the ability to undergo force-regulated conformational changes [65]. Forces applied to mechanosensitive proteins can expose cryptic protein binding sites and phosphorylation sites or induce new enzymatic activity. For example, FRET studies have revealed that repeat structures in the matrix molecule fibronectin may be partially unraveled by cell tension-generated force [66]. When physically stretched, the focal adhesion protein p130cas reveals buried phosphorylation sites subject to phosphorylation by c-Src, facilitating downstream signaling [67]. Polycystin-1 itself can be stretched by physical force [68,69]. Studies of the polycystin-1 extracellular domain using force spectroscopy demonstrate that it is dynamically extensible and able to refold when stretch forces are removed [68]. The step-wise unfolding of polycystin-1 has been linked to the tandemly repeated PKD repeats that unfold sequentially under stretch [68]. The distensibility of polycystin-1 is modulated by disease-causing mutations and environmental conditions [70,71] suggesting that force-induced changes in polycystin-1 structure may be physiologically relevant. While the current data support the idea that polycystin-1 can function as a flexible and elastic linkage between cells or between cells and the extracellular matrix, future studies will have to accommodate the findings that the entire polycystin-1 extracellular domain is autocatalytically cleaved from its transmembrane spanning domains and that cleavage is required for at least some of polycystin-1 postnatal functions [72].

5. Polycystins, matrix sensing and development

Cell adhesion based mechanosensors play a prominent role in development [53,73]. Epithelial cells require 3-D matrix attachments to complete differentiation and can sense the rigidity of their environment and respond in context dependent ways [74–79]. ADPKD cells often exhibit a partially “de-differentiated” phenotype, suggesting that disease-causing mutations in polycystins allow cells to revert to embryonic patterns of gene expression [3]. For instance, embryonic matrix genes and receptors (collagens type I, III, IV, laminins and heparan sulfate proteoglycan, β4 integrin), cell surface proteins (erb-B2, β2 NaK ATPase subunit), and secreted proteins (periostin) are re-expressed in ADPKD tissue, suggesting that ADPKD cells fail to complete an important developmental transition or revert to an immature state [20,23,39,80,81]. In this view, polycystins are likely to act as sensors of tubule development and tissue maturation that interact with the cellular environment and adjust gene expression programs to ensure orderly morphogenesis [82]. Future studies of how mechanosensory functions of polycystins may be linked to sensing and production of extracellular matrix are likely to yield fruitful insights in the pathology of ADPKD.

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