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Renal Dysplasia in the Neonate

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Abstract

Purpose of review—Renal dysplasia is classically described as a developmental disorder whereby the kidneys fail to undergo appropriate differentiation, resulting in the presence of malformed renal tissue elements. It is the commonest cause of chronic kidney disease and renal failure in the neonate. While several genes have been identified in association with renal dysplasia, the underlying molecular mechanisms are often complex and heterogeneous in nature and remain poorly understood.

Recent findings—In this review, we describe new insights into the fundamental process of normal kidney development, and how the renal cortex and medulla are patterned appropriately during gestation. We review the key genes that are indispensable for this process, and discuss how patterning of the kidney is perturbed in the absence of these signaling pathways. The recent use of whole exome sequencing has identified genetic mutations in patients with renal dysplasia, and the results of these studies have increased our understanding of the pathophysiology of renal dysplasia.

Summary—At present, there are no specific treatments available for patients with renal dysplasia. Understanding the molecular mechanisms of normal kidney development and the pathogenesis of renal dysplasia may allow for improved therapeutic options for these patients.

Keywords

renal dysplasia; whole exome sequencing; CAKUT

Introduction

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are common congenital disorders, affecting 1 in 200 humans (1). While a wide variety of renal abnormalities are classified under CAKUT, congenital unilateral or bilateral renal dysplasia represents the most common cause of chronic kidney disease and renal failure in the neonate (2). Renal dysplasia is classically described as a developmental disorder where the kidneys fail to

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Conflicts of Interest

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differentiate normally, resulting in the presence of primitive tubules, interstitial fibrosis, renal cysts and cartilage in the renal parenchyma (2). In general, renal dysplasia is thought to arise from either an intrinsic defect in the differentiation of the renal parenchyma, or as a secondary result of a functional or structural obstruction of the lower urinary tract (for example, posterior urethral valves, ureteropelvic junction obstruction or vesicoureteral reflux) (3). In contrast, renal hypoplasia refers to abnormally small kidneys (less than two standard deviations below the expected mean when correlated with age or growth parameters) with normal morphology and reduced nephron number. Current clinical practice utilizes renal ultrasonography to measure renal size and echogenicity as a means of evaluating the severity of renal hypoplasia and dysplasia. This has several limitations: 1) inability to distinguish between renal hypoplasia and dysplasia; 2) limited ability to predict renal reserve (or, the number of functioning nephrons); 3) limited information regarding the prognosis or likelihood of progression to renal failure. At present, renal transplant or dialysis are the only treatment options for renal failure, which result in significant morbidity and increased risk for mortality for patients. Given this, an improved understanding of the pathophysiology of renal dysplasia is an important prerequisite for the development of better diagnostic tools, prognostic indicators and potential novel therapies.

The underlying etiologies of renal dysplasia are complex and multifaceted, and still not fully understood (2). The heterogeneity of the phenotype likely reflects interactions amongst genetic, epigenetic and environmental factors that all impact genitourinary development. Despite this complexity, emerging information about the molecular cues and signaling pathways required for appropriate kidney development and patterning is providing significant insights into the pathogenesis of renal dysplasia.

Overview of mammalian kidney development

Mammalian kidney formation begins in the fifth week of gestation in humans, and at embryonic day 10.5 in the mouse, with the outgrowth of the ureteric bud from the Wolffian duct into the metanephric mesenchyme (Figure 1) (4,5). The subsequent formation of nephrons is classically described as dependent on reciprocal inductive signals between these two tissues. Thus, Gdnf secreted by the metanephric mesenchyme binds to its corresponding Ret tyrosine kinase receptor on the ureteric bud, and induces outgrowth and branching of the ureteric bud (6). This ultimately results in the formation of a complex ureteric tree network that gives rise to the collecting duct system. The metanephric mesenchyme condenses around each ureteric tip into a characteristic cap mesenchyme, containing Six2⁺/Cited1⁺ nephron progenitors that eventually differentiate into all other epithelial segments of the nephron following induction by Wnt9b secreted from the ureteric tips (7-9). Emerging evidence now implicates the renal stroma, which is derived from the mesenchyme adjacent to the cap mesenchyme (and is marked by the expression of FoxD1), as a third cell lineage that is crucial in nephron patterning (10-12). The renal stroma gives rise to all perivascular cells including, pericytes, glomerular mesangium, smooth muscle arterioles and renin cells (13).

In response to high levels of Wnt9b, nephron progenitors condense into pre-tubular aggregates, undergoing a mesenchymal to epithelial transition into the renal vesicle, in a β -

catenin dependent manner (14). As nephrogenesis proceeds, renal vesicles undergo further morphogenic changes to become comma and s-shaped bodies. At this stage, vascularization of the nephrons occurs where both endothelial and perivascular cells are recruited to the s-shaped body cleft. This generates a capillary loop nephron consisting of podocytes and fenestrated endothelium that form the glomerular filtration barrier, with its integrity supported by the glomerular mesangium. Eventually, a mature nephron is formed which consists of the glomerulus linked to the collecting duct system through differentiated epithelial segments including the proximal tubule, loops of Henle and distal tubule (15).

Molecular mechanisms of nephron progenitor self-renewal

Brenner's hypothesis postulated that individuals with a reduced nephron number at birth are at greater risk of developing hypertension and chronic kidney disease (16). It is reasonable to assume that final nephron numbers are predetermined by the number of nephron progenitors that are present during nephrogenesis (17). This assumption was confirmed in a recent study where diphtheria toxin ablation of a subset of nephron progenitors during gestation resulted in reduced nephron numbers without overt evidence of renal hypoplasia (18). Given that nephron progenitors are critical in establishing final nephron endowment, these progenitors must maintain their ability to self-renew so as to prevent premature exhaustion prior to cessation of nephrogenesis (7,9,19,20). Moreover, incorrect differentiation of nephron progenitors leads to renal dysplasia (21).

It is notable that recent studies from multiple groups have shown that the nephron progenitors appear to be more heterogeneous than previously thought. Thus, the primitive self-renewing nephron progenitors are thought to be marked by the co-expression of $Six2^{+}/Cited1^{+}$, and $Six2^{+}/Cited1^{-}$ cells are thought to be more committed towards differentiation (19,20). It has been proposed that the transcription factor $Six2$ acts by ensuring only a fraction of the nephron progenitors become committed to differentiate after induction (9). In the undifferentiated $Six2^{+}/Cited1^{+}$ progenitors, $Six2$ forms a complex with Lef/Tcf factors to maintain multipotency of the nephron progenitors (19). In $Six2^{low}$ pretubular aggregates, this is lost upon entry of β -catenin into the complex, which subsequently promotes transcription of genes known to be critical in the mesenchymal to epithelial transition, such as $Fgf8$ and $Wnt4$ (19). Genetic deletion of $Six2$ from nephron progenitors resulted in severe renal hypoplasia due to ectopic renal vesicle formation, and premature exhaustion of the nephron progenitors (9). Conversely, ectopic expression of $Six2$ in embryonic kidney explants resulted in preservation of the nephron progenitor population and suppression of mesenchymal to epithelial transition (9).

$Wnt9b$ has recently been shown to have a role in maintaining the multipotency of nephron progenitors, in addition to its function in inducing the nephron progenitor to commit towards differentiation (7). These divergent actions co-existing within the same cellular population are likely to be a collaborative effort between $Six2$ and Wnt/β -catenin regulatory mechanisms acting on *cis*-regulatory modules present in progenitors to suppress expression of mesenchymal to epithelial transition genes (19).

In addition to Wnt signaling, $Bmp7$ has been shown to not only promote self-renewal of the $Six2^{+}/Cited1^{+}$ nephron progenitors through a $Mapk$ dependent manner, but also to induce

transition of the Six2⁺/Cited1⁺ nephron progenitors to exit into a Six2⁺/Cited1⁻ state via phospho-Smad1/5 activation (20). Besides Bmp7, Fgf9 and Fgf20 growth factors are also critical for nephron progenitor survival and maintenance (22). More recently, it has been demonstrated that the age of nephron progenitors affects its commitment to either stay undifferentiated, or to exit from its multipotent state (23). Specifically, elevation of mTor and reduced Fgf20 with aging appears to be the main contributory factors towards determination of nephron progenitor cell fate (23). Other key signaling pathways and transcription factors that have also been demonstrated to be indispensable for nephron progenitor maintenance include Osr1, Eya1, Wt1, Sall1, Dlg1 and Cask (24-28).

In addition to these genetic factors, microRNAs (miRNAs) have also been implicated in nephron progenitor survival and self-renewal. MiRNAs function by post-transcriptionally regulating gene expression and protein translation (29). Genetic ablation of *Dicer*, the endoribonuclease enzyme required for biosynthesis of miRNAs, resulted in increased apoptosis in nephron progenitors associated with elevated levels of Bcl2L11 (Bim), a pro-apoptotic protein (30,31). Loss of one specific miRNA cluster, miR-17~92, in nephron progenitors and their derivatives resulted in decreased nephron number and pathological signatures of chronic kidney disease including proteinuria, glomerulosclerosis and podocyte foot effacement (32).

Molecular mechanisms of nephron patterning

Nephron patterning into the various highly specialized segments is essential for establishing the functional role of the nephron, and abnormalities of nephron pattern result in renal dysplasia (21). Progression of pretubular aggregates into polarized renal vesicles is dependent on the hierarchal expression of *Fgfr11*, *Fgf8*, *Wnt4* and *Lhx1* (33-36). Appropriate nephron patterning ensues, therefore ensuring that the various precursor cells undergo appropriate differentiation into their respective mature cell type as well as establishing the architecture of the nephron.

Both Hnf1 β and Notch signaling have not only been shown to be important for nephron patterning, but also to be associated with human syndromes when mutated, renal cysts and diabetes (RCAD) and Alagille syndrome, respectively (37,38). Expression of Hnf1 β within the comma and s-shaped bodies has been proposed to regulate appropriate nephron polarization patterning via the transcriptional regulation of its downstream target genes including *Lfng*, *Dll1*, *Hnf4a*, *Cdh6*, *Pcsk9* and *Tcfap2b* and Notch-associated genes including *Lfng*, *Dll1*, *Jag1* and *Irx1/2* (39). Lack of Hnf1 β results in a severe nephron patterning defect with rudimentary glomeruli that are connected to the collecting duct system via a short tubule (39). While renal vesicles do develop and appear to undergo appropriate polarization in the absence of Hnf1 β , these structures however fail to acquire an appropriate s-shaped body pattern, followed by increased apoptosis in late stage s-shaped bodies (39). Notch signaling, specifically Notch2, has been proposed to be required for optimal s-shaped body formation, differentiation into proximal tubules and podocytes as well as maintaining the proliferation capacity of the proximal precursors (40).

As mentioned earlier, miRNAs have been implicated in nephron patterning as well. The loss of *Dicer* activity in the renal stroma and its cellular derivatives resulted in elevated

apoptosis, renal hypodysplasia and glomerular mesangial defects due to ectopic accumulation of Bcl2L11 and p53-target genes (41). Other renal lineages which develop renal dysplasia related to a loss of Dicer activity include, ureteric bud (renal cyst due to altered oriented cell division), podocytes (podocyte foot effacement and proteinuria) and renin cells (loss of blood pressure regulation and striped fibrosis) (31,42-45).

Establishment of the cortical-medullary axis

Unlike nephrogenesis where a wealth of genetic information has been established, the current knowledge on embryonic medullary formation and its genetic regulation is somewhat limited. The current two main mechanisms established for tubular elongation of the collecting duct in the embryonic medulla include convergent-extension mediated by *Wnt9b* and Planar Cell Polarity (PCP) signaling-Oriented Cell Division (OCD) mediated by both *Wnt7b* and *Wnt9b* (46,47). Convergent-extension is described as the process of cytoskeletal and cell shape changes which results in dynamic cellular rearrangements and movements within the epithelial tubules (48). Such cellular reorganization leads to increased tubular length without affecting overall cell number. As the tubule elongates, it is coupled with a decrease in tubular diameter and cell number per cross-section (47).

In contrast to the process of convergent-extension, PCP signaling-OCD mediated by *Wnt7b* or *Wnt9b* directs the collecting duct cells to adopt an oriented topology such that cellular mitosis occurring in parallel to the apical-basal plane would result in tubular elongation (46,47). Studies from the *Wnt7b* mouse model have demonstrated that *Wnt7b* secretion from the collecting duct acts indirectly by first signaling to the medullary interstitium via a *Wnt*/β-catenin canonical pathway, followed by activation of interstitial *Wnt4*, *Wnt5a* or *Wnt11* acting through the non-canonical route to regulate PCP-OCD in the collecting ducts (46).

The multifaceted genetic circuit of renal dysplasia

Given the complexity of the genetic circuitry regulating kidney development, it is no surprise that mutations in a number of the genes described above result in renal dysplasia (49). Some of these renal disorders, although not exhaustive, include Pallister-Hall Syndrome, characterized by renal agenesis or hypoplasia defects due to *GLI3* mutation which disrupts Sonic hedgehog signaling and downstream genes associated with renal development such as *PAX2* and *SALL1* (50-52); Townes-Brocks Syndrome, characterized by renal agenesis due to *SALL1* mutation which results in defective ureteric bud outgrowth (53,54); Renal Coloboma Syndrome, characterized by vesico-ureteral reflux, renal hypoplasia or agenesis due to *PAX2* mutation resulting in elevated medullary apoptosis and reduced ureteric bud branching (55,56); Ochoa Syndrome, characterized by vesico-ureteral reflux, impaired urinary outflow leading to hydronephrosis due to *HPSE2* mutation (57); Branchio Oto Renal Syndrome, characterized by craniofacial and renal agenesis due to haploinsufficiency in *EYA1* (58); renal agenesis due to *FGF20* mutation (22) and Feingold Syndrome, characterized by renal anomalies due to mutations in *MIR17HG* and *MYCN* (59).

Whole exome sequencing identifies genetic mutations in CAKUT cohort

Transgenic mouse models have served as valuable tools in understanding the fundamental processes of kidney development, as well as providing molecular insights into how renal

anomalies develop when these signaling pathways are dysregulated. Based on these studies, candidate CAKUT-causing or associated genes have been shown to be of functional relevance to human health. Whole exome sequencing of CAKUT patients has now congruently provided information about genetic mutations that are associated with their renal condition including, but not limited to, BMP7, EYA1, HNF1 β , NPHS1, NPHS2, PAX2, RET, ROBO2, SIX2, SALL1, *WT1* (1,60). It is notable that several of these genetic mutations have functionally been validated in transgenic mouse models (Table 1). Moreover, the sequencing platform also has the capabilities of identifying novel genes associated with CAKUT. While whole exome sequencing is not a treatment for renal disease, it offers clinicians and geneticists the ability to provide a more defined clinical diagnosis (with potential prognostic implications) for CAKUT patients. Thus, this information may help to predict the likelihood of renal hypoplasia versus dysplasia, the degree of renal reserve, and likelihood of progression to renal failure.

Conclusion

Renal dysplasia is a common congenital renal disorder in humans and the leading cause of renal failure in the neonate. While the pathogenesis of renal dysplasia is complex and multifaceted, there is a growing body of evidence that links genetic mutations in transcription factors, signaling pathways and miRNAs (among others) associated with kidney development in this renal disorder. The advancement of whole exome sequencing has now allowed clinicians to gain a better insight into the pathogenesis of renal dysplasia, and provide more information to patients.

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Key Points

1. Genetic mutations are strongly associated with renal dysplasia
2. Whole exome sequencing is a sensitive and powerful method of genetic diagnosis of renal dysplasia in humans
3. Understanding the complex mechanisms underlying renal dysplasia may aid in future targeted therapy against the disorder.

Figure 1. Nephron differentiation and patterning during kidney development

In response to Wnt9b signaling from the ureteric tips, the surrounding nephron progenitors condense into pre-tubular aggregates (PA), and undergo a mesenchymal to epithelial transition to form the renal vesicles (RV). These RV subsequently differentiate into comma (CSB) and s-shaped bodies (SSB). Migrating perivascular cells enter into the cleft of the s-shaped bodies, followed by tubular elongation and patterning into a mature nephron with establishment of an appropriate cortical-medullary axis. Images have been obtained from the GUDMAP database (<http://www.gudmap.org/Schematics>). Originally designed by Kylie Georgas, University of Queensland) (5).

Table 1

Selected transgenic mice with functional relevance to human renal dysplasia.

Gene (Disease)	Affected component	Phenotype	Mechanisms	References
Hnf1 β (Renal Cysts and Diabetes Syndrome)	Ureteric bud and metanephric mesenchyme	Medullary hypoplasia and hydronephrosis	<ol style="list-style-type: none"> 1. Hnf1β is thought to act upstream of Wnt9b 2. Hnf1β nulls have defective ureteric bud branching 3. Wnt4Cre and Six2Cre mediated deletion of Hnf1β led to medullary hypoplasia and eventually hydronephrosis in a proportion of these mice 4. Glomerulus is connected to the collecting duct through a short tubule 	(39,61)
Hnf1 β /Pax2 compound mutants	Ureteric bud	Heterozygous mutants develop medullary hypoplasia and hydronephrosis	<ol style="list-style-type: none"> 1. Delayed nephron and medullary interstitium patterning 2. Increased apoptosis 3. Reduced <i>Bmp4</i> and <i>Tbx18</i> expression leading to ureter smooth muscle deficiency. Hence the medullary phenotype could be a secondary defect 	(62)
Pax2 (Renal Coloboma Syndrome)	Ureteric bud and metanephric mesenchyme	Renal agenesis in Pax2 homozygous mutant Reduced renal calyces in Pax2 heterozygous mutants	<ol style="list-style-type: none"> 1. Renal defects due to dysgenesis of the ureteric bud and metanephric mesenchyme 2. Absence of a Wolffian duct 3. Metanephric mesenchyme fails to undergo epithelialization 	(56)
Sall1 (Townes-Brocks Syndrome)	Nephron progenitors	Renal agenesis	<ol style="list-style-type: none"> 1. Failure of ureteric bud invasion 2. Lost of downstream target genes associated with self-renewal 	(27,54)
Six2 (CAKUT)	Nephron progenitors	Renal hypoplasia	<ol style="list-style-type: none"> 1. Premature loss of nephron progenitors 2. Ectopic differentiation 	(9)
Wt1 (Wilm's Tumor or renal agenesis)	Nephron progenitors	Wilms tumor or renal agenesis	<ol style="list-style-type: none"> 1. Failure of nephron progenitors to undergo terminal differentiation 2. Ectopic apoptosis 	(63-66)
Ret (CAKUT)	Ureteric bud	Renal dysplasia	Ureteric branching defects due to abnormal ureteric outgrowth	(6,67,68)
Eya1 (Branchio Oto Renal Syndrome)	Nephron progenitors	Renal agenesis	Lack of Eya1 results in dysregulation of Myc phosphorylation, causing cell cycle perturbations	(25,58)
miR-17~92 (Feingold Syndrome)	Nephron progenitors	Renal hypodysplasia	<ol style="list-style-type: none"> 1. Intrinsic nephron progenitor defects that are likely to be attributed by cell cycle defects. 2. Reduced nephron endowment 	(32,59)
Fgf9/Fgf20 (CAKUT)	Nephron progenitors	Renal agenesis	Premature loss of nephron progenitors	(22)