Lessons on Kidney Development from Experimental Studies

7

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Introduction

The development of human kidney is a complex process requiring intricate cell and tissue interactions to assure the concerted program of cell growth, differentiation, and morphogenesis. Although the molecular and cellular nature of each of these interactions remains currently unclear, significant findings regarding nephrogenesis and its completion among different animal species have been reported over the last two decades. Research so far indicates that there are differences regarding the completion of the process of nephrogenesis among different animal species. In human, sheep, and spiny mouse, nephrogenesis is completed prior to birth, while in rat, mouse, and swine, nephrogenesis continuous after birth [1–7]. Nevertheless, the unrecognized morphological or functional peculiarities characterizing other animal species help the scientific community to reveal and understand the physiological mechanisms during nephrogenesis in human. This has been achieved mainly due to the increased use of animal models in renal basic science laboratories, as well as to the increased expertise of researchers who study kidney development. In the present chapter we aim at presenting and reviewing the existing knowledge on kidney development acquired from experimental studies.

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Novel Structural/Molecules Components that Extend Knowledge on Kidney Development

The Pine-Cone Body

The mature kidney of mammals is the final product of three embryonic excretory organs, the pronephros, the mesonephros, and the metanephros. The latest originates from two main components, the ureteric bud and the mesenchymal cells of the metanephric mesenchyme [7, 8]. Recent studies using light electron microscopy reported that in

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the subcapsular regions of the outer portions of renal cortex, characterized by active nephrogenesis, some cap mesenchymal aggregates showed variability in shape and morphology of their cells. The center of the cap aggregates was occupied by a roundish cell, while their outer regions were characterized by the presence of thin curved shaped cell types twisted around a fixed central cluster, resembling a pine-cone-shaped structure [9].

Although early studies on nephrogenesis speculated that the sequence of morphological events leading to glomerulogenesis and tubulogenesis might start with the outgrowth of the primary nephric duct and the ureteric buds, which invade the metanephric mesenchyme and induce the differentiation of the renal epithelial precursors [10, 11], similar changes in the size and appearance of developing renal cells may be correlated to the various stages of cellular differentiation occurring during cap mesenchymal development [9]. These curved cells which may evolve from the ovoid cells found in the central area of the same aggregate could account for changes in transmembrane signaling and consequently for changes of cellular metabolic activity [12, 13]. Moreover, the presence of prominent and pleomorphic nucleoli may indicate a significant increased cellular metabolic activity associated with cellular differentiation during cap mesenchymal development [14]. These findings suggest the "pine-cone body" formation as an intermediate stage between the condensed mesenchymal nodule to the renal vesicle during conversion of mesenchyme to epithelium. At cellular level, the entire cap developmental process seems to represent the final event of a complex balance between specific intercellular signals involved in the regulation of protein synthesis, cell proliferation, cell motility, and apoptosis [9]. However, further research is necessary in order to better investigate the intimate significance of this new developmental structure.

Wnt Glycoproteins

Wnt-4 belongs to the Wnt family of secretory glycoproteins that are implicated in signaling processes operating during metanephric development. Wnt-4 is expressed in pretubular mesenchyme cells shortly before their aggregation and transformation to simple epithelial tubules [15]. Kispert et al. [16] showed that mesenchymally derived Wnt-4 is not only required, but also sufficient for induction of tubulogenesis in the mammalian kidney and can elicit the complete program of tubular differentiation in isolated metanephric mesenchyme. Interestingly, the activity of Wnt-4 contrasts with other factors thought to regulate mesenchymal development but proved not sufficient or not essential for tubulogenesis [17–23].

Wnt-4 may have a later function in tubulogenesis which is masked in the earlier requirement to form a tubule as Wnt-4 expression in the metanephric mesenchyme is initiated in the aggregating mesenchyme and maintained in the comma shaped bodies before it is downregulated in S-shaped bodies. Wnt-4 probably acts as a trigger to start an intrinsic program in the mesenchymal cells which then proceed to form complex nephron like structures. Considering that a permissive signal from the ureter to the mesenchyme triggers survival and tubulogenesis in the mesenchyme, it can be concluded that kidney tubulogenesis is a multi-step process with a hierarchy of signaling systems. In general, the role of Wnt-4 in tubulogenesis reflects that additional signaling systems control the ratio between interstitial and metanephrogenic cells, between condensing and non-condensing cells, and the maintenance of the mesenchymal stem cells in the periphery [16].

Wnt-9b is another glycoprotein expressed in the Wolffian duct and its derivative that has been implicated in the induction of the mammalian kidney development. Wnt-9b is expressed in the inductive epithelia and is essential for the development of mesonephric and metanephric tubules and caudal extension of the Müllerian duct as it is required for the earliest inductive response in metanephric mesenchym [24]. In addition, Wnt-9b-expressing cells can functionally substitute for the ureteric bud in these interactions. Interestingly, Wtn-9b acts upstream of Wnt-4, demonstrating the major role of Wnt signaling pathway in the organization of the mammalian urogenital system. Wtn-9b-dependent activation of Wnt-4 expression in the metanephric mesenchyme plays

a central role in completing the process of tubule induction. Although Wnt-9b and Wnt-4 may act through distinct receptors, existing evidence suggest that Wnt-9b encodes a permissive signal, the region-specific response being governed by either the interplay of additional signaling factors or preprogramming of the target cell response by early patterning processes [24].

MUC-1

Although human MUC-1 mucin interest has mainly been focused on its role in carcinogenesis and tumor progression, its role in human and non-human embryogenesis was unclear until now. However, recent research in mouse embryos and neonates has shown, among other organs, increased MUC-1 expression in kidney as well [25]. In kidney, MUC-1 expression was mainly restricted to the apical part of the epithelial cells, in line with the characteristic pattern of MUC-1 in adult rat epithelial tissues [26, 27]. Although non-human studies related to MUC-1 have been mainly developed to obtain animal models useful for the comprehension of cancer, MUC-1 could play a relevant role during epithelia cellular differentiation and proliferation.

Glial Cell Line-Derived Neurotrophic Factor

Glial cell line-derived neurotrophic factor (GDNF) was shown to play a key role in kidney development through actions at the RET and GFR 1 receptor and coreceptor by initiating budding of the ureteric duct from the Wolffian duct, branching of the ureteric epithelium within the metanephric mesenchyme, and the formation of new nephrons at the branch tips [28–32]. In the late 1990s, knockout studies indicated that GDNF gene dosage influenced kidney development, with the loss of one allele being sufficient to cause a significant renal phenotype [33–40]. Recently, Cullen-McEwen et al. [41] found that the kidneys of GDNF heterozygous mice at 30 days of age were 25 % smaller than their wild-type littermates despite similar body weights, while stereologic estimates of nephron number identified a 30 % decrease in nephron endowment in young heterozygous GDNF mice compared with wild-type mice [42].

Although it was hypothesized that reductions in glomerular number lead to hypertrophy of the remaining glomeruli with time, evidence indicated that such hypertrophy also occurs when glomerular numbers are reduced genetically. Cullen-McEwen et al. [42] reported that by 14 months of age, glomeruli of GDNF heterozygotes were significantly hypertrophied such that the total glomerular volume was no longer different between wild-type and heterozygous littermates. Thus, the results found in this low nephron-number mouse are in accordance with the hypothesis of Brenner et al. [43] that a reduction in nephron number from birth leads to the development of hypertension and hyperfiltration.

Sodium Transporters

Although experimental studies have so far firmly established that the prenatal environment can modify the adult blood pressure [44–47], the mechanisms in humans are poorly understood. Nevertheless, several experimental models [44, 46–49] indicate that the various manipulations work through a common pathway.

Manning et al. [50] examined the expression of 4 key apical Na transport proteins that are critical for the regulation of Na balance and extracellular volume and found that upregulation of BSC1 and TSC, the apical Na transporters of TAL and DCT, respectively, occurs at both the mRNA and the protein level, reflecting increased Na reabsorption in these two segments. Moreover, NHE3 expression was not changed, suggesting that proximal tubule Na transport, at least the major fraction mediated by NHE3, is not affected by the prenatal programming; NHE3 may be upregulated by mechanisms not associated with altered protein abundance. Interestingly, the Na transporters were not downregulated after the hypertension became manifest, at 8 week of age. Considering that downregulation of TSC is an

important component of the pressure-natriuresis response designed to correct hypertension by increasing renal Na excretion [51], prenatal programming of the Na transporters may override the normal pressure-natriuresis mechanism. Although the signal(s) from mother to fetus that result in transporter upregulation remain unknown, the fetal overexposure to maternal glucocorticoids due to decreased placental activity of the 11β-hydroxysteroid dehydrogenase type 2 enzyme was implicated as a proposed explanation [52, 53]. Indeed, maturation of renal Na transport, measured as Na-K-ATPase expression, is regulated by glucocorticoids and, therefore, abnormal glucocorticoid exposure could therefore have a direct effect on the maturing kidney [54].

Influential Factors of Kidney Development

Maternal Nutrition

The relationship between nutrition and nephrogenesis has been adequately established on animal models with experimental studies showing that maternal nutrition may have an important influence on renal programming [55]. In rats, a restricted supply of nutrients to the mother during the critical window in which nephrogenesis occurs led to a reduced number of glomeruli per kidney, activation of the renin–angiotensin system, glomerular enlargement, and hypertension in later life [47], while in another study, early postnatal overfeeding increased the number of postnatal nephrons and decreased glomerular volume, suggesting that global filtration surface area remains unchanged [56]. Under these circumstances, glomerular hyperfiltration to meet excretory demands due to early postnatal overfeeding could contribute to elevated blood pressure, proteinuria, and progressive glomerulosclerosis in aging overfed males than overfed females. Although the reasons as to why the influence of postnatal nutrition on nephron endowment is limited to male gender are unknown, it has been speculated that hyperleptinemia associated with early postnatal overfeeding may influence renal functions through specific effects involving renal sympathetic hyperactivity and decreased sodium excretion, partially due to an upregulation of Na-K-ATPase [57]. In either case, altered nephrogenesis plays an important role in the early origins of cardiovascular and renal diseases in adulthood [58–61]. Considering that hypertension may be observed in the absence of glomerular number reduction, it is possible that mechanisms different from inborn nephron number deficit to be involved. Of note, early postnatal overfeeding during the suckling period has been demonstrated to induce obesity and cardiovascular and metabolic disorders in adult rats, such as hyperinsulinism and insulin resistance, impairing vascular dilatation capacity through endothelial dysfunction [62–64].

Vitamin A has been proposed as a determinant in fetal renal programming in rats in view of its capacity to closely modulate nephron number and vascular supply [65, 66]. Moreover, the role of vitamin A in renal formation is considered essential since null mice for these genes exhibited renal agenesis or rudimental kidneys [67], while recently, vitamin A supply restored nephron endowment to normal in offspring of rat mothers exposed to protein restriction [68]. In this study, offspring exposed to maternal protein restriction during pregnancy and lactation had a significantly reduced body weight, kidney size, and nephron endowment at weaning, suggesting that administration of retinoic acid during pregnancy, early in gestation, is able to stimulate nephrogenesis per volume of kidney tissue over and above control levels [67]. Although the mechanisms by which retinoic acid stimulates nephrogenesis are not fully understood, studies suggest that it mediates its effects on nephrogenesis by stimulating ureteric branching morphogenesis [69, 70]. The same investigators suggested that the likely molecular candidate mediating these early nephrogenic effects is GDNF, acting via its cell-surface receptor GDNF-α and subsequently activating the receptor

tyrosine kinase c-ret which is known to lead to increased branching morphogenesis of the ureteric bud and in turn enhance nephron formation [29, 30, 67, 71, 72]. Alternatively, administration of retinoic acid may mediate its effects on nephrogenesis via stimulation of the metanephric mesenchyme [73].

Previous studies reported that in male rats, exposure to maternal protein restriction either in utero or whilst suckling can have profound effects on kidney telomere lengths and on urine albumin excretion during much of adult life [74]. These rats appeared to be relatively protected against future nephron damage not only due to the absence of the nephrotoxic effects of urine albumin, but, also, because of their kidney telomere length. Telomere shortening has been implicated in renal diseases, while reduced renal telomere shortening is associated with increased levels of antioxidant enzymes, suggesting the beneficial effects of protein restriction on the development of kidney [75]. On the other hand, fetal exposure to a maternal low-protein diet is associated with disproportionate patterns of fetal growth and later elevation of blood pressure in the rat, suggesting that maternal undernutrition may program the renal nephron number and hence impact upon adult blood pressure and the development of renal disease [76]. Of note, in another study in rats exposed to a maternal low-protein diet in utero, renal morphometry and creatinine clearance at older ages were not influenced by prenatal diet, although blood pressure was elevated at all ages in the low-protein-exposed offspring [77]. However, blood urea N, urinary output, and urinary albumin excretion were significantly greater in low-protein-exposed rats than in control rats at 20 weeks of age, suggesting a progressive deterioration of renal function in hypertensive rats exposed to mild maternal protein restriction during fetal life. Although the mechanisms of protein restriction-induced adulthood hypertension are not well understood, Woods et al. reported that perinatal protein restriction in the rat suppresses the newborn intrarenal renin–angiotensin system and leads to a reduced number of glomeruli, glomerular enlargement, and hypertension in the adult [47]. Nevertheless, additional mechanisms may be involved in kidney development of protein-restricted mammals. Holemans et al. [78] investigated the hypothesis that malnutrition in pregnant rats may lead to altered cardiovascular function in adult female offspring and found that food restriction during the second half of pregnancy and/or lactation does not induce hypertension in adult offspring, but may effect subtle changes in vascular function. Interestingly, two other studies showed a very pronounced blunting of the response to acetylcholine in the neonatal vasculature from offspring of streptozotocin-diabetic rats on a high-fat diet and in the adult offspring of streptozotocin-diabetic rats [79, 80]. Brawley et al. [81] assessed isolated resistance artery function from adult male offspring of control and protein-restricted pregnant dams at two different ages and reported that dietary protein restriction in pregnancy induces hypertension and vascular dysfunction in male offspring. These disorders may be mediated via nitric oxide–cGMP pathway-induced abnormalities in endothelium-dependent and -independent relaxation, reducing vasodilation, and elevating systolic blood pressure [82]. Nevertheless, disturbances in the L-arginine–nitric oxide system and blastocyst abnormalities may contribute to the early appearance of hypertension in the offspring of mothers submitted to significant food restriction during pregnancy [83–87].

Intrauterine undernutrition also increases the oxidative stress by affecting the activity of various enzymes. In a study of pregnant rats submitted to intrauterine undernutrition, Franco et al. [88] tested the participation of certain enzymes on radical generation and found that NADPH oxidase inhibition attenuated superoxide anion generation and ameliorated vascular function. Indeed, release of the superoxide anion in the kidney can be deleterious as it inactivates NO, resulting in excess Na reabsorption and enhanced TGF feedback and thus hypertension [89–91].

In addition, inactivation of NO with oxygen radical forms peroxynitrite which can nitrosylate tyrosine residues, causing renal damage and increasing renal vascular resistance [92–97]. Furthermore, studies have also shown that oxygen radical causes direct vasoconstriction in preglomerular vasculature and in the renal cortical and medullary circulation, and increases intracellular calcium in vascular smooth muscle and endothelial cells, causing renal vasoconstriction and renal damage [98–104]. Accordingly, Franco Mdo et al. [105] reported that treatment with vitamins C and E reduced oxidative stress and high blood pressure levels, and improved vascular function in intrauterine-undernourished rats.

Studies in which oxidative stress was experimentally induced, caused increases in oxidative stress and hypertension, providing strong evidence for either an initiating or a sustaining role of reactive oxygen species in hypertension [94, 98, 106–116]. In Sprague–Dawley rats that received a high Na diet for 8 weeks, a period which is much longer than that in the above-mentioned studies, the arterial pressure increased significantly, and urinary albumin excretion and renal inflammation increased, suggesting that hypertension develops slowly when Na intake is increased in normotensive rats, and the blood pressure elevations are paralleled by increases in ROS and renal damage [117]. Based on the aforementioned data, it seems that long-term exposure to intrauterine oxidative stress may cause renal inflammation, renal damage, and arterial pressure postnatally. Oxidative stress, inflammation, and arterial hypertension participate in a self-perpetuating cycle which, if not interrupted, can lead to progressive cardiovascular disease and renal complications [118].

Nephrotoxic Agents

The administration of nephrotoxic agents may seriously affect renal development when performed prior to completion of nephrogenesis. Nathanson et al. [119] examined the potential adverse effects of ampicillin, amoxicillin, and ceftriaxone in rat kidney development and reported that both penicillins altered renal development in a dose-dependent manner, while ceftriaxone weakly impaired in vitro nephrogenesis; at a dose of 1,000 mg/ml kidney development is completely blocked. In young animals exposed to penicillins in utero, a mild oligonephronia was present and cystic tubule dilation was observed in newborn and in young animals as well. Gilbert et al. [120] analyzed, in vitro, the potential direct effect of gentamicin on early nephrogenesis and found that gentamicin induced a significant reduction in the number of nephrons in metanephric explants and that this effect was more important on less differentiated metanephroi. Smaoui et al. [121–123] studied the effect of gentamicin on the renal handling and transport of proteins in proximal tubular cells and reported that gentamicin, entering the proximal tubular cells via the endocytic pathway, decreased the tubular reabsorption of proteins, thus increasing urinary protein excretion and, consequently, nephrotoxicity.

Other drugs which probably have major embryo-fetal toxic effects are the nonsteroidal anti-inflammatory drugs (NSAIDs) which cross the placenta, reach the fetal circulation, and cause a spectrum of changes in the kidneys of the offspring [124]. Hasan et al. [125] examined the hypothesis that early postnatal ibuprofen has less adverse effects on neonatal rat renal prostanoids, COX-2 expression, and angiotensin II than indomethacin in newborn rats and found that indomethacin exhibited more potent suppressive effects on renal COX-2 and vasodilator prostanoids which are important regulators of renal development and function. Kent et al. [126] studied the type of renal changes found on light and electron microscopy following administration of indomethacin, ibuprofen, and gentamicin in a neonatal rat model and reported vacuolization of the epithelial proximal tubules, interstitial edema, intratubular protein deposition but no significant glomerular changes. Moreover, they found pleomorphic mitochondria and loss

of microvilli in the tubules and extensive foot process effacement and irregularities of the glomerular basement membrane, concluding that these drugs cause significant change in glomerular and tubular structure in the neonatal rat model.

A number of studies have demonstrated the effect of angiotensin-converting enzyme (ACE) inhibition on systolic blood pressure and renal and uterine blood flow. Olsson et al. [127] studied the effects of intravenous captopril in goats during the last months of pregnancy and lactation and reported a more pronounced fall in arterial blood pressure and a larger increase in plasma renin activity during pregnancy when compared with the lactating period or with the nonpregnant state. It is quite interesting though that in a study evaluating the effect of the Renin Angiotensin System inhibition on the blood pressure and the mesenteric arteriolar reactivity of the intrauterine-undernourished rats, use of Angiotensin System inhibitors normalized the cardiovascular alterations induced by intrauterine undernutrition [128]. Blood pressure may be elevated in young rats following intrauterine exposure to a maternal low-protein diet in order to maintain glomerular filtration rate against a background of fewer nephrons via the increased expression of AT(1) receptors, which may arise as a result of the direct effect of protein restriction or in response to the reported decrease in renal tissue angiotensin II concentration [129].

Anatomical/Congenital Malformations

A number of animal models have been developed to study the pathophysiology of congenital hydronephrosis. These include ureteral obstruction in the fetal sheep, as well as in the postnatal opossum, pig, rabbit, and rodent [130–134]. In addition, the renal cellular and functional consequences of complete unilateral ureteral obstruction in the neonatal rat and mouse have been examined, which bear many similarities to human obstructive nephropathy [135, 136]. Based on previous studies showing that impairment of renal growth is directly dependent on the duration of temporary complete unilateral ureteral obstruction in the neonatal rat [137], Thornhill et al. [138] have recently developed a new model of variable partial unilateral ureteral obstruction in the neonatal rat that will aid in the elucidation of the mechanisms underlying the renal consequences of congenital ureteropelvic junction obstruction. The authors concluded that renal growth is impaired by a critical degree of partial unilateral ureteral obstruction. Persistent partial unilateral ureteral obstruction progressively reduces the number of nephrons during the period of nephron maturation (after the completion of nephrogenesis). Fixed partial ureteropelvic junction obstruction leads to a progressive dilatation of the renal pelvis and proximal ureter, tubular atrophy and interstitial fibrosis that are correlated with tubular apoptosis and are developed before detectable pelvic dilatation. Persistent moderate partial unilateral ureteral obstruction leads to a marked reduction in ipsilateral glomerular filtration rate and increased protein excretion before significant impairment of renal growth. Partial unilateral ureteral obstruction has a delayed stimulatory effect on adaptive growth of the contralateral kidney when compared to complete unilateral ureteral obstruction, and finally partial neonatal unilateral ureteral obstruction impairs somatic growth (Fig. 7.1).

Conclusion

Although the exact mechanisms governing renal development remain unclear, the increased use of animal models in renal basic science laboratories has extended our knowledge on this remarkable process. These promising results not only clarify many of the dark areas of nephrogenesis, but also they will boost the scientific efforts towards the elucidation of this phenomenon.

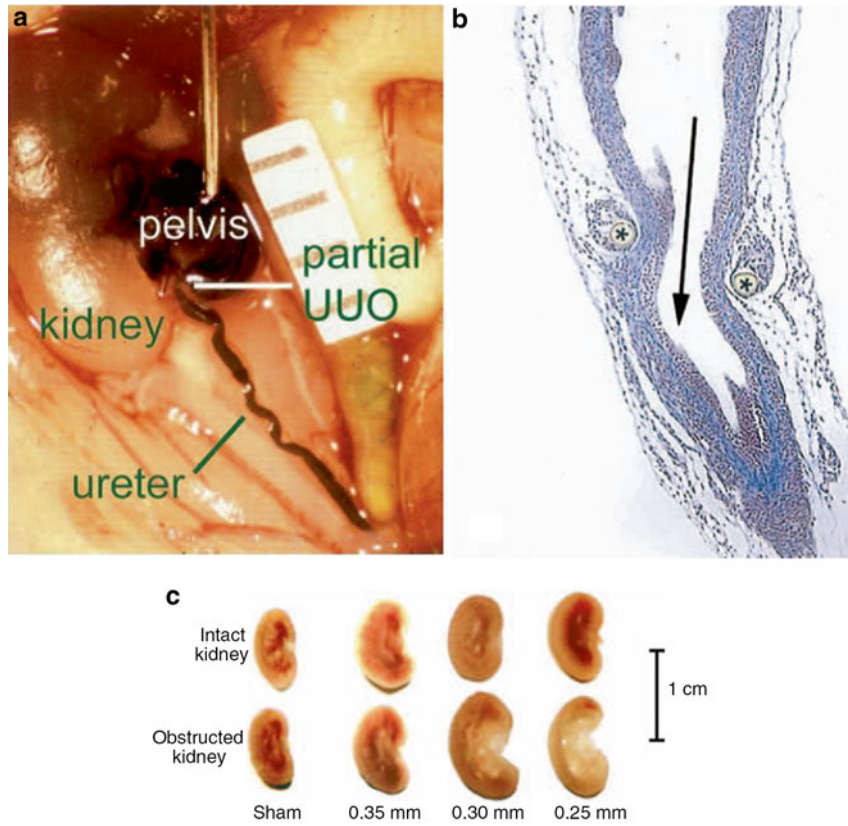

Fig. 7.1 (**a**) Fourteen-day-old rat with partial unilateral ureteral obstruction (UUO) at ureteropelvic junction (UPJ). Kidney is at upper left side, and renal pelvis has been filled with *India ink*, which traversed the obstruction and is visible in distal ureter (mm units on ruler). (**b**) Longitudinal section of ureter of 14-day-old rat showing the ureteral lumen (*arrow* indicates direction of urine flow) and cross-section of ligature (∗). The proximal ureter is dilated, and there is virtually no inflammatory response to the ligature. (**c**) Bisected representative kidneys from 14-day-old rats subjected to sham operation or partial UUO within the first 48 h of life. The contralateral kidney is shown on the *upper row* and the obstructed kidney on the *bottom row*. The luminal diameter of the partial obstruction is shown below each pair of kidneys (from [138] with permission)

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