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# 196

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# **Factors Influencing Mammalian Kidney Development: Implications for Health in Adult Life**

With 12 Figures

 Springer

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## List of Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
<b>2</b>	<b>Morphological Development of the Mammalian Kidney</b>	<b>1</b>
2.1	Pronephros	3
2.2	Mesonephros	3
2.3	Metanephros	5
2.4	Renal Vascular Development	7
2.5	Development of the Renal Nerves	9
<b>3</b>	<b>Genetic Regulation of Metanephric Development</b>	<b>9</b>
3.1	Molecular Specification of the Metanephric Blastema	10
3.2	Molecular Regulation of Ureteric Budding and Branching Morphogenesis	10
3.3	Molecular Regulation of Nephrogenesis	12
3.4	Molecular Regulation of the Stroma	14
3.5	The Renin–Angiotensin System: An Important System Regulating Renal Development and Function	14
3.6	Summary of Molecular Regulation of Metanephric Development	15
<b>4</b>	<b>Abnormalities of Renal Development in the Human</b>	<b>16</b>
4.1	Hydronephrosis	16
4.2	Congenital Anomalies of the Kidney and Urinary Tract	16
4.3	Bilateral Renal Agenesis (Potter's Syndrome)	17
4.4	Renal Abnormalities Caused by Maternal Drug Use	17
4.5	Polycystic Kidney Disease	17
<b>5</b>	<b>Methodology to Examine Kidney Development</b>	<b>18</b>
5.1	Organ Culture	18
5.2	Three-Dimensional and Four-Dimensional Imaging	20
5.3	Quantitation of Nephron Number	21
5.3.1	Unbiased Counting of Nephrons	21
5.3.2	Acid Maceration	24
5.4	Microarrays	24
5.5	Use of Knock-in/Reporter Mice to Analyse Gene Function and Expression	25
<b>6</b>	<b>Development of Function in the Fetus</b>	<b>27</b>
6.1	Mesonephric Function	27

6.2	Fetal Metanephric Renal Function .....	27
6.3	Sodium Transporters .....	28
6.4	Water Channels .....	32
6.5	Renal Renin–Angiotensin System.....	32
<b>7</b>	<b>Nephron Endowment .....</b>	<b>32</b>
7.1	Nephron Endowment in the Human .....	32
7.2	Effect of Prematurity .....	35
7.3	Factors Important for Normal Kidney Development.....	36
7.3.1	Vitamin A .....	36
7.3.2	Iron .....	36
7.4	Timing of Nephrogenesis and Nephron Endowment in Animal Models.....	37
<b>8</b>	<b>Developmental Programming of the Kidney .....</b>	<b>39</b>
8.1	Overview: The Developmental Origins of Health and Disease Hypothesis.....	39
8.2	Human Epidemiology.....	40
8.2.1	Links of Disease Outcome to Birthweight .....	40
8.2.2	Importance of Early Postnatal Growth .....	41
8.3	Common Animal Models Used to Test the DOHaD Hypothesis .....	41
8.3.1	Maternal Undernutrition.....	41
8.3.2	Placental Insufficiency .....	42
8.3.3	Maternal Glucocorticoid Exposure.....	42
8.4	Reduced Nephron Endowment: A Common Denominator in the DOHaD Hypothesis? .....	43
8.4.1	Experimental Manipulations Resulting in a Reduced Nephron Endowment .....	43
8.5	Link Between Nephron Endowment and Hypertension .....	46
8.5.1	The Brenner Hypothesis.....	46
8.5.2	The Link Between Low Nephron Number and Hypertension in Humans.....	46
8.6	Mechanisms Leading to a Reduced Nephron Endowment .....	47
8.7	Programmed Changes in Renal Gene Expression .....	48
8.7.1	Renal Renin–Angiotensin System.....	48
8.7.2	Sodium Channels .....	48
8.8	Why a Low Nephron Endowment Does Not Always Lead to Hypertension .....	49
8.8.1	Effect of Gender/Sex.....	49
8.8.2	Lifestyle Factors: A Congenital Nephron Deficit Renders the Kidney Susceptible to Secondary Insults.....	50
8.8.3	Models and Methodologies: Problems and Pitfalls .....	52
8.9	Unilateral Nephrectomy as a Model of Low Nephron Endowment .....	53
8.10	Potential Underlying Mechanisms of Developmental Programming.....	53
8.10.1	Epigenetic Regulation.....	53
8.10.2	Mitochondrial Dysfunction.....	54

<b>9</b>	<b>Future Directions</b> .....	<b>54</b>
9.1	Clock Genes .....	55
9.2	Renal Stem Cells and Renal Regeneration.....	56
9.3	New Renal Factors.....	56
<b>References</b> .....		<b>58</b>
<b>Subject Index</b> .....		<b>79</b>

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## Abstract

There are many reasons why it is timely to review the development of the mammalian kidney. Perhaps the most important of these is the increasing amount of evidence to demonstrate that factors which impinge on/alter the normal developmental processes of this organ can have lifelong consequences for the health of the adult. The 'Developmental Origins of Health and Adult Disease' (DOHaD) hypothesis, proposes that changes in the environment during the development of an organ or system, can have permanent deleterious effects leading to increased risk of cardiovascular and/or metabolic disease. The permanent metanephric kidney has been shown to be very vulnerable to such influences with many factors shown to alter both the permanent structure and the level of expression of important functional genes. Thus it is important to understand the precise timing of kidney development in terms of both structure and the genes involved at each stage. Such knowledge has been gained by significant advances in technology, which allow quantification of the number of nephrons by unbiased stereology, detections of both levels and site of gene expression, 'knock-out' and knock-in' of genes in animal (mainly mouse) models and by the ability to examine nephron development, in real time, in culture systems.



## 1 Introduction

There are many reasons why it is timely to review the development of the mammalian kidney. Perhaps the most important of these is the increasing amount of evidence demonstrating that factors which impinge on or alter the normal developmental processes of this organ can have lifelong consequences for the health of the adult. The original Barker hypothesis, more recently termed developmental origins of health and adult disease (DOHaD) hypothesis, proposed that changes in the environment (such as level of nutrition [total, protein, mineral, vitamin] or exposure to stress hormones) during the development of an organ or system, could have permanent deleterious effects leading to increased risk of cardiovascular and/or metabolic disease (Barker and Bagby 2005; Barker 2007; Gluckman and Hanson 2006; Hoy et al. 2005; Moritz et al. 2003, 2005a; Moritz and Bertram 2006).

The permanent metanephric kidney has been shown to be very vulnerable to such influences, with many factors shown to be able to alter both the permanent structure and the level of expression of important functional genes, most likely by the process of epigenetics (Moritz et al. 2003; Bagby 2006; Zandi-Nejad et al. 2006). Thus it has become increasingly important to understand the precise timing of kidney development in terms of both structure and the genes involved at each stage. Such knowledge has been gained by significant advances in technology, which allow quantification of the number of branching points and whole nephrons by unbiased stereology, detections of both levels (microarray, real-time PCR) and site (hybridization histochemistry) of gene expression, and by the ability to examine nephron development, in real time, in culture systems (3D, 4D microscopy) (Caruana et al. 2006b; Sanna-Cherchi et al. 2007; Jain et al. 2007; Bertram 1995, 2001). In addition, knowledge of the relative importance of individual genes in kidney development has been gained from knock-out and knock-in of genes in animal (mainly mouse) models.

The purpose of this review is to examine recent progress in the field of renal development and the long-term impact that poor renal development has on adult health.

## 2 Morphological Development of the Mammalian Kidney

In mammals, three pairs of excretory organs form from the intermediate mesoderm in a cranial to caudal direction. These are the pronephroi, mesonephroi and metanephroi, respectively. The pronephroi and mesonephroi are transient organs, but their existence is required for the development of the metanephroi or permanent kidneys. The development of these three excretory organs is shown diagrammatically in Fig. 1.