Bioenergetic Evolution Explains Prevalence of Low Nephron Number at Birth: Risk Factor for CKD

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Abstract

There is greater than ten-fold variation in nephron number of the human kidney at birth. Although low nephron number is a recognized risk factor for CKD, its determinants are poorly understood.

Evolutionary medicine represents a new discipline that seeks evolutionary explanations for disease, broadening perspectives on research and public health initiatives. Evolution of the kidney, an organ rich in mitochondria, has been driven by natural selection for reproductive fitness constrained by energy availability. Over the past 2 million years, rapid growth of an energy-demanding brain in *Homo sapiens* enabled hominid adaptation to environmental extremes through selection for mutations in mitochondrial and nuclear DNA epigenetically regulated by allocation of energy to developing organs. Maternal undernutrition or hypoxia results in intrauterine growth restriction or preterm birth, resulting in low birth weight and low nephron number. Regulated through placental transfer, environmental oxygen and nutrients signal nephron progenitor cells to reprogram metabolism from glycolysis to oxidative phosphorylation. These processes are modulated by counterbalancing anabolic and catabolic metabolic pathways that evolved from prokaryote homologs and by hypoxia-driven and autophagy pathways that evolved in eukaryotes. Regulation of nephron differentiation by histone modifications and DNA methyltransferases provide epigenetic control of nephron number in response to energy available to the fetus. Developmental plasticity of nephrogenesis represents an evolved life history strategy that prioritizes energy to early brain growth with adequate kidney function through reproductive years, the tradeoff being increasing prevalence of CKD delayed until later adulthood. The research implications of this evolutionary analysis are to identify regulatory pathways of energy allocation directing nephrogenesis while accounting for the different life history strategies of animal models such as the mouse. The clinical implications are to optimize nutrition and minimize hypoxic/toxic stressors in child-bearing women and children in early postnatal development.
An evolutionary basis for variability in nephron number.

Chronic kidney disease (CKD) currently affects 11-13% of the world population, and prevalence is rising due to a global epidemic of hypertension, obesity, metabolic syndrome, and diabetes. The prevalence of CKD is less than 1% in children, but increases rapidly to 5% by 30 years and 20% by 60 years. First proposed by Barry Brenner in 1988, increasing evidence reveals that low nephron endowment at birth constitutes a major risk factor for later progression of CKD. This evidence was largely propelled by growing acceptance of developmental origins of health and disease (DOHaD) introduced by David Barker. Although correlations between extremes of birth weight and chronic disease can be demonstrated in small cohorts, the original discoveries by Barker in large unselected populations revealed a graded relation across the entire normal range of birth weight. There is a significant increase in prevalence of CKD risk factors among low birth weight adolescents that becomes greater in later life. Patients with a history of low birth weight, including intrauterine growth restriction (IUGR) or preterm delivery, are at increased risk for the development of hypertension and CKD in adulthood. Low birth weight can result from maternal undernutrition, hypoxia (e.g., maternal smoking), placental insufficiency, infection, toxic exposure or genetic disorders. These observations were paralleled by the seminal discovery by John Bertram and associates that nephron number at birth varies from 200,000 to over 2 million per kidney, and that nephron number is highly correlated with birth weight (Fig. 1A). These conclusions were based on labor-intensive stereologic morphometry requiring histologic sectioning of entire kidneys to improve precision of nephron quantitation. A wide variation in nephron number in humans characterizes all populations studied to date, and there is a strong negative correlation between nephron number and glomerular volume (Fig. 1B). Although progress has been made in elucidating the cell biology of nephrogenesis, mechanisms underlying variation in nephron number remain poorly understood. Notably, human life cycle emerged as a focus for future research on CKD sponsored by the National Institutes of Health.
Kidney development is initiated in early embryonic life through the interaction of the nephric duct with the metanephric mesenchyme that expresses Hox11 genes, with GDNF signaling to RET receptors in the nephric duct to induce formation of the ureteric bud (Fig. 2A). Reciprocal interactions between stromal, ureteric tip, and nephron progenitor cells form the nephrogenic niche, with branching morphogenesis driven by GDNF, FGF, BNP and WNT signaling (Fig. 2B). This results in nascent nephrons that transition from comma- to S-shaped body stages and capillary loop formation with lengthening of the tubule. The human kidney differentiates into a multipapillary organ with papillae draining collecting ducts into the pelvis (Fig. 2C). Nephrogenesis takes place from week 4 through week 36, with branching ending by the end of 2nd trimester. Nephron patterning continues into the 3rd trimester with the formation of “arcades” (chains of nephrons), a process subject to high variation in final nephron number (Figs. 2C and D).

A complete gestational map of mouse kidney development revealed 2 developmental phases, an early phase with rapid acceleration of branching rate, and a later phase subject to greater variability. Experimental maternal nutritional deficiency resulted in mice with significantly reduced nephron number (Table 1). Moreover, experimental undernutrition in developing Japanese quail also resulted in decreased birth weight, kidney size, and nephron number. Common ancestry separates humans from mice by more than 90 million years, and from quail by over 300 million years. These studies suggest that regulation of nephron number developmental plasticity mediated by nutritional availability is a highly conserved adaptive trait. In Origin of Species, published in 1859, Charles Darwin proposed his theory of evolution by natural selection (Table 2). Although evolutionary biology has advanced rapidly with the development of molecular genetics, there had been little application of evolutionary principles to medicine until George Williams and Randolph Nesse published The Dawn of Darwinian Medicine in 1991. Since then, evolutionary medicine has developed into a discipline that has led to major advancements in cancer, autoimmune disease, and pathogenesis of emerging diseases. However, few
reports have addressed evolution and kidney disease.\textsuperscript{33-35} The present review is an attempt to draw on available evidence for the evolution of bioenergetic mechanisms as a determinant of nephron number in fetal life.

**Evolutionary bioenergetics: the long view.**

The earth was formed approximately 4.5 billion years ago, and the first prokaryotes appeared 700 million years later, evolving to produce 2 mol ATP/mol glucose through anaerobic glycolysis (Table 3, Fig. 3). The first eukaryotes did not emerge until 2 billion years later, fueled by the generation of an oxygen-rich environment following the evolution of cyanobacteria. A unique watershed event, bacterial symbionts were incorporated into eukaryotic cells as mitochondria, markedly enhancing the energy-producing capacity of cells through oxidative phosphorylation (OXPHOS), generating 36 mol ATP/mol glucose (Table 3). Over the next billion years, genes were exchanged between nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), with net transfer of the bulk of mitochondrial genes to the nucleus of the host cell. This process was driven by natural selection for significant energy savings by the symbiont, enabling eukaryotes to create and occupy new niches, leading to the evolution of multicellular organisms by 900 million years ago (Fig. 3). Evolution of increasing complexity derives from the continuous flow of energy from the environment, a state of non-equilibrium thermodynamics based on the concept of negative entropy introduced by Schrödinger.\textsuperscript{36} There is, however, an evolutionary tradeoff for high-energy mitochondrial metabolism. Although mitochondrial reactive oxygen species (ROS) constitute an important signal transduction system, excessive ROS generated by environmental stress can induce mitochondrial injury and cell death.

Douglas Wallace has taken a bioenergetic perspective on evolution, contrasting this with the anatomic perspective favored by Darwin.\textsuperscript{37} He has proposed an extension of Darwin's theory, emphasizing that natural selection optimizes efficiency of energy-generated information and is constrained by energy
Coupling of the energetic environment with cellular behavior is accomplished through signal transduction into metabolic intermediates through gene transcription and epigenetic responses regulated by counterbalancing anabolic and catabolic pathways (Fig. 4). Key metabolic signaling pathways are ancient, common to both prokaryotes and eukaryotes, with an increased AMP/ATP ratio stimulating the catabolic release of energy stores through activation of AMP-activated protein kinase (AMPK) interacting reciprocally with anabolic mechanistic target of rapamycin (mTOR), inducing protein synthesis in response to available energy (Figs. 3 & 5).

**Evolutionary adaptations by Homo sapiens: allostasis, brain and kidney.**

In contrast to *homeostasis* which maintains short term metabolic balance, *allostasis* preserves energy balance through the life history, with allocation of available energy to reproduction, growth, maintenance, or immune response. These tradeoffs must be adapted to environmental stress: the degree of stress-induced energy imbalance determines transition from moderate stress compatible with survival to extreme stress where survival depends on duration of the stress. Based on the tracking of mtDNA variants, the radiation of humans from Africa across the entire globe took place in 70,000 years, with colonization of the Americas in the last 15,000 years. Distinct haplogroups were founded by functional mitochondrial variants regionally adapted to climate and altitude. Human disease is associated with ancestry traced to populations from these haplogroups, and mitochondria provide a direct link between the environment, cell physiology, and genes (Fig. 4).

The rapid evolution of hominids was a product of increased nutrient availability ~2 million years ago, with climate change resulting in the transition of the east African environment from forest to savannah. This environmental transformation increased the energy expenditure required for foraging a varied diet, but was followed by the availability of a higher quality diet that is easier to digest and that led to evolution of smaller digestive tracts. These factors contributed to natural selection favoring
doubling brain size from *Homo habilis* to *Homo sapiens* over a period of 1 million years, during which the fraction of resting metabolism consumed by the brain increased from 10% to 20%. Selection pressure for this brain growth likely resulted from the need to store information relating to environmental sources of energy. A significant negative correlation between brain size and adipose tissue in mammals indicates that encephalization and fat storage are balanced compensatory strategies to buffer against starvation. Thus, evolution of a larger brain facilitated the acquisition of nutrients in a wide range of environments, balanced by a reduction in adipose tissue no longer needed to store energy. Increase in brain size entailed some tradeoffs, however: brain oxygen delivery is constrained by the cerebral circulation and brain metabolism is primarily dependent on OXPHOS with a constant supply of glucose as a substrate. Nevertheless, a narrow range of oxygen tension must be maintained in the mammalian brain, with mean tissue levels below 40 mmHg, to ensure function while minimizing generation of ROS. A robust fetal brain-sparing physiologic response to acute hypoxia is mediated by a carotid chemoreflex leading to bradycardia favoring a fall in fetal oxygen consumption, and peripheral vasoconstriction shifting blood flow to the brain. Bradycardia is mediated by vagal stimulation and vasoconstriction is maintained by endocrine vasoconstrictors and modulated by vascular oxidant tone. Chronic fetal hypoxia can result from increased placental vascular resistance leading to IUGR, with greater hypoxic stress to the kidneys than brain.

Required for the reabsorption of 99% of the glomerular filtrate, kidneys have an oxygen consumption index similar to brain and liver, and like the brain, the kidney is therefore under selection pressure to conserve energy (Table 4). Humans developed a unique evolutionary life history strategy, representing the only primate with an extended period of somatic growth (childhood) that includes plasticity of brain development, allowing adaptation of the individual to the environment. Importantly, brains of modern human newborns consume 87% of resting metabolism, decreasing to 44% by 5 years of age and 23% in adulthood. It should be noted that rodent life history strategy differs greatly from that of the human,
with shorter life span, higher number of offspring, and smaller relative brain size (Table 4). Such differences must be taken into account when interpreting studies in animal models of human disease.\textsuperscript{34, 57}

**Maternal-fetal energy balance and metabolism: the placenta.**

Energy requirements for women during pregnancy increase by approximately 20%, which continues throughout the period of breastfeeding.\textsuperscript{58} Maternal nutrient insufficiency is one of the stresses in the maternal environment transmitted to the placenta, which functions as a nutrient and oxygen sensor regulating energy transmission to the fetus (Table 5). During the early first trimester, placental pO\textsubscript{2} (~18 mmHg) is lower than endometrial pO\textsubscript{2} (~40 mmHg), but this gradient is lost by the early second trimester.\textsuperscript{59} The increase in placental pO\textsubscript{2} at the end of the first trimester is likely due to the establishment of continuous maternal blood flow in the intervillous space. By late third trimester, umbilical artery pO\textsubscript{2} is 16-28 mmHg, reflecting the low oxygen tension normally perfusing fetal kidneys, at the brink of hypoxia.\textsuperscript{60} The vulnerability of the fetal kidneys to placental insufficiency was demonstrated by the development of fetal renal hypoxia and medullary dysplasia in pregnant mice with targeted deletion of placental Cited1, a transcription factor.\textsuperscript{61} Hypoxic stress resulting in IUGR leads to decreased activation of placental mTOR signaling, whereas knockdown of AMPK in placental trophoblasts reduces glycolysis and ATP coupling efficiency.\textsuperscript{62-65} Even moderate maternal nutrient restriction in pregnant baboons resulted in dysregulation of genes in pathways related to mTOR signaling, RNA, DNA and protein biosynthesis, metabolism and catabolism in fetal kidneys.\textsuperscript{66-68}

Hypoxia-inducible transcription factor (HIF), a global regulator of oxygen-sensitive homeostasis, developed with the evolution of metazoa 700 million years ago (Fig. 3).\textsuperscript{69} Michelle Lampl has proposed a novel concept of bioenergetics in fetal development based on oxygen and energy substrate as complementary drivers of growth, with HIF-1 serving as a master modulator of cell-cell and multiorgan...
communication through the life cycle (Fig 6). By restricting net energy available for growth, both hypoxia and malnutrition are integrated by the fetal HIF pathway to modulate metabolism to increase available glucose and to enhance oxygen delivery by stimulating erythropoietin, nitric oxide synthesis, and VEGF production. From an evolutionary perspective, natural selection acting on mothers favors physiological processes that increase the overall number of surviving offspring rather than survival of a particular fetus (Tables 2 and 5). In the setting of a restricted maternal nutritional environment, evolutionary fitness would tend to favor the mother over the fetus, because having reached reproductive age, she is more likely than the fetus to reproduce in the future. There are 3 possible outcomes of a stressed pregnancy: preterm delivery, IUGR, or fetal death (Table 5). The maternal capacity to support a pregnancy depends on past environmental factors impacting parental genotype and phenotype. Barker has underscored the importance of transgenerational epigenetics with the concept of 100 years of nutritional flow: the grandmother formed the grandchild’s egg, the mother released the egg, provided nutrients and influenced the placenta, and the fetus generated the placenta and allocated available energy to organ growth (Table 6). All of these can play a role in determining constraints on nutrient transfer by the placenta to the fetus.

The buffering capacity of the placenta protects the fetus from transient reduced maternal macronutrient intake. Placental buffering does not extend to micronutrients, however. In pregnant rats subjected to vitamin A deprivation, nephron number of 21 day-old fetuses was reduced in direct proportion to maternal plasma retinol concentration. Self-renewal of embryonic stem cells is sustained by retinol signaling through mTORC1, revealing a growth factor-like function for vitamin A (Fig. 5). A link between fetal undernutrition or overnutrition and diabetes has also been demonstrated, with a “U-shaped” relation between birth weight and later-life risk of type 2 diabetes. Mitochondrial dysfunction and decreased mtDNA content precede the development of type 2 diabetes. Both extremes of birth weight are associated with decreased umbilical cord mtDNA, consistent with the epigenetic modification
of mtDNA (Fig. 4).\textsuperscript{78, 79} Notably, mtDNA is elevated in IUGR placentas, but diminished in cytotrophoblast cells, suggesting that increased placental oxygen consumption may prevent adequate oxygen delivery to the fetus.\textsuperscript{80}

The process of birth itself represents a critical transition in energy supply from placenta to oral feeding, an interval during which infants face starvation. Autophagy evolved from precursors in prokaryotes to recycle degraded cytosolic components through lysosomes for reuse in metabolism (Fig. 3).\textsuperscript{81} The level of autophagy in mice is low during embryogenesis, but is upregulated in various tissues within hours of birth, returning to basal levels within 2 days.\textsuperscript{82} Mice deficient for \textit{Atg5}, essential for autophagy, appear normal at birth, but die less than 24 hours later with signs of energy depletion (AMPK activation, hypoglycemia, and hypolipidemia). Mice with mutation of \textit{Atg5} or \textit{Atg7} during nephrogenesis develop mitochondrial dysfunction with mild podocyte and tubular dysfunction within 2 months, and focal glomerulosclerosis with kidney failure by 6 months.\textsuperscript{83}

\textbf{Metabolic control of nephron number}

Maternal nutritional restriction results in fetal DNA hypomethylation, and deletion of methyltransferase \textit{Dnmt1} in nephron progenitor cells mimics the phenotype of fetal nutritional restriction with renal hypoplasia and reduced nephron number.\textsuperscript{84} RNA sequencing revealed that global hypomethylation in the \textit{Dnmt1} knockout resulted in downregulation of \textit{Wt1} and \textit{Wnt4}, crucial for initiating nephrogenesis, as well as inhibitors of cell cycle progression (Figs. 2 and 5).\textsuperscript{84} The impact of severe fetal undernutrition on long-term health was revealed in people born in Amsterdam at the time of the Dutch famine of 1944-1945, who in adulthood had hypomethylation of the insulin-like growth factor-2 (IGF-2) gene, and microalbuminuria.\textsuperscript{85, 86}

Transition from fetal to extrauterine life shifts excretory function from placenta to kidneys. Despite a preponderance of anaerobic metabolism in the embryo, metabolic reprogramming to OXPHOS
metabolism is critical for organogenesis, and mitochondrial maturation begins prenatally and accelerates after birth. Human mesenchymal cells from umbilical cord blood isolated form preterm infants contain immature mitochondrial reticulum and low expression of mitochondrial fission/fusion genes compared to cells from term infants (Table 3). It is likely that glycolysis in the immature fetus represents an adaptation to the hypoxic fetal environment: exposure of preterm infants to oxygen results in the accumulation of ROS, causing tissue damage. In the human fetus, 90% of nephrons are formed between 26 and 36 weeks gestation (Fig. 2C). Nephrogenesis is dysregulated by preterm birth, with the formation of abnormal nephrons and a significant reduction in functioning nephron number. Prematurity in mice also leads to reduced nephron number, hypertension, and proteinuria.

Nephrogenesis is modulated by tissue oxygen concentration, regulated by von Hippel-Lindau protein (VHL) and HIFs (Fig. 5). By E15.5, kidneys of nephron progenitor cell-specific VHL knockout mice have decreased OXPHOS metabolism, with persistence of glycolysis accompanied by reduced maturation of nephron progenitors, resulting in a 50% decrease in nephron number. Metabolic reprogramming mediated by VHL provides a direct link between available energy and the determination of nephron number. In the 1920s, Otto Warburg showed that cancer cells upregulate glycolysis even in the presence of abundant oxygen (Table 3). The Warburg effect is now recognized as a mechanism for synthesis of molecules (nucleic acids, amino acids, and fatty acids) necessary for proliferation either in normal development or neoplasia, while glycolytic intermediates are diverted to the pentose phosphate pathway for production of NADPH which reduces oxidative stress (Fig. 7). Fuel use by murine nephron progenitor cells switches from glycolysis to OXPHOS between embryonic days E12 and E19 (Figs. 5 and 7). Importantly, inhibition of glycolysis enhances nephrogenesis in cultured embryonic kidneys, demonstrating that metabolic reprogramming is responsible for redirecting progenitor cell fate from self-renewal to differentiation. Maintenance of a self-renewing population of renal progenitor cells is dependent on glycolytic metabolism via mTOR/HIF-1α pathways, whereas inhibition of glycolysis
enhances Wnt/β catenin signaling leading to increased nephrogenesis (Table 3, Figs. 2 and 5).96 These effects are mediated by histone modifications driven by glycolysis-stimulated acetyl CoA production in embryonic stem cells; inhibition of glycolysis promotes histone deacetylation and consequent differentiation (Fig. 7). Pluripotent stem cells generate acetyl-CoA through a glycolytic pathway, which promotes histone acetylation; downregulation of this pathway represents the earliest metabolic switch that programs deacetylation and switch to differentiation (Fig. 7).97 Linkage between the Warburg effect, OXPHOS and the epigenome provides a metabolic explanation for the earliest triggers of differentiation.98

Regulation of glomerular filtration rate is dependent on metabolic rate,99 and is determined by the product of nephron number and aggregate nephron size. Patients with low birth weight or low nephron number have higher glomerular volume, a reflection of adaptive nephron hypertrophy (Fig. 1B).21 Although nephrons are not formed after term birth in humans, nephron number increases by 45-50% in fetal sheep subjected to unilateral nephrectomy, whereas glomerular volume is actually decreased.100 An evolutionary perspective of homeostasis integrates bioenergetics, life history theory, and responses to pregnancy.101 In addition to classical negative feedback homeostatic loops, James Houk has proposed the inclusion of feedforward and adaptive control mechanisms with regulators compensating for disturbances (Fig. 8A).102 Using this framework, available energy can be channeled to nephrogenesis and nephron growth through evolved control mechanisms responding to environmental stimuli (Fig. 8B). This model of developmental plasticity emphasizes the environmental constraint of available energy and the physiologic constraint of excretory function to meet metabolic demand. In evolutionary theory, developmental plasticity has been modeled as determined by immediate constraints or as anticipatory of the adult environment. The “developmental constraints” model proposed here entails tradeoffs in later life to protect critical developmental processes in fetal development. This suggests that group selection attempts to optimize overall fitness (relative to individuals without developmental plasticity)
by accepting long-term costs (relative to individuals not subjected to resource limitation).\textsuperscript{103} The alternative is a “predictive” model, whereby environmental cues in early life predict the adult environment, favored in species with short lifespans. When (as in humans) environment varies on a timescale shorter than the species’ generation time, early life exposure would favor the developmental constraints model.\textsuperscript{103}

In conclusion, the 10-fold variation in human nephron number at birth likely evolved to enhance adaptive flexibility to the maternal environment, with selection constrained by available energy (oxygen and nutrients). Of relevance to risk for CKD, there is even greater variation in the number of human pancreatic islet cells, also demonstrated for different strains of mice.\textsuperscript{104, 105} Maternal protein restriction affects the development of islet cells through metabolic responses similar to those responsible for nephrons. Low protein diet in rat dams increases fetal transcription factors that stimulate differentiation at the expense of proliferation of β-cells, resulting in premature maturation and decreased β-cell numbers.\textsuperscript{106} Evolution of developmental plasticity in both nephrons and islet cells may therefore contribute to the dominance of diabetic nephropathy as a cause of adult CKD. It should be noted that genetic factors, such as mutation of the $PAX2$ gene, are also linked to reduced kidney size at birth (Fig. 2). The homozygous AAA haplotype of $PAX2$ shifts mean kidney volume downward across the whole population,\textsuperscript{107} whereas certain heterozygous $PAX2$ mutations underlie cases of oligomeganephronia, a rare congenital anomaly characterized by renal hypoplasia and a reduced number of enlarged nephrons.\textsuperscript{108} Congenital anomalies of the kidneys and urinary tracts can result from genomic, epigenomic, or environmental stressors in any combination, and the more severe the nephron deficit, the sooner the onset of CKD and the more rapid its progression.\textsuperscript{109}

Human life history strategy favors allocation of energy to the developing brain through physiologic adaptation by the fetal cerebral circulation,\textsuperscript{53} and by metabolic regulation of organ development by nuclear and mitochondrial gene transcription regulated epigenetically (Fig. 4). The number of nephrons
and podocytes is fixed before birth: physiologic adaptation to prenatal and postnatal stressors is accomplished by glomerular and tubular hypertrophy that is limited by physical and metabolic constraints leading to CKD, an evolutionary tradeoff for the maintenance of homeostasis through reproductive years. Reproductive fitness is favored by this strategy, whereby low nephron number in the stressed fetus permits survival through adolescence. While variation in nephron number is adaptive, severe maternal stress leading to very low fetal nephron number represents a tradeoff that leads to CKD and reduced postnatal fitness. The corollary to this strategy is a prediction that unless severe, most subjects with low nephron number will not develop ESRD until after peak reproductive years, when selection pressure is low. Consistent with this prediction, a Norwegian study of over 2 million subjects revealed that low birth weight, IUGR, and preterm birth represent cumulative risk factors for development of ESRD that is delayed until later adulthood.

The aging kidney.

The senescent kidney has diminished proliferative reserve, increased tendency to apoptosis, and altered immune responses, all of which contribute to impaired regenerative responses to injury, such as hypoxia and ischemia. Early postnatal overnutrition in rat pups leads to hypertension, renal cortical apoptosis, glomerular sclerosis and reduced nephron number with advancing age. Rats subjected to maternal undernutrition but weaned onto a high-calorie diet exhibited catch-up growth, but with aging renal p16 and p21 (markers of stress-induced senescence) increased significantly, along with p66Shc and Ero1α (markers of mitochondrial stress). These studies reveal the dramatic negative impact on the aging kidney of nutritional restriction in early development. By contrast, caloric restriction in middle-aged rats reduced the abundance of cytochrome c oxidase-deficient tubular epithelial cells containing mtDNA deletion mutations, thereby attenuating progression to atrophy. A salutary effect of caloric restriction on aging is found in a number of species, suggesting that it has an evolutionary basis. Thomas Kirkwood’s original “disposable soma” theory proposed that aging progresses because energy
investments in somatic maintenance are limited, thereby sparing resources for growth and reproduction.\textsuperscript{116} To accommodate this paradigm to periods of famine, he later proposed that when available energy is restricted, resources are shifted from reproduction to somatic maintenance until the environment improves, as supported by mathematical modeling based on rodent studies.\textsuperscript{117}

Studies in kidney transplant donors reveal that nephron number decreases by 50\% with aging, and remaining nephrons hypertrophy.\textsuperscript{118} A murine study also revealed decreasing nephron number and glomerular hypertrophy with aging, which was compounded in aging mutant mice with congenital nephron deficit.\textsuperscript{119} These observations are consistent with Nick Lane’s “double-agent” theory of aging, based on oxidative stress through reproductive years serving as a redox signal to promote a homeostatic response (e.g., inflammation stimulated by infection), but becoming injurious due to rising free radical leakage from aging mitochondria in postreproductive years.\textsuperscript{120} The NADPH oxidase family of Nox enzymes first evolved in professional phagocytes (neutrophils and macrophages) that generate ROS to kill pathogens.\textsuperscript{121} In addition to this function (retained in innate immunity), ROS produced by NADPH oxidase in kidney cells serve as signaling molecules mediating calcium signaling, cell differentiation, and other vital functions, that have been subjected to positive selection.\textsuperscript{121} With increasing age beyond reproductive years, selection pressure is reduced, allowing the accumulation of somatic mutations resulting from environmental stressors compounded by mitochondrial ROS leakage, leading to increasing oxidative injury and progression of CKD.

**Implications for future study.**

At the present time, 155 million children under 5 years of age are stunted, a reflection of undernutrition.\textsuperscript{122} Addressing the global epidemic of CKD must include prenatal and postnatal care, with adequate maternal nutrition to optimize nephrogenesis and nephron maturation. Although noninvasive methods for measuring nephron number are not currently available for clinical use, tracking of nephron
number by magnetic resonance-based imaging may revolutionize the management of those at risk.\textsuperscript{123-125}

Combined serial measurements of glomerular number and kidney metabolic status could provide new biomarkers of kidney health through the life cycle, allowing intervention before the development of significant nephron injury. Kidney organoids are providing new insight into the molecular basis for human kidney development, and lend themselves to the study of environmental stressors on the epigenome.\textsuperscript{25} Future research should also address the effects of early environmental stress on gene regulatory networks, including epigenomic as well as genomic data from diverse populations (human or across species) followed longitudinally.

Disclosures

The author has nothing to disclose.

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Author Contributions

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Glossary of terms

**Allostasis.** Maintenance of balance between energy input and expenditure throughout the stages of life history, increasing the probability of reproductive success. By contrast, **homeostasis** refers to the stability of physiological systems essential within each life history stage.\(^{42}\)

**AMPK**, adenosine monophosphate-activated protein kinase. An enzyme that stimulates fatty acid oxidation, ketogenesis, and glucose uptake.

**Atg**, autophagy-related (gene or protein). The abbreviation derives from the first word, autophagy, as in AuToPhaGy-related.

**Autophagy.** A homeostatic process in which cytosolic components are degraded and recycled through lysosomes.

**BMP**, bone morphogenetic protein, a metabologen and morphogenetic signaling molecule.

**Developmental plasticity**, the capacity of genetically similar individuals to produce different phenotypes determined by environmental conditions in early life.

**Dnmt**, DNA methyltransferase, a cytosine methylase that catalyzes the transfer of a methyl group to DNA, an epigenetic process.

**DOHaD**, developmental origins of health and disease, is a concept that links the state of health and risk from disease in later childhood and adult life with the environmental conditions of early life.

**FGF**, fibroblast growth factor, an extracellular signaling protein that binds to heparin and heparan sulfate.

**Fitness** describes individual reproductive success determined by the average contribution to the gene pool of the next generation that is made by individuals of a specified genotype or phenotype.
**Fox**, forkhead box family of transcription factors, which originated in unicellular eukaryotes, has expanded over time through multiple duplication events, and sometimes through gene loss, to over 40 members in mammals.

**GDNF**, glial cell line-derived neurotrophic factor, promotes survival of neurons and plays a critical role in nephron development.

**Glycolysis**, the metabolic pathway that converts glucose into pyruvate, an aerobic or anaerobic process.

**Haplogroup**, a genetic population sharing a common ancestor on the patriline or the matriline.

**HIF-1**, hypoxia-inducible factor-1. A transcriptional heterodimer composed of an alpha and a beta subunit that responds to hypoxia.

**Hominid**, a member of the family *Hominidae* that includes humans, their extinct ancestors, and some of the great apes.

**Hox** gene, a homeobox transcription factor that determines cell position in early development.

**IUGR**, intrauterine growth restriction, a fetal weight that is below the 10th percentile for gestational age, also known as small-for-gestational-age.

**Lhx1**, encodes a transcription factor which contains the LIM domain, a unique cysteine-rich zinc-binding domain.

**Life history theory** seeks to explain how natural selection and other evolutionary forces shape organisms to optimize their survival and reproduction in the face of ecological challenges posed by the environment.
**Metabolic rate**, sum of all the chemical reactions occurring in an organism: systems responsible for internal distribution of nutrients (cardiovascular system) and excretion of metabolic waste products (kidneys) are designed to meet these metabolic requirements.\(^9^9\)

**Metabolic reprogramming**, a term borrowed from cancer biology, refers to cellular bioenergetic switching between glycolysis and oxidative phosphorylation.

**Mitophagy**, selective degradation by autophagy of defective mitochondria following damage or stress.

**mTOR**, mechanistic target of rapamycin. A protein kinase that regulates cell growth, proliferation, motility, survival, and autophagy.

**mTORC1**, mechanistic target of rapamycin complex 1. A protein complex that functions as a nutrient sensor and controls protein synthesis.

**mtDNA**, mitochondrial DNA.

**nDNA**, nuclear DNA.

**Notch1**, (Notch homolog 1, translocation-associated) a human gene encoding a single-pass transmembrane receptor. Notch family members play a role in a variety of developmental processes by controlling cell fate decisions.

**Organism**, an open system that exchanges energy and matter with the environment.\(^1^2^6\)

**OXPHOS**, oxidative phosphorylation, is the process in which ATP is formed as a result of the transfer of electrons from NADH or FADH\(_2\) to O\(_2\) by a series of electron carriers.

**Pax2**, Paired box gene 2, a transcription factor controlled by the signaling molecules Wnt1 and Fgf8.
**PGC-1α**, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha. A transcriptional coactivator that regulates the genes involved in energy metabolism—the master regulator of mitochondrial biogenesis, PPAR-γ, which permits its interaction with multiple transcription factors.

**PPAR**, peroxisome proliferator-activated receptor. A nuclear receptor proteins that function as a transcription factor that regulates development and metabolism.

**RET** ("rearranged during transfection") proto-oncogene encodes a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor (GDNF) family of extracellular signaling molecules.

**Robo2**, (Roundabout Guidance Receptor 2), a transmembrane receptor for the slit homolog 2 protein and functions in axon guidance and cell migration; mutated in some cases of vesicoureteral reflux.

**ROS**, reactive oxygen species, are chemically reactive chemical species containing oxygen, formed as a natural byproduct of metabolism of oxygen, important in cell signaling and homeostasis. However, following environmental stress ROS levels can increase, leading to cell damage.

**Six2**, a gene which encodes proteins (transcription factors) homologous to the Drosophila 'sine oculis' homeobox protein.

**Slit**, a family of secreted extracellular matrix proteins which play an important signaling role in neural and nephron development. Its canonical receptor is Robo.

**Systems biology**, the computational and mathematical modeling of complex biological systems.

**Tradeoffs** reflect necessary compromises among the functions of multiple traits, as when energy must be allocated among competing metabolic functions.

**VEGF**, vascular endothelial growth factor is a member of the platelet-derived growth factor family of cystine-knot growth factors, involved in both vasculogenesis and angiogenesis.
**VHL**, Von Hippel–Lindau tumor suppressor, has ubiquitin ligase activity that results in specific target proteins (such as hypoxia inducible factor 1α) being “marked” for degradation.

**WNT** (“Wingless” and “Int-1”) signaling pathways transmit signals through cell surface receptors.

**WT1**, Wilms tumor protein, a transcription factor that contains four zinc finger motifs and plays a central role in nephrogenesis.
References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al.: Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One* 11: e0158765, 2016.
2. Bowe B, Xie Y, Li T, Mokdad AH, Xian H, Yan Y, et al.: Changes in the US Burden of Chronic Kidney Disease From 2002 to 2016: An Analysis of the Global Burden of Disease Study. *JAMA Netw Open* 1: e184412, 2018.
3. Centers for Disease Control and Prevention. Chronic Kidney Disease (CKD) Surveillance System, Prevalence of CKD by age (adults) https://nccd.cdc.gov/CKD/detail.aspx?QNum=Q9&Strat=Age. 2018.
4. USRDS annual data report. Epidemiology of kidney disease in the United States, Volume 1: Chronic Kidney Disease in the United States. Chapter 6: CKD among Children and Adolescents, Table 6.1 Demographic characteristics of pediatric patients among Optum Clinformatics, 2016 https://www.ushrsds.org/2018/view/v1_06.aspx. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2018.
5. Brenner BM, Garcia DL, Anderson S: Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* 1: 335-347, 1988.
6. Luyckx VA, Brenner BM: Clinical consequences of developmental programming of low nephron number. *Anat Rec (Hoboken)*, 2019.
7. Barker DJP, Osmond C: Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1: 1077-1081, 1986.
8. Barker DJP: The origins of the developmental origins theory. *Journal of Internal Medicine* 261: 412-417, 2007.
9. Barker DJ, Lampl M, Roseboom T, Winder N: Resource allocation in utero and health in later life. *Placenta* 33 Suppl 2: e30-34, 2012.
10. Calderon-Margalit R, Golan E, Twig G, Leiba A, Tzur D, Afek A, et al.: History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease. *N Engl J Med* 378: 428-438, 2018.
11. Khalsa DD, Beydoun HA, Carmody JB: Prevalence of chronic kidney disease risk factors among low birth weight adolescents. *Pediatr Nephrol* 31: 1509-1516, 2016.
12. White SL, Perkovic V, Cass A, Chang Cl, Poulter NR, Spector T, et al.: Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kid Dis* 54: 248-261, 2009.
13. Lee YQ, Collins CE, Gordon A, Rae KM, Pringle KG: The Relationship between Maternal Nutrition during Pregnancy and Offspring Kidney Structure and Function in Humans: A Systematic Review. *Nutrients* 10, 2018.
14. Crump C, Sundquist J, Winkleby MA, Sundquist K: Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study. *BMJ* 365: i1346, 2019.
15. Eriksson JG, Salonen MK, Kajantie E, Osmond C: Prenatal Growth and CKD in Older Adults: Longitudinal Findings From the Helsinki Birth Cohort Study, 1924-1944. *Am J Kidney Dis* 71: 20-26, 2018.
16. Shen Q, Xu H, Wei L-M, Chen J, Liu H-M, Guo W: A comparative proteomic study of nephrogenesis in intrauterine growth restriction. *Pediatr Nephrol* 25: 1063-1072, 2010.
17. Lewis RM, Hanson MA: Review: placenta, evolution and lifelong health. *Placenta* 33, Supplement A, Trophoblast Research, Vol. 26: S28-S32, 2012.
18. Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K: Nephron Number, Hypertension, Renal Disease, and Renal Failure. *J Am Soc Nephrol* 16: 2557-2564, 2005.
19. Hughson MD, Farris AB, Douglas-Denton R, Hoy WE, Bertram JF: Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int* 63: 2113-2122, 2003.
20. Puelles VG, Hoy WE, Hughson MD, Diouf B, Douglas-Denton RN, Bertram JF: Glomerular number and size variability and risk for kidney disease. *Curr Opin Nephrol Hypertens* 20: 7-15, 2011.
21. Hoy WE, Hughson MD, Diouf B, Zimanyi M, Samuel T, McNamara BJ, et al.: Distribution of volumes of individual glomerauli in kidneys at autopsy: association with physical and clinical characteristics and with ethnic group. *Am J Nephrol* 33 Suppl 1: 15-20, 2011.
22. McMahon AP, Aronow BJ, Davidson DR, Davies JA, Gaido KW, Grimmond S, et al.: GUDMAP: the genitourinary developmental molecular anatomy project. *J Am Soc Nephrol* 19: 667-671, 2008.
23. Bates CM, Charlton JR, Ferris ME, Hildebrandt F, Hoshizaki DK, Warady BA, et al.: Pediatric kidney disease: tracking onset and improving clinical outcomes. *Clin J Am Soc Nephrol* 9: 1141-1143, 2014.
24. Little MH, Brown D, Humphreys BD, McMahon AP, Miner JH, Sands JM, et al.: Defining biology to understand disease. *Clin J Am Soc Nephrol* 9: 809-811, 2014.
25. Little MH, Combes AN: Kidney organoids: accurate models or fortunate accidents. *Genes Dev* 33: 1319-1345, 2019.
26. Sampogna RV, Schneider L, Al-Awqati Q: Developmental programming of branching morphogenesis in the kidney. *J Am Soc Nephrol* 26: 2414-2422, 2015.
27. Nishimura H, Yang Y, Lau K, Kuykindoll RJ, Fan Z, Yamaguchi K, et al.: Aquaporin-2 water channel in developing quail kidney: possible role in programming adult fluid homeostasis. *Am J Physiol Regul Integr Comp Physiol* 293: R2147-2158, 2007.
28. Lea AJ, Tung J, Archie EA, Alberts SC: Developmental plasticity: Bridging research in evolution and human health. *Evol Med Public Health* 2017: 162-175, 2017.
29. Bonduriansky R, Day T: *Extended Heredity. A New Understanding of Inheritance and Evolution*, Princeton Princeton University Press, 2018.
30. Darwin C: *On the Origin of Species*, Cambridge and London, Harvard University Press, 2003.
31. Williams GC, Nesse RM: The dawn of Darwinian medicine. *Quart Rev Biol* 66: 1-22, 1991.
32. Stearns SC: Frontiers in Molecular Evolutionary Medicine. *J Mol Evol* 88: 3-11, 2020.
33. Chevalier RL: Evolutionary Nephrology. *Kidney Int Rep* 2: 302-317, 2017.
34. Chevalier RL: Evolution and kidney development: A Rosetta stone for nephrology. *J Am Soc Nephrol* 29: 705-709, 2018.
35. Chevalier RL: Evolution, kidney development, and chronic kidney disease. *Semin Cell Dev Biol* 91: 119-131, 2019.
36. Schrodinger E: *What is Life? The Physical Aspect of the Living Cell*, Cambridge, Cambridge University Press, 1944.
37. Wallace DC: Bioenergetic origins of complexity and disease. *Cold Spring Harb Symp Quant Biol* 76: 1-16, 2011.
38. Wallace DC: Colloquium paper: bioenergetics, the origins of complexity, and the ascent of man. *Proc Natl Acad Sci U S A* 107 Suppl 2: 8947-8953, 2010.
39. Wallace DC: Mitochondria, bioenergetics, and the epigenome in eukaryotic and human evolution. *Cold Spring Harb Symp Quant Biol* 74: 383-393, 2009.
40. Wallace DC: Bioenergetics in human evolution and disease: implications for the origins of biological complexity and the missing genetic variation of common diseases. *Philos Trans R Soc Lond B Biol Sci* 368: 20120267, 2013.
41. Seebacher F: The evolution of metabolic regulation in animals. *Comp Biochem Physiol B Biochem Mol Biol* 224: 195-203, 2018.
42. McEwen BS, Wingfield JC: The concept of allostatic in biology and biomedicine. *Horm Behav* 43: 2-15, 2003.
43. Lee DY, Kim E, Choi MH: Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. *BMB Rep* 48: 209-216, 2015.
44. Wallace DC: Genetics: Mitochondrial DNA in evolution and disease. *Nature* 535: 498-500, 2016.
45. Wallace DC: A mitochondrial bioenergetic etiology of disease. *J Clin Invest* 123: 1405-1412, 2013.
46. Leonard WR, Robertson ML: Nutritional requirements and human evolution: A bioenergetics model. *Am J Hum Biol* 4: 179-195, 1992.
47. Ungar PS: Diet in early Homo: a review of the evidence and a new model of adaptive versatility. *Annu Rev Anthropol* 35: 209-228, 2006.
48. Aiello LC: The expensive-tissue hypothesis. The brain and the digestive system in human and primate evolution. *Curr Anthro* 36: 199-221, 1995.
49. Du A, Zipkin AM, Hatala KG, Renner E, Baker JL, Bianchi S, et al.: Pattern and process in hominin brain size evolution are scale-dependent. *Proc Biol Sci* 285, 2018.
50. Navarrete A, van Schaik CP, Isler K: Energetics and the evolution of human brain size. *Nature* 480: 91-93, 2011.
51. Erecinska M, Silver IA: Tissue oxygen tension and brain sensitivity to hypoxia. *Respir Physiol* 128: 263-276, 2001.
52. Carreau A, El Hafny-Rahbi B, Matejuk A, Grillon C, Kieda C: Why is the partial oxygen pressure of human tissues a crucial parameter? Small molecules and hypoxia. *J Cell Mol Med* 15: 1239-1253, 2011.
53. Giussani DA: The fetal brain sparing response to hypoxia: physiological mechanisms. *The Journal of physiology* 594: 1215-1230, 2016.
54. Rolfe DF, Brown GC: Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol Rev* 77: 731-758, 1997.
55. Hochberg Z: Juvenility in the context of life history theory. *Arch Dis Child* 93: 534-539, 2008.
56. Holliday MA: Body composition and energy needs during growth. In: *Human Growth Vol 2 Postnatal Growth Neurobiology*. 2nd edition ed. edited by Falkner F, Tanner JM, New York, Springer, 1986, pp 101-117.
57. Perlman RL: Mouse models of human disease: an evolutionary perspective. *Evol Med Public Health* doi: 10.1093/emph/eow014: 170-176, 2016.
58. Rylander C, Odland JQ, Sandanger TM: Climate change and the potential effects on maternal and pregnancy outcomes: an assessment of the most vulnerable--the mother, fetus, and newborn child. *Glob Health Action* http://dx.doi.org/10.3402/gha.v6i10.19538, 2013.
59. Rodesch F, Simon P, Donner C, Jauniaux E: Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. *Obstet Gynecol* 80: 283-285, 1992.
60. Nye GA, Ingram E, Johnstone ED, Jensen OE, Schneider H, Lewis RM, et al.: Human placental oxygenation in late gestation: experimental and theoretical approaches. *J Physiol* 596: 5523-5534, 2018.
61. Sparrow DB, Boyle SC, Sams RS, Mazuruk B, Zhang L, Moeckel GW, et al.: Placental insufficiency associated with loss of Cited1 causes renal medullary dysplasia. *J Am Soc Nephrol* 20: 777-786, 2009.
62. Dimasuay KG, Boeuf P, Powell TL, Jansson T: Placental Responses to Changes in the Maternal Environment Determine Fetal Growth. *Front Physiol* 7: 12, 2016.
63. Carey EA, Albers RE, Doliboa SR, Hughes M, Wyatt CN, Natale DR, et al.: AMPK knockdown in placental trophoblast cells results in altered morphology and function. *Stem Cells Dev* 23: 2921-2930, 2014.
64. Kimball R, Wayment M, Merrill D, Wahlquist T, Reynolds PR, Arroyo JA: Hypoxia reduces placental mTOR activation in a hypoxia-induced model of intrauterine growth restriction (IUGR). *Physiol Rep* 3, 2015.
65. Waker CA, Albers RE, Pye RL, Doliboa SR, Wyatt CN, Brown TL, et al.: AMPK Knockdown in Placental Labyrinthine Progenitor Cells Results in Restriction of Critical Energy Resources and Terminal Differentiation Failure. *Stem Cells Dev* 26: 808-817, 2017.

66. Cox LA, Nijland MJ, Gilbert JS, Schlabritz-Loutsevitch NE, Hubbard GB, McDonald TJ, et al.: Effect of 30 per cent maternal nutrient restriction from 0.16 to 0.5 gestation on fetal baboon kidney gene expression. *J Physiol* 572: 67-85, 2006.

67. Nijland MJ, Schlabritz-Loutsevitch NE, Hubbard GB, Nathanielsz PW, Cox LA: Non-human primate fetal kidney transcriptome analysis indicates mammalian target of rapamycin (mTOR) is a central nutrient-responsive pathway. *J Physiol* 579: 643-656, 2007.

68. Pereira SP, Oliveira PJ, Tavares LC, Moreno AJ, Cox LA, Nathanielsz PW, et al.: Effects of moderate global maternal nutrient reduction on fetal baboon renal mitochondrial gene expression at 0.9 gestation. *Am J Physiol Renal Physiol* 308: F1217-F1228, 2015.

69. Graham AM, Presnell JS: Hypoxia Inducible Factor (HIF) transcription factor family expansion, diversification, divergence and selection in eukaryotes. *PLoS One* 12: e0179545, 2017.

70. Lamp M: Cellular life histories and bow tie biology. *Am J Hum Biol* 17: 66-80, 2005.

71. Haig D: Cooperation and conflict in human pregnancy. *Curr Biol* 29: R455-r458, 2019.

72. Gluckman P, Hanson M: *The Fetal Matrix: Evolution, Disease and Development*, Cambridge, Cambridge University Press, 2005.

73. Thayer ZM, Rutherford J, Kuzawa CW: The Maternal Nutritional Buffering Model: an evolutionary framework for pregnancy nutritional intervention. *Evol Med Public Health* 2020: 14-27, 2020.

74. Perera F, Herbstman J: Prenatal environmental exposures, epigenetics, and disease. *Reprod Toxicol* 31: 363-373, 2011.

75. Lelièvre-Pegorier M, Vilar J, Ferrier ML, Moreau E, Freund N, Gilbert T, et al.: Mild vitamin A deficiency leads to inborn nephron deficit in the rat. *Kidney Int* 54: 1455-1462, 1998.

76. Chen L, Khillan JS: A novel signaling by vitamin A/retinol promotes self renewal of mouse embryonic stem cells by activating PI3K/Akt signaling pathway via insulin-like growth factor-1 receptor. *Stem Cells* 28: 57-63, 2010.

77. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A: Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol* 165: 849-857, 2007.

78. Gemma C, Sookoian S, Alvarinas J, Garcia SI, Quintana L, Kanevsky D, et al.: Mitochondrial DNA depletion in small- and large-for-gestational-age newborns. *Obesity (Silver Spring)* 14: 2193-2199, 2006.

79. Sharma N, Pasala MS, Prakash A: Mitochondrial DNA: Epigenetics and environment. *Environ Mol Mutagen* 60: 668-682, 2019.

80. Mando C, De Palma C, Stampalija T, Anelli GM, Figus M, Novielli C, et al.: Placental mitochondrial content and function in intrauterine growth restriction and preeclampsia. *Am J Physiol Endocrinol Metab* 306: E404-413, 2014.

81. Hughes T, Rusten TE: Origin and evolution of self-consumption: autophagy. *Adv Exp Med Biol* 607: 111-118, 2007.

82. Kuma A, Hatano M, Matsui M, Yamamoto A, Nakaya H, Yoshimori T, et al.: The role of autophagy during the early neonatal starvation period. *Nature* 432: 1032-1036, 2004.

83. Kawakami T, Gomez IG, Ren S, Hudkins K, Roach A, Alpers CE, et al.: Deficient Autophagy Results in Mitochondrial Dysfunction and FSGS. *J Am Soc Nephrol* 26: 1040-1052, 2015.

84. Wanner N, Vornweg J, Combes A, Wilson S, Plappert J, Rafflenbeul G, et al.: DNA methyltransferase 1 controls nephron progenitor cell renewal and differentiation. *J Am Soc Nephrol* 30: 63-78, 2019.

85. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al.: Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 105: 17046-17049, 2008.
86. Painter RC, Roseboom TJ, van Montfrans GA, Bossuyt PM, Krediet RT, Osmond C, et al.: Microalbuminuria in adults after prenatal exposure to the Dutch famine. *J Am Soc Nephrol* 16: 189-194, 2005.

87. Baker CN, Ebert SN: Development of aerobic metabolism in utero: requirement for mitochondrial function during embryonic and foetal periods. *OA Biotechnology* 2: 1-7, 2013.

88. Ravera S, Podesta M, Sabatini F, Fresia C, Columbaro M, Bruno S, et al.: Mesenchymal stem cells from preterm to term newborns undergo a significant switch from anaerobic glycolysis to the oxidative phosphorylation. *Cell Mol Life Sci* 75: 889-903, 2018.

89. Hinchcliffe SA, Sargent PH, Howard CV, Chan YF, Van Velzen D: Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the dissector method and Cavalieri principle. *Lab Invest* 64: 777-784, 1991.

90. Rodriguez MM, Gomez AH, Abitbol CL, Chandar JJ, Duara S, Zilleruelo GE: Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. *Pediatr Dev Pathol* 7: 17-25, 2004.

91. Sutherland MR, Gubhaju L, Moore L, Kent AL, Dahlstrom JE, Horne RS, et al.: Accelerated maturation and abnormal morphology in the preterm neonatal kidney. *J Am Soc Nephrol* 22: 1365-1374, 2011.

92. Stelloh C, Allen KP, Mattson DL, Lerch-Gaggl A, Reddy S, El-Meanawy A: Prematurity in mice leads to reduction in nephron number, hypertension, and proteinuria. *Transl Res* 159: 80-89, 2012.

93. Cargill K, Hemker SL, Clugston A, Murali A, Mukherjee E, Liu J, et al.: Von Hippel-Lindau acts as a metabolic switch controlling nephron progenitor differentiation. *J Am Soc Nephrol* 30: 1192-1205, 2019.

94. Vander Heiden MG, Cantley LC, Thompson CB: Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324: 1029-1033, 2009.

95. Chen X, Qian Y, Wu S: The Warburg effect: evolving interpretations of an established concept. *Free Radic Biol Med* 79: 253-263, 2015.

96. Liu J, Edgington-Giordano F, Dugas C, Abrams A, Katakam P, Satou R, et al.: Regulation of nephron progenitor cell self-renewal by intermediary metabolism. *J Am Soc Nephrol* 28: 3323-3335, 2017.

97. Moussaieff A, Rouleau M, Kitsberg D, Cohen M, Levy G, Barasch D, et al.: Glycolysis-mediated changes in acetyl-CoA and histone acetylation control the early differentiation of embryonic stem cells. *Cell Metab* 21: 392-402, 2015.

98. Shyh-Chang N, Daley GQ: Metabolic switches linked to pluripotency and embryonic stem cell differentiation. *Cell Metab* 21: 349-350, 2015.

99. Singer MA: Of mice and men and elephants: metabolic rate sets glomerular filtration rate. *Am J Kidney Dis* 37: 164-178, 2001.

100. Douglas-Denton R, Moritz KM, Bertram JF, Wintour EM: Compensatory renal growth after unilateral nephrectomy in the ovine fetus. *J Am Soc Nephrol* 13: 406-410, 2002.

101. Perlman R: An evolutionary view of homeostasis: Bioenergetics, life history theory, and responses to pregnancy. In: *Integrating Evolutionary Biology into Medical Education—for maternal and child healthcare students, clinicians, and scientists*. First edition ed. edited by Schulikin J, Power ML, New York, Oxford University Press, 2020.

102. Houk JC: Control strategies in physiological systems. *FASEB* 2: 97-107, 1988.

103. Lea AJ, Tung J, Archie EA, Alberts SC: Developmental plasticity research in evolution and human health: Response to commentaries. *Evol Med Public Health* 2017: 201-205, 2017.

104. Dybala MP, Olehnik SK, Fowler JL, Golab K, Millis JM, Golebiewska J, et al.: Pancreatic beta cell/islet mass and body mass index. *Islets* 11: 1-9, 2019.

105. Bock T, Pakkenberg B, Buschard K: Genetic background determines the size and structure of the endocrine pancreas. *Diabetes* 54: 133-137, 2005.
106. Rodriguez-Trejo A, Ortiz-Lopez MG, Zambrano E, Granados-Silvestre Mde L, Mendez C, Blondeau B, et al.: Developmental programming of neonatal pancreatic beta-cells by a maternal low-protein diet in rats involves a switch from proliferation to differentiation. *Am J Physiol Endocrinol Metab* 302: E1431-1439, 2012.

107. Quinlan J, Lemire M, Hudson T, Qu H, Benjamin A, Roy A, et al.: A common variant of the PAX2 gene is associated with reduced newborn kidney size. *J Am Soc Nephrol* 18: 1915-1921, 2007.

108. Salomon R, Tellier AL, Attie-Bitach T, Amiel J, Vekemans M, Lyonnnet S, et al.: PAX2 mutations in oligomeganephronia. *Kidney Int* 59: 457-462, 2001.

109. Murugapoopathpy V, Gupta IR: A Primer on Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT). *Clin J Am Soc Nephrol* 15: 1915-1921, 2007.

110. Schmitt R, Cantley LG: The impact of aging on kidney repair. *Am J Physiol Renal Physiol* 294: F1265-1272, 2008.

111. Kirkwood TB: Evolution of ageing. *Nature* 270: 301-304, 1977.

112. Kirkwood TB, Shanley DP: Food restriction, evolution and ageing. *Mech Ageing Dev* 126: 1011-1016, 2005.

113. Denic A, Lieske JC, Chakkera HA, Poggio ED, Alexander MP, Slng P, et al.: The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 28: 313-320, 2016.

114. Geraci S, Chacon-Caldera J, Cullen-McEwen L, Schad LR, Sticht C, Puelles VG, et al.: Combining new tools to assess renal function and morphology: a holistic approach to study the effects of aging and a congenital nephron deficit. *Am J Physiol Renal Physiol* 313: F576-f584, 2017.

115. Lane N: A unifying view of ageing and disease: the double-agent theory. *J Theor Biol* 225: 531-540, 2003.

116. Lambeth JD: Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. *Free Radic Biol Med* 43: 332-347, 2007.

117. Malnutrition. WHO Factsheet. [https://www.who.int/news-room/fact-sheets/detail/malnutrition](https://www.who.int/news-room/fact-sheets/detail/malnutrition). World Health Organization, 2018.

118. Bennett KM, Baldelomar EJ, Morozov D, Chevalier RL, Charlton JR: New imaging tools to measure nephron number in *vivo*: Opportunities for developmental nephrology. *J Dev Orig Health Dis* in press, 2020.

119. Charlton JR, Pearl VM, Denotti AR, Lee JB, Swaminathan S, Scindia YM, et al.: Biocompatibility of ferritin-based nanoparticles as targeted MRI contrast agents. *Nanomedicine* 12: 1735-1745, 2016.
127. Bertram JF, Douglas-Denton RN, Diouf B, Hughson MD, Hoy WE: Human nephron number: implications for health and disease. Pediatr Nephrol 26: 1529-1533, 2011.
128. Georgas KM, Chiu HS, Lesieur E, Rumballe BA, Little MH: Expression of metanephric nephron-patterning genes in differentiating mesonephric tubules. Dev Dyn 240: 1600-1612, 2011.
129. Little MH: Improving our resolution of kidney morphogenesis across time and space. Curr Opin Genet Dev 32: 135-143, 2015.
130. Potter EL: Normal and Abnormal Development of the Kidney, Chicago, Year Book, 1972.
131. Roustan V, Jain A, Teige M, Ebersberger I, Weckwerth W: An evolutionary perspective of AMPK-TOR signaling in the three domains of life. J Exp Bot 67: 3897-3907, 2016.
132. Craig PM, Moyes CD, LeMoine CMR: Sensing and responding to energetic stress: Evolution of the AMPK network. Comp Biochem Physiol B Biochem Mol Biol 224: 156-169, 2018.
133. Fothergill-Gilmore LA, Michels PA: Evolution of glycolysis. Prog Biophys Mol Biol 59: 105-235, 1993.
134. Dumesic PA, Egan DF, Gut P, Tran MT, Parisi A, Chatterjee N, et al.: An Evolutionarily Conserved uORF Regulates PGC1alpha and Oxidative Metabolism in Mice, Flies, and Bluefin Tuna. Cell Metab 30: 190-200.e196, 2019.
135. Gutierrez-Mazariegos J, Schubert M, Laudet V: Evolution of retinoic acid receptors and retinoic acid signaling. Subcell Biochem 70: 55-73, 2014.
136. Jurkowski TP, Jeltsch A: On the evolutionary origin of eukaryotic DNA methyltransferases and Dnmt2. PLoS One 6: e28104, 2011.
137. Kucharski R, Maleszka J, Foret S, Maleszka R: Nutritional control of reproductive status in honeybees via DNA methylation. Science 319: 1827-1830, 2008.
138. Susztak K: Understanding the epigenetic syntax for the genetic alphabet in the kidney. J Am Soc Nephrol 25: 10-17, 2014.
139. Wallace DC, Fan W: Energetics, epigenetics, mitochondrial genetics. Mitochondrion 10: 12-31, 2010.
140. Morita M, Gravel SP, Hulea L, Larsson O, Pollak M, St-Pierre J, et al.: mTOR coordinates protein synthesis, mitochondrial activity and proliferation. Cell Cycle 14: 473-480, 2015.
141. Bhargava P, Schnellmann RG: Mitochondrial energetics in the kidney. Nat Rev Nephrol 13: 629-646, 2017.
142. Green DR, Galluzzi L, Kroemer G: Cell biology. Metabolic control of cell death. Science 345: 1250256, 2014.
143. Vollovelsky O, Nguyen T, Jarmas AE, Combes AN, Wilson SB, Little MH, et al.: Hamartin regulates cessation of mouse nephrogenesis independently of Mtor. Proc Natl Acad Sci U S A 115: 5998-6003, 2018.
144. Goda N, Kanai M: Hypoxia-inducible factors and their roles in energy metabolism. Int J Hematol 95: 457-463, 2012.
145. Stangenberg S, Chen H, Wong MG, Pollock CA, Saad S: Fetal programming of chronic kidney disease: the role of maternal smoking, mitochondrial dysfunction, and epigenetic modification. Am J Physiol Renal Physiol 308: F1189-F1196, 2015.
146. Bernhardt WM, Schmitt R, Rosenberger C, Munchenhagen PM, Grone H-J, Frei U, et al.: Expression of hypoxia-inducible transcription factors in developing human and rat kidneys. Kidney Int 69: 114-122, 2006.
147. Lampl M, Kuzawa CW, Jeanty P: Growth patterns of the heart and kidney suggest inter-organ collaboration in facultative fetal growth. Am J Hum Biol 17: 178-194, 2005.
148. Paldi A: What makes the cell differentiate? Prog Biophys Mol Biol 110: 41-43, 2012.
Table 1. Relationship of nephron number to ureteric tree branching at the end of early branching phase (E15.5 days) in fetal mouse kidneys.26

|                                      | Wild type | FGF7-/- | Vitamin A deficient | Protein deficient |
|--------------------------------------|-----------|---------|---------------------|------------------|
| Maximum branching generation number  | 15        | 12      | 17                  | 13               |
| Glomerular number at E15.5           | 101±6     | 71±7    | 44±5                | 25±4             |
| Impact of growth factor mutation or nutrient restriction on nephrogenesis | Delay in development (↓ branching generation #) | Normal branching rate, but impaired glomerular induction | Global impairment: 50%↓ segment # 75%↓ glomerular # 90%↓ tree volume |

FGF7-/-, fibroblast growth factor 7 knockout.
Table 2. Tenets of Charles Darwin’s theory of evolution (1859).  

- Existence of inter-individual variation within any population
- Selection by the environment for reproductive fitness (organisms that differentially reproduce)
- Heritability of variations
### Table 3. Bioenergetics and nephrogenesis.

|                         | Glycolysis                              | OXPHOS metabolism                   |
|-------------------------|-----------------------------------------|-------------------------------------|
| **Tissue oxygen tension** | Hypoxia (anaerobic glycolysis)          | Normoxia                            |
|                         | Normoxia (aerobic glycolysis)           |                                     |
| **Energy efficiency**   | 2 mol ATP/mol glucose (anaerobic)       | 36 mol ATP/mol glucose              |
|                         | 4 mol ATP/mol glucose (aerobic)         |                                     |
|                         | “Warburg effect”                        |                                     |
| **Nephron progenitor cells** | Self-renewal                           | Differentiation                     |
|                         | ↓nephron number                         |                                     |
| **Fetus ➔ extrauterine life** | Immature mitochondria                   | Mature mitochondria                 |

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96: Immature mitochondria
87: Mature mitochondria

Table 4. Contribution of major oxygen-consuming metabolic organs to body mass.

| Organ  | Human | Rat |
|--------|-------|-----|
|        | % Body mass | % Oxygen use | OCI | % Body mass | % Oxygen use | OCI |
| Kidney | 0.5  | 6 | 12 | 0.9 | 7 | 7.8 |
| Liver  | 2    | 17 | 8.5 | 5  | 20 | 4 |
| Brain  | 2    | 20 | 10 | 1.5 | 3 | 2 |

OCI (oxygen consumption index) = % oxygen consumption / % body mass

Derived from data by DFS Rolfe and GC Brown, 1997.54
Table 5. Evolutionary bioenergetic maternal-fetal Interactions.\textsuperscript{17, 72}

- Pregnancy and breastfeeding increase maternal energy requirement by 20%
- The placenta balances energy resources and needs of mother vs. fetus
- Restricted maternal nutrition favors fitness of mother (having reached reproductive age, she is more likely than the fetus to reproduce in the future)
- In response to maternal undernutrition, the fetus can reduce its energy consumption by
  - Slowed somatic growth
  - Accelerated maturation through cortisol release and premature delivery
  - Death (abortion)
Table 6. Transgenerational epigenetics: 100 years of nutritional flow, 1,000 days of development.9

| Grandmother                     | Mother                        | Placenta                     | Fetus                        | Infant/Child                  |
|---------------------------------|-------------------------------|------------------------------|------------------------------|--------------------------------|
| Made grandchild’s egg           | Released egg                 | Transported nutrients       | Made placenta                | Consumed nutrients            |
| Donated genes                   | Provided nutrients            | Produced hormones           | Consumed nutrients           | Grew body                     |
|                                 | Influenced placenta          | Exported wastes             | Developed organs             |                                |
|                                 | Fed & nurtured baby          |                              | Grew body                    |                                |

100 years of nutritional flow (3 generations)

1,000 days of development (fetal & child development)
**Figure 1.**

**A.** Relationship between birth weight and total glomerular number for kidneys obtained at autopsy from 56 American subjects without known kidney disease. Each data point represents one individual, linear regression (solid line), 95% confidence intervals (dashed lines), regression predicted interval (dotted lines), $r = 0.43$, $p = 0.0012$. The range in glomerular number (227,327 to 1,825,380) represents an 8.0-fold difference; reproduced from M.D. Hughson et al. (2003) with permission from Elsevier Publishing Company. A subsequent series incorporating 398 subjects from North America, Australia and Africa yielded a range from 210,332 to 2,702,079, a 13-fold span.

**B.** Distribution of individual glomerular volume by category: ↑BW (birth weight >3.46 kg), ↓BW (birth weight ≤3.25 kg), ↑NN (nephron number, top quintile), ↓NN (nephron number bottom quintile); 30 glomeruli per subject, 6 subjects per group. Glomerular enlargement with volume heterogeneity marks lower birth weight and relative nephron deficiency ($p<0.0001$); adapted from W.E. Hoy et al. (2011) with permission from S. Karger AG, Basel.
Figure 2. An overview of mammalian kidney development. A. Gene expression and nephron induction in the metanephric mesenchyme. Solid arrows indicate known regulatory relationships. (RV) renal vesicle; (UB) ureteric bud. Adapted from Georgas et al. (2011) with permission. B. Overview of reciprocal signaling and inductive relationships in the nephrogenic niche, nephron patterning, and maturation. (NZS) Nephrogenic zone stroma; (NP) nephron progenitor; (UT) ureteric tip; (PA) pretubular aggregate; (MET) mesenchyme to epithelial transition; (RV) renal vesicle; (CSB and SSB) comma- and S-shaped body; (cns) connecting segment. C. Timeline and gross morphology of kidney development in humans. 90% of nephrons are formed between 26 and 36 weeks gestation. Adapted from Little and Combes (2015) with permission. D. Illustration of nephron arcading in the human kidney, showing the most common arrangement (left) with possible variations (right). Adapted from E. L. Potter, Normal and Abnormal Development of the Kidney, page 43 (1972) with permission.
Figure 3. Timeline of evolution of life on earth. Timing of the appearance of each component of cellular complexity is an approximation based on current molecular and fossil data. Prokaryotes evolved in an anoxic environment with the early development of key metabolic pathways: glycolysis, adenosine monophosphate-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) that have been adapted with modification by all extant life forms.\textsuperscript{131-133} A key event in the evolution of eukaryotes was the rise in environmental oxygen generated by photosynthetic cyanobacteria over 2 billion years ago. This enabled the symbiotic acquisition of mitochondria and the rise in complexity of metazoa over 700 million years ago, and the evolution of metabolic regulators such as hypoxia-inducible factor-1 (HIF1), peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1), retinoic acid
receptor (RAR), and autophagy.\textsuperscript{69, 81, 134, 135} DNA methyltransferases (Dnmt) have regulated organ differentiation in response to nutritional energy signals for over 700 million years.\textsuperscript{136} This is evidenced by silencing the expression of Dnmt3 in newly hatched honeybee larvae, which produces a royal jelly-like effect on larval development, with adults emerging as queens with fully developed ovaries.\textsuperscript{137}
Figure 4. The mitochondrion as the primary environmental sensor, responding to external stressors such as hypoxia or reduced nutrient availability.\textsuperscript{44} Crosstalk between mtDNA-derived and nDNA derived proteins achieves a balance between available energy and energy demands of the cell. mtDNA mutation occurs more frequently than nDNA mutation, and provides rapid adaptation for migrating populations to varying environments (haplogroups). This is tempered by inheritance of nDNA mutation which is slower, but modified by epigenetic modification which responds to signaling from mitochondria. The epigenome can also act as a sensor of environmental stress, adjusting cellular metabolic state to nutrient availability, and through phenotypic changes can promote evolution.\textsuperscript{138} With the availability of abundant calories through stimulation of mTORC1 and the tricarboxylic acid (TCA) cycle, high-energy intermediates increase (ATP, acetyl-CoA and S-adenosylmethionine), driving modification of chromatin histone tails, activating transcription, and stimulating growth and reproduction.\textsuperscript{139} With calorie restriction, the intermediates decrease, and phosphatases, deacetylases, and demethylases promote chromatin condensation, arresting transcription.
Figure 5. Mediated by the placenta, maternal energy balance regulates metabolic pathways in the fetal kidney, determined by the activity of AMPK and mTOR. Whereas AMPK activates catabolic pathways, mTORC1 activates anabolic pathways. Once activated by stressors such as hypoxia and nutrient restriction, AMPK restores energy homeostasis, reducing energy consumption by inhibiting mTORC1 and phosphorylating substrates such as PGC1α that stimulate mitochondrial biogenesis. mTORC1 is a nutrient sensor activated by growth factors, amino acids, glucose, and oxidative stress. mTORC1 co-activates the master regulator of mitochondrial biogenesis PGC1α, and transcription of mitochondrial genes. Mitochondrial biogenesis, regulated by PGC1α, requires a balance between fission, fusion, and mitophagy (removal of defective mitochondria from cells by autophagy). Mitochondria determine
whether cells respond to stress in an adaptive or suicidal manner: metabolic cues regulate activation of cell death pathways by acting on nutrient sensors.\textsuperscript{141, 142} In response to nutritional deprivation, AMPK also activates autophagy, ensuring survival of organs whose energy supply cannot be interrupted.

The importance of the mTOR pathway in nephrogenesis was revealed by marked reduction in nephron number in mice with conditional knockout of mTOR in nephron progenitor cells.\textsuperscript{143} More dramatic was the demonstration of a 25\% increase in nephron number in mice with conditional knockout of one allele of the tuberous sclerosis gene, \textit{tsc1}, which codes for hamartin, a protein that complexes with tuberin, thereby inhibiting mTORC1.\textsuperscript{143} HIF1 triggers a switch from OXPHOS to anaerobic conditions and reduces oxygen consumption in mitochondria by suppressing biogenesis and activating mitophagy.\textsuperscript{144} Nephron progenitor cells subjected to a hypoxic environment undergo glycolytic metabolism favoring cell proliferation, whereas higher oxygen environment favors OXPHOS metabolism and nephron differentiation driven by progenitor cell maturation in response to VHL-driven HIF1 suppression.\textsuperscript{93} Inhibition of glycolysis enhances Wnt/β catenin signaling leading to increased nephrogenesis.\textsuperscript{96} Atg1, autophagy-related 1; Dnmt, DNA methyltransferase; HIF1, hypoxia-inducible factor-1; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1α; Tsc1, tuberous sclerosis 1; ULK1, Unc-51 like autophagy activating kinase; VHL, von Hippel-Lindau tumor suppressor; Wnt, Wingless int-1.
Figure 6. Hypoxia inducible factor (HIF): regulator of fetal energy flow. At low oxygen tension HIF-1α escapes degradation and initiates a cascade of signaling steps resulting in transcription of hypoxia-response element-containing genes. Energy delivery to the fetus can be reduced by maternal nutritional insufficiency, hypoxia due to maternal smoking, or increased hemoglobin-oxygen affinity resulting from gestational diabetes. Maternal smoking also impairs fetal mitochondrial biogenesis via hypermethylation of PGC1α, leading to impaired nephrogenesis. The HIF pathway represents an integrated signaling system that coordinates fetal cellular
development with environmental stimuli by modulating metabolism to coordinate allocation of energy between processes occurring at multiple levels (cells, organs, organisms) through time (fetal development, life cycle, and across generations). The output of this process is manifested as tradeoffs in fetal organ development. In human fetal kidneys 14-24 weeks gestation, HIF-1α is expressed in glomeruli and collecting ducts, whereas HIF-2α is present in interstitial and peritubular cells. After completion of nephrogenesis (33 weeks) both isoforms of HIF are undetectable, consistent with a regulatory role for oxygen tension in nephrogenesis. In fetuses subjected to maternal smoking, kidney growth is stimulated between 23 and 27 weeks gestation, then markedly slowed through 32 weeks (a period of maximal nephrogenesis). By contrast, cardiac growth in fetuses of smoking mothers is suppressed at 23-27 weeks, but increases by 32 weeks. These adaptive changes are likely driven by HIF stimulating early renal EPO production and later cardiac hypertrophy. EPO, erythropoietin; NOS, nitric oxide synthase; VEGF, vascular endothelial growth factor.
A. PROLIFERATION

B. DIFFERENTIATION

Glucose → G6P → Pyruvate → Ac-CoA → Citrate → Histone Acetylation CHROMATIN OPEN

Pentose phosphate pathway

NADPH

PROGENITOR CELL RENEWAL (sufficient nutrient availability)

Histone Deacetylation CHROMATIN RESTRICTED

Glucose → G6P → Pyruvate → Ac-CoA → Citrate → Lactate → ATP, ADP

Fatty Acids

Oxidative phosphorylation

↑O₂/nutrient
Figure 7. Metabolic reprogramming drives progenitor cell renewal and nephron differentiation through control of histone acetylation.\textsuperscript{97} A. Aerobic glycolysis drives increased Ac-CoA production, which along with increasing pyruvate and NAD generation, promotes histone acetylation, thereby maintaining progenitor cell renewal. Glycolysis also shunts glucose to the pentose phosphate pathway, generating NADPH and nucleotides required for proliferation. B. Upon early differentiation, glycolysis is downregulated and cytosolic pyruvate and Ac-CoA are consumed in the TCA cycle, resulting in histone de-acetylation and increased ATP generation needed for nephron differentiation.\textsuperscript{97}

The stimulus to shift from proliferation to differentiation may be driven by an increase in the ambient O\textsubscript{2}/nutrient ratio.\textsuperscript{148} Low O\textsubscript{2}/nutrient ratio maintains continuous energy flux through aerobic glycolysis, with oxidation of NADH by conversion of pyruvate to lactate, and incorporation of excess pyruvate or Ac-CoA into macromolecules by proliferation. Biosynthesis therefore serves as a mechanism for maintaining continuous energy flux. By contrast, a high O\textsubscript{2}/nutrient ratio oxidizes all carbon to CO\textsubscript{2} and reduces oxygen to H\textsubscript{2}O, leaving no substrates for biosynthesis. However, although generating ATP, increased mitochondrial activity also increases the risk for production of toxic ROS. Energy-demanding differentiation may therefore serve as an adaptive mechanism to reduce this threat to cellular homeostasis. The response of chromatin stability to metabolic flux provides a mechanistic explanation for the regulation of nephrogenesis.\textsuperscript{148}

Ac-CoA, acetyl coenzyme A; G6P, glucose 6-phosphate; NAD, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; R5P, ribose 5-phosphate; TCA, tricarboxylic acid cycle.
A control system is defined as a set of communication channels interconnecting subsystems that process information. The feedforward controller translates goals, targets and information about potential disturbances into commands that are sent to a feedback controller that sends forcing functions to the controlled system to control the output (controlled variable). Whereas feedforward and feedback function on a moment-to-moment basis, adaptive control functions on a slower time scale. The adaptive controller evaluates measures of performance and regulates the properties of the other information-processing subsystems. Reproduced with permission from Wiley Publishing Company.

B. Application of Houk’s control strategies systems analysis to regulation of nephron number. The goal of the control strategy is for renal excretory function to meet metabolic demand, controlled by a feedback loop mediated by metabolic rate. Disturbances in the control system are created by constrained available energy (maternal hypoxia or nutritional restriction). The feedforward controller (process of nephrogenesis) commands the feedback controller (balance between progenitor cell proliferation and nephron differentiation) that forces the controlled system (number of nephrons vs. nephron size) which determines the controlled variable (nephron number). There is a time variable in the feedback controller: the longer progenitor cells maintain proliferative potential, the more nephrons can be generated. There is a reciprocal relationship between nephron number and nephron size (controlled system). This is true for the fetus (see Fig. 1B) as well as for compensatory nephron growth in response to ongoing nephron loss throughout postnatal life.