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REVIEW

Evolutionary Nephrology

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Progressive kidney disease follows nephron loss, hyperfiltration, and incomplete repair, a process described as "maladaptive." In the past 20 years, a new discipline has emerged that expands research horizons: evolutionary medicine. In contrast to physiologic (homeostatic) adaptation, evolutionary adaptation is the result of reproductive success that reflects natural selection. Evolutionary explanations for physiologically maladaptive responses can emerge from mismatch of the phenotype with environment or from evolutionary tradeoffs. Evolutionary adaptation to a terrestrial environment resulted in a vulnerable energy-consuming renal tubule and a hypoxic, hyperosmolar microenvironment. Natural selection favors successful energy investment strategy: energy is allocated to maintenance of nephron integrity through reproductive years, but this declines with increasing senescence after ~40 years of age. Risk factors for chronic kidney disease include restricted fetal growth or preterm birth (life history tradeoff resulting in fewer nephrons), evolutionary selection for APOL1 mutations (which provide resistance to trypanosome infection, a tradeoff), and modern life experience (Western diet mismatch leading to diabetes and hypertension). Current advances in genomics, epigenetics, and developmental biology have revealed proximate causes of kidney disease, but attempts to slow kidney disease remain elusive. Evolutionary medicine provides a complementary approach by addressing ultimate causes of kidney disease. Marked variation in nephron number at birth, nephron heterogeneity, and changing susceptibility to kidney injury throughout the life history are the result of evolutionary processes. Combined application of molecular genetics, evolutionary developmental biology (evo-devo), developmental programming, and life history theory may yield new strategies for prevention and treatment of chronic kidney disease.

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> "*I conceive that primordially what protoplasm wants is to be left alone, but environment being what it is, it never for long achieves this nirvana of undisturbed quietude.*"
>
> —Homer W. Smith[1]

An expanding global epidemic of chronic kidney disease (CKD) has prompted new approaches to elucidate the underlying mechanisms: the incidence of end-stage kidney disease (ESKD) in children is <10/million, but in adults, lifetime risk for ESKD rises to over 5%.[2,3] Diabetic nephropathy is now the leading cause of ESKD in adults,[3] whereas congenital anomalies of the kidneys and urinary tract (CAKUT) account for the majority of pediatric cases.[2] More recently, epidemiologic studies have shown that incomplete recovery from episodes of acute kidney injury (AKI) constitutes a risk factor for progressive CKD, and CKD in turn increases susceptibility to AKI: the proximal tubule therefore becomes a primary target of injury and progression of CKD.[4,5]

Physiologic Versus Evolutionary Adaptation (Proximate vs. Ultimate Cause)

Advances in nephrology have emerged through incremental understanding of kidney structure and function, and of the central role of the nephron in maintenance of homeostasis. Elegant morphologic studies performed by Jean Oliver in the early 20th century revealed the formation of intermixed hypertrophied and atrophied nephrons in the kidneys of patients with CKD (Bright's disease), an important observation (Figure 1).[6] Using microdissection techniques, Oliver also described the widespread formation of atubular glomeruli and aglomerular tubules in kidneys of patients with advanced CKD.[7] Subsequent morphometric studies of kidneys from patients with CKD due to vascular, glomerular, tubulointerstitial, or toxic etiologies demonstrated that the formation of atubular glomeruli as a result of proximal tubular destruction is a hallmark of late CKD.[5,8] Micropuncture studies by Barry Brenner and his associates in the 1980s

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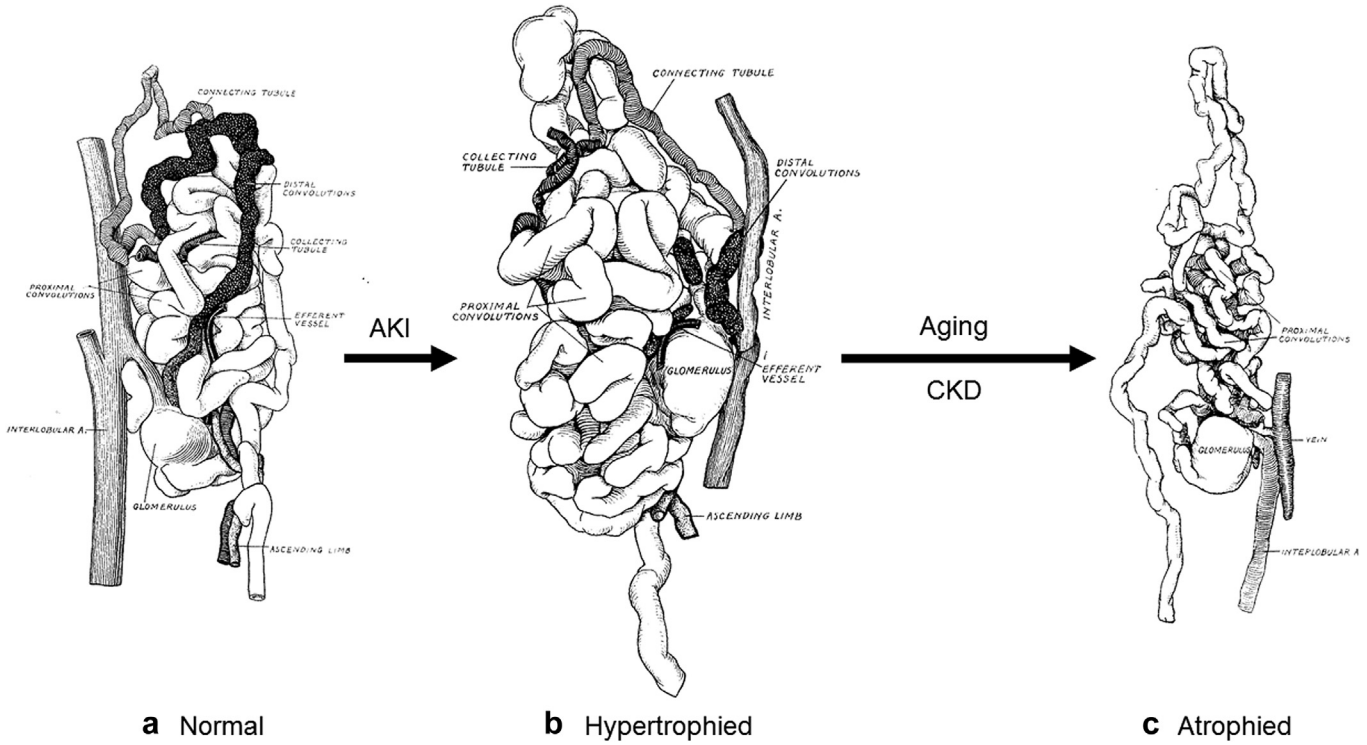

Figure 1. Three-dimensional reconstructions of individual nephrons from serial sections of human kidneys, depicting the fate (atrophy or hypertrophy) of the nephron population in chronic Bright's disease. (a) Glomerulotubular unit from a normal kidney, redrawn from Peter K. *Untersuchungen uber Bau und Entwickelung der Niere*. Jena, Germany: Gustav Fischer; 1909. (b) Hypertrophic unit and (c) atrophic unit from an adult with hemorrhagic Bright's disease following streptococcal tonsillitis. AKI, acute kidney injury; CKD, chronic kidney disease. Reproduced with permission from College of American Pathologists from Oliver J, Lund EM. The two architectural units in chronic Bright's disease and their possible functional significance. *Arch Pathol.* 1933;15:755–774.[6] Copyright © 2010 College of American Pathologists.

revealed that following experimental renal ablation, the remaining nephrons undergo hyperfiltration that maintains short-term homeostasis but that results in eventual glomerulosclerosis, a response described as "maladaptive".[9] In the terminal phases of CKD, widespread deposition of extracellular matrix in the renal interstitium is recognized as a final common pathway for nephron destruction, resulting from maladaptive repair of damaged nephrons.[10]

Throughout the 19th century and to the present day, disease has been regarded as a disorder of homeostasis, requiring an understanding of its *proximate* cause, or stimulus (physiologic adaptation).[11] Physiologists expect to find "optimal" homeostatic responses (adaptations) in biological systems; the term "maladaptation" implies deviation from an optimal adaptation to environment, a theoretical ideal that more often reflects the perspective of the physiologist (or physician) than the evolutionist, who recognizes that natural selection leads to traits that are better than the alternatives, but never optimal (Table 1).[12] It remains a term that is difficult to identify, because genetic/epigenetic adaptations cannot accurately predict future environmental changes.[13] This approach led to the development of angiotensin inhibitors, which are widely used in slowing hyperfiltration injury but do not arrest progression.[14] Similarly, inhibitors of mediators of interstitial fibrosis, such as transforming growth factor−β, have also proved to be disappointing.[15] A complementary paradigm is needed to understand the behavior of the nephron in CKD: this may lead to the discovery of new biomarkers of progression, and new effective therapies.

In contrast to its *proximate* cause, the *ultimate* cause of a biologic response can be revealed by an understanding of its evolutionary origins through the process of natural selection.[11] Evolutionists look for ancestral environments and selective pressures that determine disease vulnerability; traits that increase reproductive success at the cost of disease vulnerability (Table 1).[13] In his book, *From Fish to Philosopher*, Homer Smith argued that the complex structure of the kidney can be explained by a series of evolutionary adaptations in our vertebrate ancestors, who transitioned from marine to fresh water environments and ultimately to survival on land (Figure 2).[16] Written by the leading American renal physiologist of the mid-20th century, this book reveals how an evolutionary perspective explains the dependence of renal excretory function on filtration of 180 L of plasma per day and

Table 1. Chronology of the introduction of evolutionary terms relevant to the progression of chronic kidney disease

Year, author, title	Evolutionary term	Definition
1859: Charles Darwin *The Origin of Species*[26]	Darwinian evolution	The result of natural selection of inherited variations that increase the individual's reproductive success
1930: Ronald A. Fisher *The Genetical Theory of Natural Selection*[42]	Life history theory	Evolution of major features of a life cycle: age distribution of birth and death rates, growth rates, and size of offspring[43]
1967: G.C. Williams *Adaptation and Natural Selection*[22]	Evolutionary adaptation	The result of reproductive success (fitness) that reflects natural selection[18]
	Physiologic adaptation	The result of a homeostatic mechanism (adaptive trait) that responds to an immediate environmental stimulus[18]
1970s	Evolutionary physiology	Elucidation of evolutionary adaptations through a synthesis of comparative physiology and physiological ecology by comparing physiological, cellular, and molecular characteristics[69]
1977: S.J. Gould *Ontogeny and Phylogeny*[72]	Evolutionary developmental biology ("evo-devo")	Elucidation of the evolution of developmental processes, linking molecular mechanisms (primarily gene regulatory networks) to phenotypic change[73,74]
1988: D.J.P. Barker, C. Osmond *Infant Mortality, Childhood Mortality and Ischaemic Heart Disease*[63]	Developmental origins of health and disease (developmental programming)	Elucidation of environmental factors during early animal and human development, and interactions between environmental and genetic factors, that influence health in later life and risk of disease[64]
1991: G.C. Williams, R.M. Nesse *The Dawn of Darwinian Medicine*[20]	Evolutionary medicine (Darwinian medicine)	The study of disease mechanisms through the application of evolutionary theory, leading to the elucidation of factors underlying disease susceptibility[21]
2005: R.M. Nesse *Maladaptation and Natural Selection*[13]	Maladaptation	Deviation from an optimal adaptation to environment, which can never be perfect—very difficult to identify because of asynchronous changes in genetic systems and environments over time[12,13]

reclamation of 99% of the filtrate. Many of the early advances in renal physiology were based on animal studies that required an understanding of evolution to apply the results to human beings.[17] The context of the word "adaptation" has major consequences: physiologic adaptation (adaptive trait) is a homeostatic mechanism that responds to an immediate environmental stimulus, whereas evolutionary adaptation is the result of reproductive success that reflects natural selection (Table 1).[18] Quantitative analysis of the relationship between physiologic and evolutionary adaptation in hemoglobin oxygen saturation across 25 mammals under varying physiologic conditions demonstrates that the 2 forms of adaptation operate on different parameters so that the adaptive ranges can be maintained in new environments.[19] This remarkable study reveals the relationship between homeostatic and evolutionary adaptation.

Evolutionary Medicine

Although evolutionary theory has traditionally been applied to studies of comparative anatomy and physiology, an evolutionary approach to disease continued to be largely neglected until a new discipline was developed in the 1990s by G.C. Williams and Randolph Nesse, now recognized as "evolutionary medicine" (Table 1).[20,21] In 1957, Williams argued that natural selection of deleterious effects must be ascribed to other effects of the same genes.[22] He reasoned that senescence can be explained by antagonistic pleiotropy, whereby a gene has a beneficial effect through reproductive age, but has detrimental effects afterward.[23] Antagonistic pleiotropy remains the basis for the evolutionary origin of senescence in all animals.[24] However, additional factors may play a role in species with prolonged life after reproduction (only human beings and some whales have evolved menopause), but these remain to be elucidated.[25] The core concept of Darwinian evolution, as proposed in *The Origin of Species,* first published in 1859, is the process of natural selection of inherited variations that increase an individual's reproductive success.[26]

The primary challenge to the adoption of an evolutionary approach to disease rests on the practice of medicine itself: physicians are charged with the responsibility for diagnosing and treating a particular disorder in an individual patient, a process that appears far removed from evolutionary concerns. However, the history (present illness, past history, and family history) is the key component in diagnosis. Seeking concordance with established medical sciences (genetics, anatomy, physiology, biochemistry), evolutionary medicine relies on evolutionary biology to create a "deep" history of human populations. The rationale for the evolutionary perspective is that rather than causing disease, our evolutionary history determines our risk of disease in a given environment, a context that overlaps with public health, global health, and health care disparities. Thus, in addition to the current investigation of cellular and physiologic processes resulting from nephron injury, a complementary

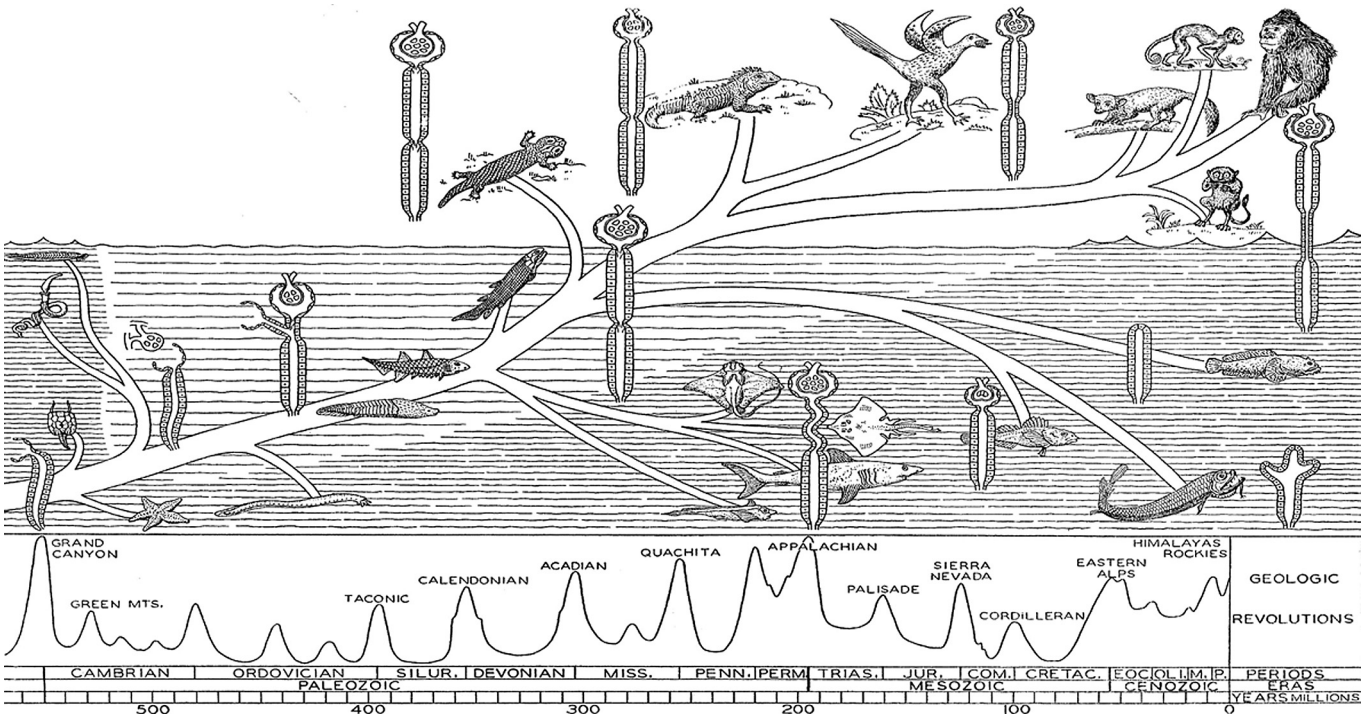

Figure 2. The more important steps in the evolution of the vertebrate kidney in relation to saltwater (darkly shaded) and freshwater (lightly shaded) environments. Schematic nephrons are depicted, beginning with glomerular nephrons in freshwater chordates. The evolutionary tree is followed through primitive fish, amphibians, reptiles, birds, and mammals with adaptation to a terrestrial environment (differentiation of proximal and distal tubules, and loop of Henle). In the Devonian period, major changes in the earth's crust forced fish to adapt to saltwater: high-filtering glomeruli became a liability in this hyperosmolar environment, and were lost in some fish (sculpin and deep sea fishes [lower right]). The timeline at the bottom shows the geologic periods and eras, with the final Pleistocene being compressed. Reproduced with permission from University Extension Division, University of Kansas from Smith HW. The evolution of the kidney. In: *Studies in the Physiology of the Kidney*. Lawrence, KS: University of Kansas; 1939 (subsequently reproduced as endpapers in Smith HW. *From Fish to Philosopher*. Boston, MA: Little, Brown and Company; 1953[16]).

approach would include the study in defined populations of variation in genotype and phenotype, as well as its interaction with environmental factors from early nephrogenesis through senescence (life history). Coupled with advances in genomics, epigenetics, and developmental biology, the evolutionary perspective has already contributed significantly to understanding human health and disease (Table 2).[27] Overuse of antibiotics in human beings and domestic animals has led to a global epidemic of microbial resistance resulting from rapid evolution of antibiotic resistance in bacteria through horizontal as well as vertical gene transfer.[27] The recognition of lymphocyte clonal selection by Macfarlane Burnet was based on the application of

Table 2. Evolutionary explanations for medical questions: application to nephrology

	Question	Evolutionary explanation
Examples of successful application of evolutionary medicine	What drives antibiotic resistance in microorganisms?	Rapid evolution with exchange of genetic information stimulated by the host environment
	What explains the diversity of antibodies in the immune response?	Adaptive immunity results from clonal selection of lymphocytes by a process analogous to natural selection
	What accounts for the development of resistance to cancer chemotherapy?	As for antibiotic resistance and adaptive immunity, selection of malignant mutant clones can be prevented by application of evolutionary principles to the design of chemotherapy
Application of evolutionary medicine to nephrology	What accounts for vulnerability of the kidney to injury in AKI?	Kidney evolution through transition from marine to freshwater environment to land necessitated high GFR with energy-consuming tubular sodium reclamation in a hypoxic, hyperosmolar microenvironment subject to ischemia
	What accounts for maladaptation in CKD (nephron loss through cell death with interstitial fibrosis)?	Nephron loss → hypertrophy of remaining nephrons → increased energy consumption that cannot be maintained → tubular cell death and formation of atubular glomeruli, a response shared with certain marine fish as they mature

AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate.

evolutionary principles, leading more recently to the design of individualized chemotherapy to suppress the emergence of mutant clones of malignant cells.[28]

In the 2 decades since Nesse and Williams published their landmark book, *Evolution and Healing: The New Science of Darwinian Medicine*,[21] a number of additional texts have been published, greatly expanding the scope of evolutionary medicine, but none of which includes more than cursory references to kidney disease.[24,29–35] An Arthur M. Sackler Colloquium of the National Academy of Sciences, "Evolution in Health and Medicine," was held in Washington in 2009,[36] and a major policy paper was published in the journal Proceedings of the National Academy of Sciences, emphasizing the importance of including evolutionary biology in the basic science curriculum of medical schools.[37] Subsequently, in collaboration with the Biological Sciences Curriculum Studies (BSCS), the National Institutes of Health published a comprehensive curriculum for American high school teachers entitled *Evolution and Medicine*.[38,39] The authors propose that "evolution's greatest benefits will be to provide a theoretical framework for understanding the following: (i) why organisms are vulnerable to disease; (ii) how infectious agents evolve; and (iii) how common ancestry helps scientists use the results from animal models to understand issues related to human health."[39] As is the case for the published textbooks, the medical disciplines included in the NIH curriculum do not include kidney disease.[39] To fill this gap, the present review seeks to present the case for an evolutionary perspective to enhance our understanding of progressive kidney disease, by explaining why the kidney is vulnerable to maladaptive nephron loss. The noted philosopher of science Karl Popper was initially critical of evolutionary theory, because he believed that it could not be tested.[40] However, he subsequently concluded, "I have changed my mind about the testability and the logical status of the theory of natural selection; and I am glad to have an opportunity to make a recantation. … What is important is to realize the explanatory task of natural selection."[41]

Life History, Tradeoff, and Mismatch

On one hand, species have evolved different life histories as a consequence of living in different environments. On the other hand, individual species have evolved flexible life histories and so are able to respond physiologically to life in different environments (Tables 1 and 3).[42,43] This explains the remarkable diversity of body plans, number and size of offspring, rates of growth and maturation, life span, and senescence. The life history for human beings entails the production of few offspring, with a prolonged period of maturation to sexual maturity, followed by a long period of senescence. Mortality rate follows a "V" curve, explained by high fetal/infant mortality, with a nadir at 12 years, and a steady increase after peak reproductive years (Figure 3a).[44] The majority of early fetal death (spontaneous abortion) is shaped by natural selection of lethal chromosomal abnormalities (Table 3). Higher mortality for males than for females (Figure 3a) has been regarded as a maladaptation, but may result from sex-specific optimization of a tradeoff between reproduction and survival.[45] Regarding risk factors for CKD, the V-curve can be separated into 2 overlapping curves, the first reflecting a predominance of genetic/epigenetic risk factors associated with CAKUT and determined largely by natural selection, and the second

Table 3. Life history in epidemiology and pathogenesis of chronic kidney disease (CKD)

	Question	Evolutionary explanation
Epidemiology	Why are congenital anomalies of the kidney and urinary tract the leading cause of CKD, but CKD is rare in childhood?	Mutations and intrauterine environmental stress alter normal renal development. Natural selection reduces the incidence of severe malformations (lethal mutations)
	How does variability in nephron number at birth contribute to adult CKD (developmental programming)?	Intrauterine stress impairs fetal and neonatal renal growth, an adaptation to restricted energy supplies, favoring early infant survival, but the tradeoff is reduced nephron number; additional nephrons can be formed *in utero*, but not after birth
	Why are diabetes and cardiovascular disease the leading causes of adult CKD?	The Western diet (developed only 10,000 years ago), high in fat and sodium, is mismatched to the Pleistocene diet of 100,000 years ago
Nephron heterogeneity and selection	How does mammalian nephron heterogeneity account for selective nephron vulnerability in progression of CKD?	Nephron heterogeneity evolved in adapting to life on land (enhanced urine concentration and sodium conservation); the tradeoff: short-loop nephrons are more susceptible to hypoxia and ischemia
	Why is there a 50% reduction in nephron number during adulthood?	Accumulated stresses and insults combined with senescence (decreased energy available for repair) lead to continued nephron selection through cycles of hypertrophy → atrophy unresponsive to natural selection in postreproductive period; this is accompanied by an interstitial inflammatory response and leads to interstitial fibrosis

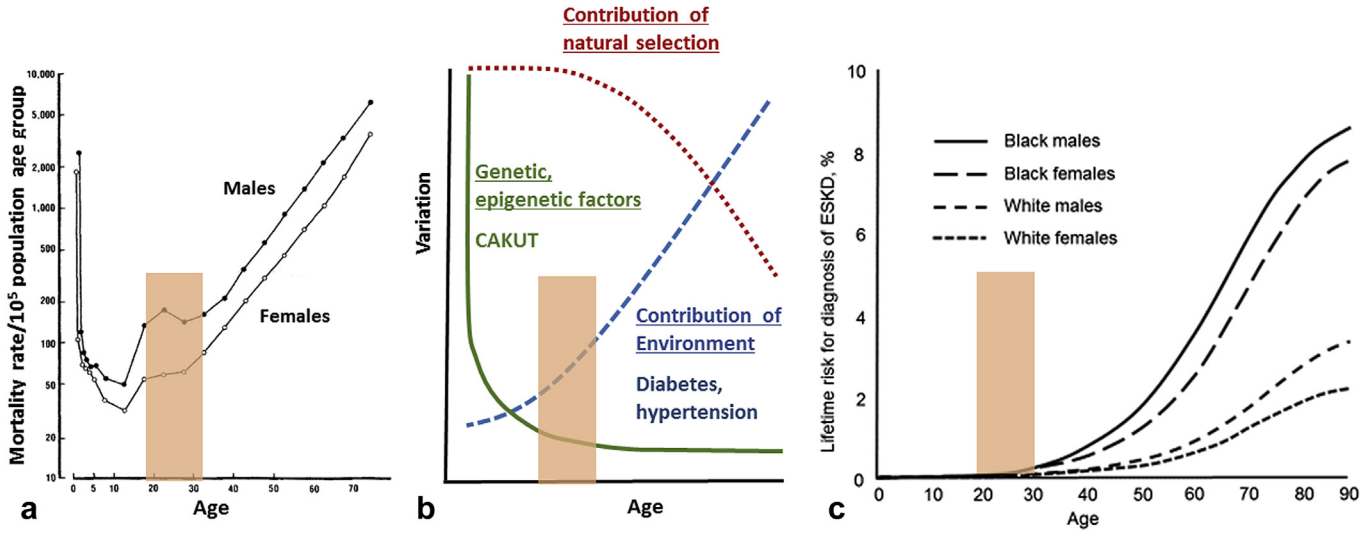

Figure 3. Relationship of maturation and aging to overall mortality and the progression of chronic kidney disease. (a) Age- and sex-specific mortality (all causes) over the life span in a modern developed country (Canada, 1971). A decline in mortality from ~2000 per 100,000 in fetal life to a nadir of 50 per 100,000 at 12 years of age reflects the dramatic contribution of lethal mutations to mortality in prereproductive life, followed by a logarithmic rise in mortality in the postreproductive period of senescence. Reproduced with permission from John Wiley and Sons from Costa T, Scriver CR, Childs B. The effect of Mendelian disease on health: a measurement. *Am J Med Genet.* 1985;21:231–242.[44] Copyright © John Wiley & Sons. (b) Relative contribution to chronic kidney disease of natural selection, genetic/epigenetic factors, and experience (environment) according to age at onset. Fetal/neonatal disorders (e.g., congenital anomalies of the kidneys and urinary tract [CAKUT]) are primarily attributable to genetic/epigenetic factors largely influenced by natural selection, whereas later mortality is primarily governed by environmental factors (e.g., diabetes, hypertension). Adapted with permission from Nature Publishing Group from Childs B. Acceptance of the Howland Award. *Pediatr Res.* 1989;26:390–393.[46] Copyright © Nature Publishing Group. (c) Lifetime risk for diagnosis of end-stage kidney disease (ESKD) over the life span. Risk of ESKD remains <1% until after peak reproductive age (30 years), after which risk accelerates more rapidly in black than in white cohorts and in males than in females. Reprinted with permission of Elsevier from Grams ME, Chow EKH, Segev DL, et al. Lifetime incidence of CKD Stages 3–5 in the United States. *Am J Kidney Dis.* 2013;62:245–252.[87] Copyright © National Kidney Foundation, Inc. Colored box indicates peak reproductive years.

reflecting primarily environmental factors, leading to diabetes and hypertension (Figure 3b).[46] Notably, for most children with CAKUT progressing to ESKD, renal replacement therapy is delayed until adulthood.[47] New genomic analysis reveals an expanding number of mutations that account for CAKUT,[48,49] and epigenetic mechanisms may be of even greater importance.[50] The lifetime risk for developing ESKD remains below 1% throughout the reproductive years, then increases markedly, with greater rates in males than in females and in black than in white race/ethnicity (Figure 3c).[3] This can be explained by the dominance of natural selection through reproductive years, and its decrease in the postreproductive period, characterized by senescence and cumulative environmental insults (Fig. 3B). A greater increase in males than in females may be explained in part by estrogen receptor modulation of mitochondrial oxidative status and ovulatory cycle–dependent metabolic responses by proximal tubular cells.[51,52] The relevance of evolutionary principles to understanding the racial disparity in CKD has been recently underscored by the discovery of increased risk for CKD in populations of West African ancestry with APOL1 mutations (Table 4).[53] This is the result of adaptive selection of the heterozygous state that confers protection from infection with *Trypanosoma brucei rhodesiense*, but homozygosity markedly increases susceptibility to glomerular injury and progressive CKD, a classic tradeoff.[54] Similar tradeoffs have been established for malaria (hemoglobinopathies and G6PD deficiency) and tuberculosis (cystic fibrosis).[24] The discovery of the association of APOL1 mutation

Table 4. Evolutionary explanations for physiologic maladapatation in kidney disease[a,13]

Evolutionary explanation	Natural selection	Factors that increase susceptibility to CKD
Tradeoff	Selection is determined by reproductive fitness, not by long-term health	APOL1 mutation increases resistance to trypanosome infection but→FSGS[53] CKD bears similarities to senescence, and accelerates after reproductive peak[67,87,110,120]
	Selection cannot solve some problems irrespective of time	Adaptation to land required energy-consuming proximal tubule susceptible to injury[16,85] Glomerulotubular disconnection→energy conservation in fish and CKD[8,96] Homeothermic physiology imposes regenerative constraints on nephrons[77,78]
Mismatch of phenotype to environment	Selection cannot keep pace with rapid environmental change	Low nephron number in growth-restricted fetus[65] and preterm infant[81] Hyperfiltration response to Western diet[58]

[a]CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis.

with risk of CKD resulted from combining genome analysis with the geographic distribution of mutations, revealing its protective role in trypanosome infection and its prevalence to the present. This suggests a model for future studies of polymorphisms that increase risk of CKD driven by ancestors' exposure to microbes or parasites.

The development of agriculture about 10,000 years ago led to a decline in potassium intake and a marked increase in sodium intake, major risk factors for the development of hypertension.[55] This has been compounded by a modern western diet that leads to excessive formation of uric acid that contributes to metabolic syndrome[56] and that yields a daily net acid load of 50 mEq, leading to low-grade metabolic acidosis that worsens as a consequence of age-related nephron loss: a case of environmental mismatch (Tables 3 and 4).[55,57,58]

Evolutionary Physiology: Mismatch Explained

The number of nephrons in man is fixed at birth, with completion of nephrogenesis by the 36th week of gestation, and nephron number ranging more than 10-fold, from 200,000 to 2,700,000 (Figure 4a).[59–61] This should not be surprising, as our species is characterized by wide variation in our metabolic and anatomic parameters (phenotypic plasticity). The hyperfiltration theory would predict that nephron number below the median represents a risk factor for CKD.[62] This appears to be the case. In the 1980s, David Barker, an epidemiologist, reported that adults dying of cardiovascular disease have significantly lower birth weight than the median, and follow-up studies revealed an increased incidence of hypertension and cardiovascular disease in individuals with lower nephron numbers.[63,64] Barker's insight into the significance of fetal and perinatal impact on the entire life cycle spawned an entire new discipline: developmental programming of health and disease (Tables 1, 3, and 4).[65,66] Formation of a reduced number of nephrons by fetuses in an unfavorable maternal environment can be explained by investing in fewer energy-consuming nephrons, favoring early reproductive success over a predicted short life span.[67] If, on the other hand, the infant is born into a rich nutritional environment, there will be a mismatch between a low nephron number and the resultant hyperfiltration, leading to CKD, physiologic maladaptation (Tables 1, 3, and 4).[58,68]

Garland and Carter have proposed a discipline entitled "evolutionary physiology" (Table 1).[69] Applying these principles to the nephron, gene polymorphisms, and environmental stimuli/stressors during development determine its phenotypic characteristics, including nephron number (Figure 5). Modulated by epigenetics, homeostatic function of the nephron is determined by its performance capacity and limited by its defenses against cell death and capacity for hypertrophy, proliferation, and repair (Figure 5). Maximal tubular size is limited by luminal diameter and tubular length that optimize reabsorption while minimizing resistance to tubular fluid flow. Thus, physical factors constrain adaptation by hypertrophy alone. In the whale, the kidney is multi-renculated, effectively

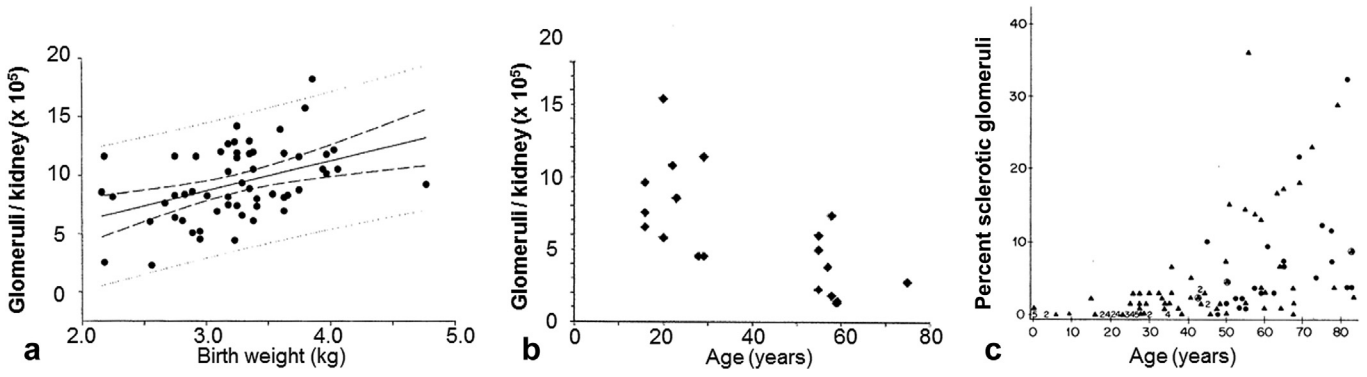

Figure 4. The kidney over the life span: the nephron number is highly variable at birth and decreases with increasing fraction of glomerulosclerosis following the reproductive years. (a) Relationship between birth weight and glomerular number among infants, children, and adults. Solid line, regression; dashed line, 95% regression confidence interval; $r = 0.423$, $P = 0.0012$, N = 56. Reprinted with permission from Elsevier from Hughson MD, Farris AB, Douglas-Denton R, et al. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int.* 2003;63:2113–2122.[61] Copyright © International Society of Nephrology. (b) Number of functioning (nonsclerosed) glomeruli per kidney in renal allograft cadaveric donors younger than 40 years (N = 12) and older than 55 years (N = 13). Reproduced with permission from the American Society of Nephrology from Tan JC, Workeneh B, Busque S, et al. Glomerular function, structure, and number in renal allografts from older deceased donors. *J Am Soc Nephrol.* 2009;20:181–188.[103] Copyright © American Society of Nephrology. (c) Percentage of sclerotic glomeruli from 122 autopsied patients plotted against age. Reprinted with permission from Elsevier from Kaplan C, Pasternack B, Shah H, et al. Age-related incidence of sclerotic glomeruli in human kidneys. *Am J Pathol.* 1975;80:227–234.[104] Copyright © American Society for Investigative Pathology.

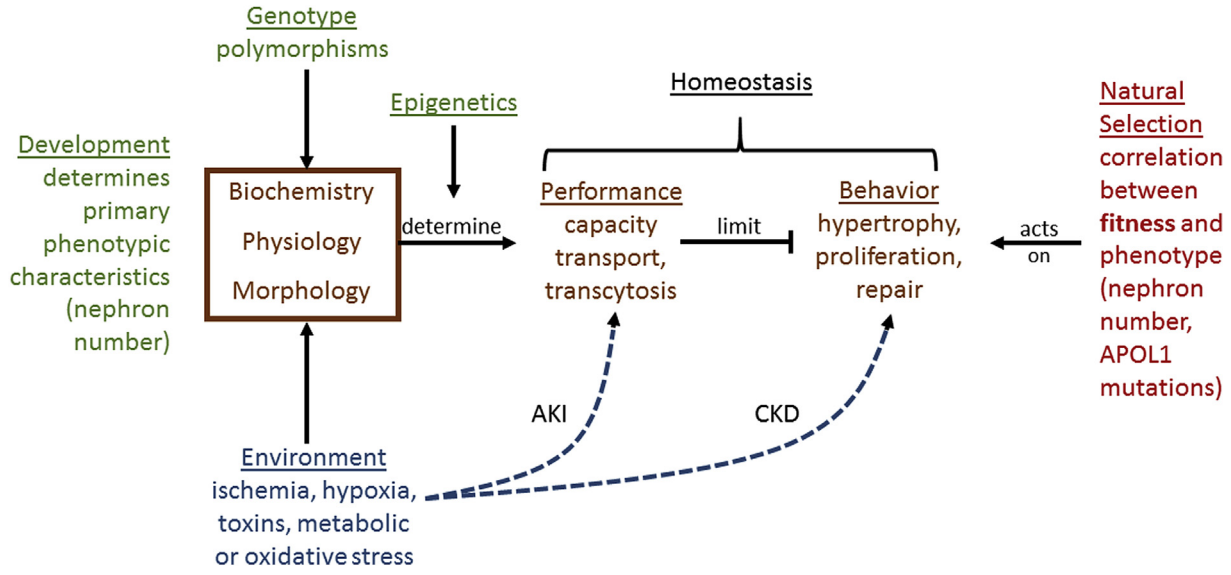

Figure 5. Relationship of homeostasis to natural selection in determining nephron responses to environmental stress in acute kidney injury (AKI) and chronic kidney disease (CKD). Primary phenotypic characteristics of the proximal tubule (biochemistry, physiology, and morphology) are determined by the interaction of the genotype and environment on the developing nephrons. Epigenetic factors also influence the performance capacity of the nephron, which in turn limits the behavior of tubular cells in response to environmental stressors. Natural selection acts on the reproductive success (fitness) of the organism as affected by maintenance of proximal tubular homeostasis in the face of AKI and CKD. Adapted with permission from the American Physiological Society, Annual Reviews, Inc., from Garland T Jr, Carter PA. Evolutionary physiology. *Annu Rev Physiol.* 1994;56:579–621.[69] Copyright © Annual Reviews Inc.

packaging 30,000 nephrons in each of 7,000 discrete capsules joined to a common collecting system (approximately 200 million nephrons on either side).[70] In addition to effects on early development, environmental factors can have an impact on homeostatic responses to injury that are activated by AKI and CKD. The accelerating change in global climate with increasing water shortage is testing the limits of the performance capacity of renal sodium and water conservation, leading to new epidemics of CKD attributable to this mismatch.[71]

Plasticity Versus Robustness: A Necessary Tradeoff

The relatively new discipline of evolutionary developmental biology ("evo-devo") fosters comparison of embryonic development to the response to injury across phylogeny (Table 1).[72–74] This involves the study of phenotypic variation resulting from mutations of regulatory genes, thereby establishing the evolutionary history of developmental programs.[73] Patrick Bateson and Peter Gluckman have summarized a useful concept to elucidate the maladaptation paradox: the tension between plasticity and robustness (Table 5).[75] Drawing on evo-devo, the case is made for the importance of robustness of developmental regulatory mechanisms, to buffer this critical early phase of life from environmental or genetic perturbation.[75] Homeostatic feedback loops and mechanisms of repair and regeneration are regarded as robust, with responses that are determined by evolutionary history. Thus, injury can result either in the formation of blastema (limb or tail regeneration in reptiles and amphibians) or fibrosis (in mammals). The robustness bestowed by homeothermy in mammals reduced liability to kidney injury below the threshold needed to preserve energy-consuming regrowth, a tradeoff (Table 4).[76] In the course of evolution, mammals have developed sophisticated pathways of wound healing that, by blocking formation of blastema, can actually inhibit energy-consuming regeneration (Table 5).[77,78] Mammalian physiologic adaptation to acute tissue injury reduces hemorrhage and infection by activating inflammatory and fibrotic responses—these are shared by AKI. However, the response to persistent nephron injury (tubular atrophy and interstitial fibrosis) leads to CKD.

Table 5. Evolutionary tension: tradeoff between plasticity and robustness[18,75]

Plasticity	Robustness
Adaptive: accommodates to disruptions of development, often in response to environmental cues	Buffers plasticity: maintains phenotypic consistency despite environmental perturbations
Late development—adult	Early development—embryo
Must outweigh cost of disadvantageous phenotype	Maintained by repair/regeneration
Must deal with responses to ambiguous cues	Promotes increased fitness but may result in physiologic maladaptation

The complementary process, plasticity, accommodates disruptions of normal development caused by mutation, toxins, or accident, and are regulated by epigenetic processes, such as reduced nephron number in the growth-restricted fetus (Tables 3, 4, and 5). Although mammals cannot form additional nephrons after the completion of nephrogenesis, unilateral nephrectomy in fetal lambs or pigs results in a 45% to 50% increase in nephron number of the remaining kidney, a testament to the importance of the stage of life history in the regenerative response to renal injury.[79,80] Protection from infection and injury provided by the intrauterine environment is likely to play a role in this adaptive response: preterm birth in human infants results in impaired nephrogenesis in the very–low-birth-weight neonate.[81,82] Urine of preterm neonates born before the completion of nephrogenesis is rich in progenitor cells, which apparently fail to differentiate in the extrauterine environment.[83] There is a tradeoff between the number of progenitor cells in maturing tissues required for maintenance and repair: their persistence beyond reproductive years increases the risk of malignancy.[28] Notably, reduced nephron number in preterm infants increases lifetime risk for the development of CKD.[84]

Conservation of Energy: Tradeoff Explained

The kidney constitutes 1% of body weight but uses 10% of total body oxygen consumption, primarily devoted to proximal tubular sodium reabsorption.[85] As pointed out by Homer Smith, the necessity for reabsorption of 180 L of glomerular filtrate per day is the result of our evolutionary heritage.[16] Transition from a marine to freshwater environment gave rise to a high filtering glomerulus that was necessary to counteract the osmotic gradient, but adaptation to land and homeothermy necessitated reclamation of 99% of the filtrate, leading to a large energy requirement (Fig. 2).[16,85] A diet rich in meat such as that consumed by our Pleistocene ancestors would have provided the selection pressure to maintain a high glomerular filtration rate, necessary to excrete urea produced by protein metabolism.[86]

There is growing evidence that energy is the unifying principle of life (comprising evolution, ecology, allometry, and metabolism).[67] Life history strategies are driven by the balance between acquisition and allocation of energy.[31] Natural selection favors a species' successful investment strategy, exchanging energy for offspring: a fundamental tradeoff (Table 4).[67] Growth slows with attainment of reproductive age, because energy resources are increasingly spent on maintenance, rather than expansion (Table 4). Throughout the reproductive years, energy is allocated to maintenance of nephron integrity in the face of constant threats of hypoxia and oxidative stress, but this selection pressure is reduced after 20 years (Figure 3b), reflected by the sharp rise in ESKD in later adulthood (Tables 3 and 4, Figure 3c).[87] Life expectancy for our Paleolithic ancestors who survived infancy was approximately 35 to 40 years, and this changed little until the industrial revolution in the past 200 years, during which life expectancy doubled.[24] A mathematical model has been developed to describe the relationship among growth, maintenance, and reproduction in the determination of fitness, the Euler–Lotka formula.[35] This reveals that the influence of natural selection begins to decline in women by approximately 20 years of age.[24] The comorbidities associated with senescence of other organs (dementia, cardiovascular disease, diabetes, cancer) compound the management of CKD, and share common mechanisms involving oxidative injury and inflammation.[88]

Following renal ablation, oxygen consumption by the remaining hypertrophied nephrons initially doubles.[89] However, consistent with evolutionary conservation of energy, persistent upregulation of oxygen consumption by hypertrophied proximal tubules is not sustainable, thereby contributing to aging or the progression of CKD (Tables 2 and 3). Prolonged renal artery stenosis in the rat treated with an angiotensin-converting enzyme inhibitor results in atrophic tubules and 90% reduction in Na-K-ATPase activity, which is reversible within 3 weeks following removal of the clip and discontinuation of angiotensin inhibition.[90,91] However, patients with severe chronic renal artery stenosis undergo widespread irreversible tubular atrophy and formation of atubular glomeruli.[92] These observations indicate that short-term tubular energy consumption increases in parallel with hyperfiltration and increased tubular reabsorption (physiologic adaptation), but that prolonged renal ischemia reduces energy consumption, a response that can be reversed in mild but not severe injury (evolutionary adaptation).

The model of complete unilateral ureteral obstruction (UUO), currently the most widely used animal model of CKD,[5,93] results in profound reduction in tubular energy consumption, followed within 2 weeks by proximal tubule cell death and widespread formation of atubular glomeruli.[94,95] Formation of atubular glomeruli in CKD may represent an atavism that harks back to a common ancestor with fish that were faced with adaptation from freshwater back to saltwater. The daddy sculpin (a marine fish) belongs to 1 of these groups, and, with increasing age, nephrons undergo progressive degeneration of the glomerulotubular

junction, resulting in atubular glomeruli and aglomerular tubules (Table 2).[96] When viewed from an evolutionary perspective, the physiologically maladaptive response to hypoxic and oxidative stress resulting from complete UUO emerges as a tradeoff to suppress a major source of energy loss in a nonfunctioning organ that no longer enhances fitness. Studies of gene activation responsible for glomerulotubular disconnection in the sculpin may reveal similar gene regulatory networks leading to proximal tubular cell death and formation of atubular glomeruli in CKD (Table 6).

The pattern of short-term successful adaptation to renal injury but long-term maladaptation with progression to CKD shares many characteristics with those of chronic inflammatory systemic diseases, such as rheumatoid arthritis and diabetes.[97] The common evolutionary basis for these disorders resides in an adaptive commitment of energy (inflammatory response) to suppress infection or to repair acute injury, but which can only be sustained through the reproductive period of the life cycle, after which progression accelerates and fitness is reduced.[97] Derived from the ancestral innate immune response, the gene regulatory networks that are activated in the acute phase of chronic inflammatory systemic diseases were likely selected in response to prevalent infectious diseases.[97] Genome-wide association studies were used to test the hypothesis that selection simultaneously increased fitness and susceptibility to complex disease. Results showed a predominance of alleles increasing susceptibility to type 1 diabetes and rheumatoid arthritis, consistent with the hypothesis.[98]

Nephron Heterogeneity From Birth Through Senescence

There is marked internephron heterogeneity in the developing kidney, with over 50% of nephrons forming after ureteral epithelial branching has ceased.[99] Nephron heterogeneity contributes to a number of vital functions of the mature mammalian kidney, including the regulation of sodium, water, phosphate, and osmolar balance, and is linked to variations in vascular and neural connections as well as to variations in nephron size and length.[100,101] In mammals, long-loop thin descending limbs of nephrons are highly permeable to sodium, whereas short loops are highly permeable to urea,[102] thereby enhancing urine concentration.[101] The tradeoff: short-loop nephrons are more susceptible to hypoxia and ischemia than long-loop nephrons because the latter have a more robust vascular supply (Table 3).[101] There is a 50% reduction in nephron number in cadaveric renal transplant donors older than 55 years compared to those younger than 40 years (Figure 4b),[103] and this is correlated with a marked increase in the fraction of sclerotic glomeruli in the normal population beyond reproductive age (Figure 4c).[104] In healthy kidney transplant donors, hyperfiltration and mild albuminuria are associated with hypertrophied nephrons, whereas hypertension and older age are associated with glomerulosclerosis (Figure 6).[105] Nephron loss with aging appears to result from atrophy and reabsorption of globally sclerotic glomeruli and hypertrophy of remaining nephrons.[106] Nephron hypertrophy may result from either lower congenital nephron endowment or from metabolic risk factors later in life, highlighting the importance of both developmental plasticity and lifestyle environmental factors superimposed on senescence (Table 3) (Figure 6).[105] Of note, albuminuria is associated with increasing parenchymal volume in apparently healthy adults, suggesting hypertrophy in hyperfiltering nephrons.[107]

Table 6. Future research guided by evolutionary nephrology

1	By combining physiologic and genomic techniques across large sample sizes of many species' life histories, application of systems biology could provide new evolutionary insight into maladaptation in CKD
2	The study in defined human populations from early nephrogenesis through senescence of variation in genotype and phenotype, coupled with its interaction with environmental factors, is likely to reveal age-specific mechanisms of renal injury and repair
3	The search for factors responsible for selection (survival or death) of individual cells or nephrons in the microenvironment of the injured kidney may lead to new biomarkers or therapies for progressive CKD
4	Studies of gene activation responsible for glomerulotubular disconnection in the sculpin (a marine fish) may reveal similar gene regulatory networks leading to proximal tubular cell death and formation of atubular glomeruli in CKD
5	Because additional nephrons are generated in fetal mammals subjected to renal ablation, experimental manipulation of the critical period of late nephrogenesis may lead to new approaches to increase nephron number in the developing kidney

CKD, chronic kidney disease.

AKI and CKD as Accelerated Senescence: Nephron Selection

These considerations provide strong support for better understanding the biology of senescence[108,109]: a high concordance between the human urinary proteome for the normal aging population and patients with CKD suggests common mechanisms.[110] Aging as a risk factor for disease reflects evolutionarily conserved pathways selected for early in life, but decreasing selection pressure later in life (Figure 3b).[111] Following AKI, injured proximal tubular cells can either undergo proliferation or G2/M cell cycle arrest—a fate that can lead to senescence in the case of multiple episodes of AKI progressing to CKD.[112] This raises a key unanswered question: what are the factors determining the survival or death of individual nephrons (the fate depicted in Figure 1)? Similar to animal or human populations, the population of nephrons in the patient

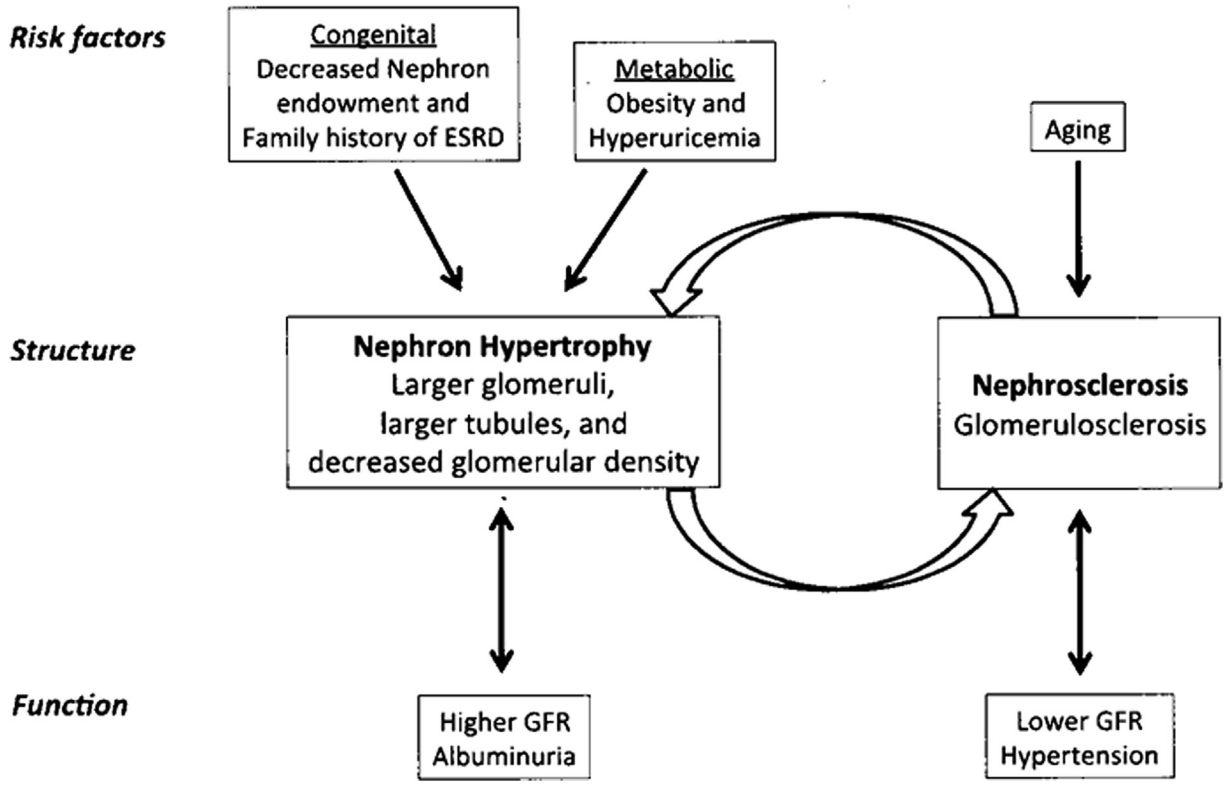

Figure 6. The aging kidney: 2 interrelated pathways in early chronic kidney disease (CKD): relationship of risk factors and kidney function to nephron hypertrophy and glomerulosclerosis among 1395 healthy living kidney donors. Nephron hypertrophy and lower nonsclerotic glomerular density were correlated with aging, male sex, family history of end-stage renal disease (ESRD), obesity, hyperuricemia, hyperfiltration, and albuminuria. Glomerulosclerosis was associated with aging, lower glomerular filtration rate, and hypertension. Adaptive hypertrophy of functional nephrons with aging may create a positive feedback loop with glomerulosclerosis, a process that is accelerated in CKD. GFR, glomerular filtration rate. Reproduced with permission from the American Society of Nephrology from Elsherbiny HE, Alexander MP, Kremers WK, et al. Nephron hypertrophy and glomerulosclerosis and their association with kidney function and risk factors among living kidney donors. *Clin J Am Soc Nephrol.* 2014;9:1892–1902.[105] Copyright © American Society of Nephrology.

with CKD may behave as an ecosystem within an environmental landscape contained in the renal capsule. The selection process (for survival or death of nephrons) then becomes a function of the microenvironment and epigenetic variation among nephrons (Table 3). Of particular relevance to the role of microenvironment in CKD, tumor necrosis factor–related weak inducer of apoptosis (TWEAK, a cytokine) induces tubular cell proliferation following unilateral nephrectomy (a noninflammatory microenvironment), but stimulates apoptosis in folic acid–induced AKI (an inflammatory microenvironment).[113] With this paradigm in mind, the search for factors responsible for selection of individual nephrons for survival or death may lead to new biomarkers of progressive CKD.

Nephron or Cellular Selection?

In describing an organism's response to threat or injury, Walter Cannon coined the phrase "fight or flight" that could result either in restoration of homeostasis, or in a deleterious response.[114] Michael Goligorsky has extended this formulation to the cellular level, demonstrating how fight reactions are directed to attenuate the stressor (e.g., production of antioxidant enzymes), or flight reactions using cell motility or exfoliation: the switch between responses is dictated by the intensity of the insult and the threshold for response by the cell.[115] Stressors leading to DNA damage activate 1 of the following programs: DNA repair, cell cycle arrest, or programmed cell death. A key question is the nature of the metabolic checkpoint that tilts the balance between cell death and survival.[116] Death and survival use the same mechanisms conserved by evolution: as is the case for development and differentiation, death mechanisms are robust to avoid being hijacked by opportunistic parasitic organisms.[117]

John Torday has developed a novel concept of the process of evolution based on cell–cell communication directed by gene regulatory networks.[118] Citing Cannon's original use of the term "homeostasis," Torday proposes a central role for homeostasis in driving "internal" selection, or adaptation due to modification of visceral organs.[118] Rather than focusing

on the level of the nephron or tubule, attention is focused on individual cells, the behavior of which is dictated by homeostatic constraints within microenvironments. Close examination of proximal tubules in a rat model of AKI reveals injured individual cells adjacent to normal cells with normal basement membrane and interstitium.[119] It appears that even on a single-cell basis, selection shapes regulatory mechanisms according to the costs and benefits of responding versus not responding to ambiguous cues (Table 5). As noted above for variation and selection at the nephron level, investigation of factors determining the selection of individual cells in the microenvironment of the injured kidney may lead to new insights into the progression of CKD (Table 6).

Evolutionary Nephrology: A Complementary Paradigm for Future Research

Through the circuitous evolutionary process that brought our ancestors from marine and freshwater environments to homeothermic life on land, mammals inherited energetically expensive nephrons that are susceptible to ischemic and hypoxic injury. Physiologic maladaptation may be explained by underlying evolutionary adaptation: the concepts of life history, mismatch, and tradeoffs provide insight into the expanding epidemic of CKD that should lead to the identification of new risk factors.[120] The recent combination of the retrospective view provided by evo-devo and the prospective power of population genetics reveals rapid change in allele frequencies in cancer.[28] Techniques used in the investigation of "tissue ecosystems" in these studies can be applied to the kidney in models of AKI and CKD. Current models of acute severe injury in rodents, such as temporary complete renal ischemia (a model of AKI) or ureteral ligation (a model of CKD) should be complemented by animal models with divergent life histories to seek evolutionary explanations for physiologic maladaptation.[121] Vampire bats are azotemic secondary to high dietary protein intake, but do not develop hyperfiltration or CKD; the hibernating bear can reuse urea nitrogen for protein synthesis.[122] Comparison of metabolic responses and gene activation in models of kidney injury across species may yield new insights through the evo-devo paradigm. Not only mammals but yeast, flies, and fish should be included,[123–127] and studied in the context of evolved differences between species, not just their genetic homologies.[128]

Because additional nephrons are generated in fetal mammals subjected to renal ablation,[79,80] the critical period of late nephrogenesis may provide an optimal opportunity to manipulate the fate of progenitor cells and to enhance nephron number.[99] Refined magnetic resonance imaging techniques permit accurate measurement of glomerular number and volume in intact rodent and human kidneys, potentially valuable biomarkers of progression.[129,130] Renal metabolism provides the key to understanding the link between AKI and CKD[5]: novel targets in epithelial cells include mitochondrial biogenesis and function, cellular senescence/cell cycle, and microRNAs.[121,131] Consideration of the evolutionary context may be of particular relevance in developing novel renal regenerative therapies, with the identification of progenitor cell microenvironments, and signaling pathways to enhance plasticity.[78] Rapid advances in molecular genetics have revealed that mutations are not the sole drivers of evolution: heritable variation can be generated by proteins (prions or chaperones) or by errors in mRNA synthesis.[132] By combining physiologic and genomic techniques across large sample sizes of many species' life histories, the application of systems biology could provide new evolutionary insights into maladaptation in CKD.[19] New therapies could be developed to target the processes that drive selection of the population of cells in diseased or injured tissue. By framing kidney research in the context of life history theory, the clues to renal senescence may be found in the epigenetic mechanisms of fetal programming, accounting for the transition from pediatric to adult CKD.

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