Novel treatment strategies for chronic kidney disease: insights from the animal kingdom

Peter Stenvinkel[1], Johanna Painer[2], Makoto Kuro-o[3], Miguel Lanaspa[4], Walter Arnold[2], Thomas Ruf[2], Paul G. Shiels[5] and Richard J. Johnson[4]

Abstract | Many of the >2 million animal species that inhabit Earth have developed survival mechanisms that aid in the prevention of obesity, kidney disease, starvation, dehydration and vascular ageing; however, some animals remain susceptible to these complications. Domestic and captive wild felids, for example, show susceptibility to chronic kidney disease (CKD), potentially linked to the high protein intake of these animals. By contrast, naked mole rats are a model of longevity and are protected from extreme environmental conditions through mechanisms that provide resistance to oxidative stress. Biomimetic studies suggest that the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) offers protection in extreme environmental conditions and promotes longevity in the animal kingdom. Similarly, during months of fasting, immobilization and anuria, hibernating bears are protected from muscle wasting, azotaemia, thrombotic complications, organ damage and osteoporosis — features that are often associated with CKD. Improved understanding of the susceptibility and protective mechanisms of these animals and others could provide insights into novel strategies to prevent and treat several human diseases, such as CKD and ageing-associated complications. An integrated collaboration between nephrologists and experts from other fields, such as veterinarians, zoologists, biologists, anthropologists and ecologists, could introduce a novel approach for improving human health and help nephrologists to find novel treatment strategies for CKD.

The evolution of species — mediated by genetic and epigenetic modifications over the past 3.8 billion years — has given rise to a wide variety of adaptations to different environments. This observation has led to the proposal that insights into adaptive mechanisms observed in nature could aid the development of therapeutic approaches for human disease[1]. Comparative physiology — a subdiscipline of physiology that is based on Krogh's principle, which states "for such a large number of problems there will be some animal of choice, or a few such animals, on which it can be conveniently studied" — involves the comparison of organ systems within different taxa[2]. Homer Smith's insightful work, for example, used a comparative physiology approach based on studies of fish and amphibians[3] to form the basis of many aspects of renal physiology. Similarly, Sperber[4] studied correlations between dietary habits, ecological distribution, urine-concentrating ability and kidney morphology in 1944. The emerging field of biomimetics explores adaptative mechanisms of a given species and imitates — or takes inspiration from — these mechanisms to solve human problems (TABLE 1; Supplementary information S1 (table)). Biomimetics is a particularly interdisciplinary field that can be used to identify new approaches to disease (FIG. 1), such as the underlying mechanisms of longevity in naked mole rats[5], resistance to long-term renal hypoxia in seals[6] and preserved renal function in hibernating bears[7,8]. However, it is important to emphasize that when interpreting data from biomimetic studies, one should consider the likelihood of comparative animal data offering meaningful solutions when extrapolated to human disease. The physiological mechanisms that have evolved to enable adaptation of healthy animals to extreme environments may not necessarily be the same mechanisms that should be harnessed to avoid disease in humans.

The prevalence of chronic kidney disease (CKD) is rising worldwide. Approximately 10–15% of the global population suffers from CKD and its associated complications[9], particularly cardiovascular disease, infectious complications, osteoporosis, muscle wasting, frailty and

Correspondence to P.S.
peter.stenvinkel@ki.se
Divison of Renal Medicine M99, Karolinska University Hospital, Karolinska Institutet, Hälsovägen 13, 14157 Stockholm, Sweden.

doi:10.1038/nrneph.2017.169
Published online 15 Jan 2018

Key points

- Biomimetic studies of non-laboratory wild animals are useful for identifying mechanisms that protect or increase susceptibility to disease
- Domestic and captive felids are vulnerable to chronic kidney disease (CKD), supporting the hypothesis that high protein intake — particularly from red meats and in combination with dehydration — is nephrotoxic
- Extreme models of ageing, such as Hutchinson–Gilford progeria syndrome and the naked mole rat, can be used to investigate the mechanisms of vascular progeric processes in CKD
- Current evidence suggests that elevated serum phosphate levels promote ageing and cellular senescence
- The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) may offer protection against diseases in extreme environmental conditions and may promote longevity in the animal kingdom; NRF2 agonists (such as resveratrol and sulforaphane) might improve the uraemic complications of CKD
- Lipid composition of membranes has a role in seasonal acclimatization of metabolic activities in the animal kingdom
- Hibernating wild bears with anuria are protected against many of the complications observed in humans with CKD, such as muscle wasting, osteoporosis and azotaemia; future studies should investigate the mechanisms behind these protective effects

premature ageing[10,11]. Nephrologists are faced with limited treatment options for patients with CKD, and advances in dialysis technology have not yet translated into markedly better outcomes[10]. As the majority of randomized controlled trials for CKD therapies have been negative[10], an urgent need exists to find novel treatment options for this patient group. Here, we discuss some examples of renal biomimetics and how studies of the mechanisms by which animals adapt to hypoxia, oxidative stress, food deprivation and, conversely, to high-protein or high-phosphate diets may result in a better understanding of the uraemic phenotype (FIG. 1). Although biomimetic studies usually focus on the adaptive mechanisms that protect species from disease, changing environments (such as global warming, water availability or salinity in the oceans) can also lead to adaptations that may not offer full protection from these changes but may still shed light on disease mechanisms. Examples include the study of mechanisms that lead to the extinction of a species and the inability of that species to adapt to a changing environment.

Uraemic phenotype
Phenotype that includes several physical characteristics, such as vascular stiffness, sarcopenia, frailty, osteoporosis and left ventricular hypertrophy.

Chronic tubulointerstitial fibrosis
Diseases that affect the physiology of non-glomerular structures (tubules and/or the interstitium) in the kidney.

High-protein diets and dehydration

High-protein diets that are rich in red meat accelerate the progression of both experimental and human CKD[12,13]. The link between a high-protein diet and CKD (FIG. 2) suggests that one can obtain mechanistic insights from studying mammals that live almost exclusively on a high-protein diet, such as the Felidae family (felids) and Desmodontinae (vampire bats). Interestingly, one group (felids) seems to be susceptible to CKD, while the other (vampire bats) seems to be protected.

CKD in felids

Felids consist of 37 species in the wild. Although they are considered among the world's most successful carnivore families, they are particularly susceptible to kidney diseases, including polycystic kidney disease[14], glomerulonephritis[15], acute pyelonephritis, hypertension-ssociated CKD[16] and nephrolithiasis[17]. The most common kidney pathology in domestic felids is chronic tubulointerstitial fibrosis, which is sometimes observed with glomerulosclerosis[14]. The prevalence of CKD in domestic cats has increased 75-fold (from 0.04% to 3%) during the past 4 decades, although this increase might be partially due to improved diagnostics[14,18,19] and to increased non-steroidal anti-inflammatory drug (NSAID) consumption in the past decade[20]. Even so, CKD is thought to affect 35–80% of geriatric domestic cats and is the most common cause of death in domestic cats >5 years of age[18]. Likewise, a necropsy study found renal lesions in 87% of large felids (mainly tigers, leopards and lions) held at zoos and safari parks in Germany[21]. In the wild, free-ranging felids experience a range of kidney diseases of differing origins, such as viral infections or amyloid deposition; however, free-ranging animals typically die from other causes before renal disease manifests or show only a mild form of disease[19]. Extrinsic environmental or dietary factors that might promote the development of kidney disease among felids in captivity seem to be absent among wild felids[19].

As mentioned above, the most common renal pathology among captive and domestic felids is chronic tubulointerstitial fibrosis, which is associated with minimal or mild proteinuria, normal blood pressure, hypokalaemia, hyponatraemia or hypernatraemia, polydipsia and polyuria[14,22] and an absence of diabetes mellitus[23]. Hypertension, if present, is usually thought to be secondary to renal disease[14]. Microvascular lesions observed in chronic hypertensive renal injury are absent or only minimally present[24]. The cause of this type of CKD remains unknown; however, it is unlikely that felids have evolved a selective susceptibility to CKD. Hence, one might hypothesize that the dramatic increase in felid CKD might reflect a new environmental exposure to which felids are particularly susceptible. Insights into the underlying mechanisms might be gained from comparisons with populations of humans and other animals that are either affected by or protected from renal disease, as discussed in further detail below. As CKD among felids has been best described in domestic cats and felids in wildlife parks, one possibility is that this disease might reflect the contamination of meat with a nephrotoxic substance. This scenario is similar to the epidemic of renal disease that occurred in vultures in India and Pakistan, which was ascribed to the practice of treating cattle with NSAIDs that contaminated the cattle meat[25].

Author addresses

[1]Divison of Renal Medicine M99, Karolinska University Hospital, Karolinska Institutet, Hälsovägen 13, 14157 Stockholm, Sweden.
[2]Konrad Lorenz Institute of Ethology and Research Institute of Wildlife Ecology, Department of Integrative Biology and Evolution at the University of Veterinary Medicine, Savoyenstreet 1, 1160 Vienna, Austria.
[3]Division of Anti-Aging Medicine, Center for Molecular Medicine, Jichi Medical University, 3311–1 Yakushiji, Shimotsuke, Tochigi 329–0498, Japan.
[4]Division of Renal Diseases and Hypertension, 12700 East 19th Avenue, Room 7015 Mail Stop C281, University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045, USA.
[5]Wolfson Wohl Translational Research Centre, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1QH, UK.

Table 1 | **Selected animal models that are useful for comparative physiology studies**

Species, family and/or order	Area	Mechanisms and possibilities
Naked mole rat (*Heterocephalus glaber*)	• Gerontology • Nephrology • Oncology • Cardiology	These animals have developed protective mechanisms against cancer, hypoxia, cardiovascular ageing and oxidative stress (high NRF2 expression levels).
Vampire bat (*Desmodus rotundus*)	Nephrology	Blood-ingesting bats have a very high intake of proteins, which causes azotaemia (high serum urea levels). Studies of vampire bats may help to better understand how kidneys can be protected against protein overload.
Ursidae family (bears)	• Nephrology • Endocrinology • Cardiology • Orthopaedics • Transplantology	Bears do not develop insulin resistance during summer despite a 25–50% accumulation in body weight (fat mass) from spring to autumn. Moreover, despite prolonged fasting, anuria and immobilization during hibernation, bears are protected from muscle wasting, pressure ulcers, thrombotic complications and osteoporosis. Studies of hibernating bears may help identify novel strategies to handle and prevent these complications as well as better ways of organ preservation.
Felidae family (cats)	Nephrology	Domestic and captive felids have a high incidence of chronic kidney disease. As members of this family are obligate carnivores, studies of felids may provide information on links between red meat consumption, gut microbiota and renal disease.
Phocidae family (seals)	Nephrology	Seals can survive prolonged asphyxia during underwater dives that last up to 120 min. Although their kidneys are subjected to prolonged vasoconstriction during diving, seals do not develop acute kidney injury.
Elephantidae family (elephants)	Oncology	The risk of elephants developing cancer is only 5% compared with 25% in humans, although they have 100 times as many cells. This protection may be due to the 20 copies of the tumour suppressor gene *TP53*, whereas humans have only one copy (two alleles).
Chimpanzee (*Pan troglodytes*)	Pharmacology	Chimpanzees have developed ways to protect themselves against pathogens by self-medicating with various plant leaves. Because one of these plants (thiarubine A) contains an antibiotic, systematic studies of these plants may help us find novel antibiotics.
Trochilidae family (hummingbirds)	Diabetology	Hummingbirds can switch their energy source from glucose to fructose, which maximizes fat storage and optimizes energy use to power their high-energy lifestyle (their heart rate can reach >1200 beats/min). Despite hyperglycaemia, they do not seem to develop diabetic complications.
Testudines order (turtles)	Neurology	Turtles have a high anoxic tolerance, and studies of these animals may help scientists to develop novel therapeutic strategies for cerebral ischaemia.
Wood frog (*Rana sylvatica*)	Physiology	Frozen wood frogs have 10–13-fold higher glucose concentrations in muscle and heart than other frog species that have been frozen in the laboratory. In addition, they have natural antifreeze glycolipids in muscle and internal organs to protect their cells. These mechanisms help them to survive over-wintering in average temperatures of −6.3 °C (minimum −18.1 °C) between October and May in the interior of Alaska. Studying wood frogs can help to understand limits to freezing tolerance.

The effect of red meat intake. Another potential mechanism underlying the high prevalence of CKD in felids might relate to their high intake of red meat (FIG. 2). To meet the high energy demands of their brain, which is relatively large in comparison with their body size[26], greater quantities of proteins are required, predominantly to generate glucose from amino acids through *de novo* gluconeogenesis. High-protein diets induce vasodilation of afferent renal arterioles, glomerular hypertension and hyperfiltration, which together accelerate the progression of pre-existing CKD in a variety of domestic and laboratory animals, including mice, rats and dogs[27]. A high consumption of salt and animal proteins has also been linked to progression of CKD in humans[12,28], with increasing evidence indicating a greater effect of red meat consumption compared with that of other animal and vegetable protein sources[12,13].

Whether high-protein diets can induce *de novo* renal disease is less certain. One study reported that a commercial diet low in potassium and high in meat (40% protein) and phosphoric acid led to the development of tubulointerstitial lesions in five of nine domestic cats[29]. In a human study, maintenance of a high-protein diet for 6 weeks increased estimated glomerular filtration rate (eGFR) by 4 ml/min/1.73 m^2 compared with a carbohydrate and unsaturated-fat diet in healthy individuals[30]; however, whether long-term consumption of a high-protein diet promotes CKD is unclear. Although felids are obligate carnivores, their dietary acquisition of protein in the wild is intermittent and separated by days of fasting[24]. By contrast, domestic cats and felids kept in zoos are often fed high-protein diets on a daily basis.

An examination of published data on 12 biochemical parameters of serum that can be used to evaluate renal

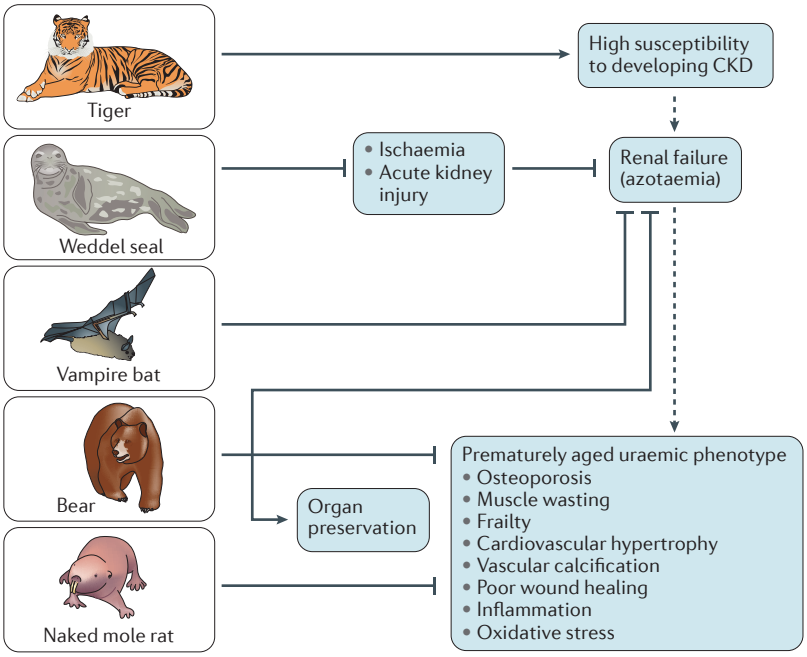


Figure 1 | **Novel insight into treatment strategies of CKD from studies of wild animals.** Several species in the animal kingdom have developed protective mechanisms against environmental stresses, and studying these mechanisms can provide insights into novel approaches to chronic kidney disease (CKD). For example, despite a long period of immobilization during hibernation, bears do not develop azotaemia, osteoporosis, inflammation, thrombosis, atherosclerosis and substantial muscle wasting, which could provide clues for better organ preservation. Naked mole rats (*Heterocephalus glaber*) are protected from oxidative stress, which could help to develop strategies to prevent or slow down premature ageing. As Weddell seals (*Leptonychotes weddellii*) are protected against prolonged episodes of kidney ischaemia during long periods of deep sea diving, they could provide insight to prevent acute kidney injury. Vampire bats (*Desmodus rotundus*) are protected against the consequences of high-protein intake, whereas felids (such as tigers) are particularly susceptible to CKD, most likely owing to their high intake of red meat.

functions in 97 mammalian species shows that differences in patterns of these parameters result in a clustering of species, separating carnivorous mammals from omnivorous or herbivorous mammals (Supplementary information S2 (figure)). This clustering is mainly due to higher levels of urea (+57%) and chloride (+13%), as well as reduced levels of alkaline phosphatase (−56%) among carnivores compared with mean values of the other species. This finding highlights the importance of diet, including protein source, on parameters of renal function and leads to the hypothesis that in humans, different types of diets (for example, vegetarian or highly carnivorous) might lead to similar differences in parameters of renal function.

Although the classical view is that renal injury induced by a high-protein diet is caused by changes in glomerular haemodynamics[31] (FIG. 2), increasing evidence suggests that CKD risk is associated with protein originating from red meat and not with protein from dairy or vegetable-based sources[32]. For example, epidemiological studies conducted in Singapore[12] and the USA[33,34] have shown that among different protein sources (including red meat, poultry, dairy products, fish, eggs and legumes), only red meat (beef, pork and lamb) and processed meat increased the risk of CKD. In one study, individuals in the highest quartile of dietary red meat intake had a 1.4-fold greater risk of end-stage renal disease than those in the lowest quartile of red meat intake[12]. Interestingly, diets rich in other protein sources, such as legumes and low-fat dairy products, were actually protective against CKD[33]. Red and processed meat therefore seem to have direct nephrotoxic effects that increase the risk of CKD. Indirect support for differences in plant and animal proteins comes from studies in vegetarians. A study conducted in Taiwan showed that eGFR did not differ among 102 vegetarian Buddhist nuns compared with an equal number of age-matched omnivorous females[35]. However, serum levels of sodium, glucose, urea and cholesterol, as well as blood pressure and urinary specific gravity, were lower among individuals in the vegetarian group[35]. As vegetable proteins have different renal effects (lower GFR and renal plasma flow) than meat proteins[36] and as plant-based diets might protect against the development of CKD[37] and its complications[38], patients with CKD should be encouraged to consider a vegetarian diet[39].

In addition to CKD, red and processed meat have been linked to an increased mortality[40] and risk of other chronic diseases, such as cancer[41], stroke[42], coronary heart disease[43] and type 2 diabetes mellitus (T2DM)[44]. Moreover, one study reported that the withdrawal of red meat from the diet of patients with T2DM reduced albuminuria and improved their serum fatty acid profile compared with their usual diet[45]. Another study in patients with T2DM showed that adherence to a chicken meat-based diet for 1 year reduced urinary albumin excretion to levels comparable to those achieved by treatment with an angiotensin-converting enzyme (ACE) inhibitor[46]. These findings imply that renal toxicity is generated by red meat per se and not total protein intake. Dietary management of CKD in domestic cats with a low-protein and low-phosphate (PO_4) diet was associated with increased survival compared with that of cats that did not undergo the dietary change[47]. Further investigation is required to elucidate the potential differential effects of processed red meat, game meat and white meat (that is, chicken or fish) on renal function in felids.

Mechanism of red meat-induced CKD. Several factors have been proposed to be implicated in the disease-promoting effects of red meat[48] (FIG. 2). These include an associated high intake of sodium chloride (which increases blood pressure and stimulates vasopressin production and release by increasing serum osmolality), saturated fats (which drive mitochondrial oxidative stress), increased net acid production (which causes metabolic acidosis and acidic urine), the pro-oxidative effects of haem iron (which promotes oxidative stress), DNA damage caused by *N*-nitroso compounds (which leads to purine degradation and uric acid formation), the incorporation of non-human sialic acid into tissue (which promotes interaction with inflammation-provoking antibodies) and changes in the composition and/or metabolism of gut microbiota. For example, trimethylamine-*N*-oxide (TMAO), which is produced from the metabolism of red meat, eggs and fish by gut microbiota, induces

Glomerular haemodynamics
The regulation of efferent and afferent glomerular arteriolar resistance required to maintain a stable glomerular filtration rate.

Urinary specific gravity
Test that compares the density of urine to that of water.

N-Nitroso compounds
Compounds found in processed meat that are formed endogenously from the intake of nitrite and nitrate.

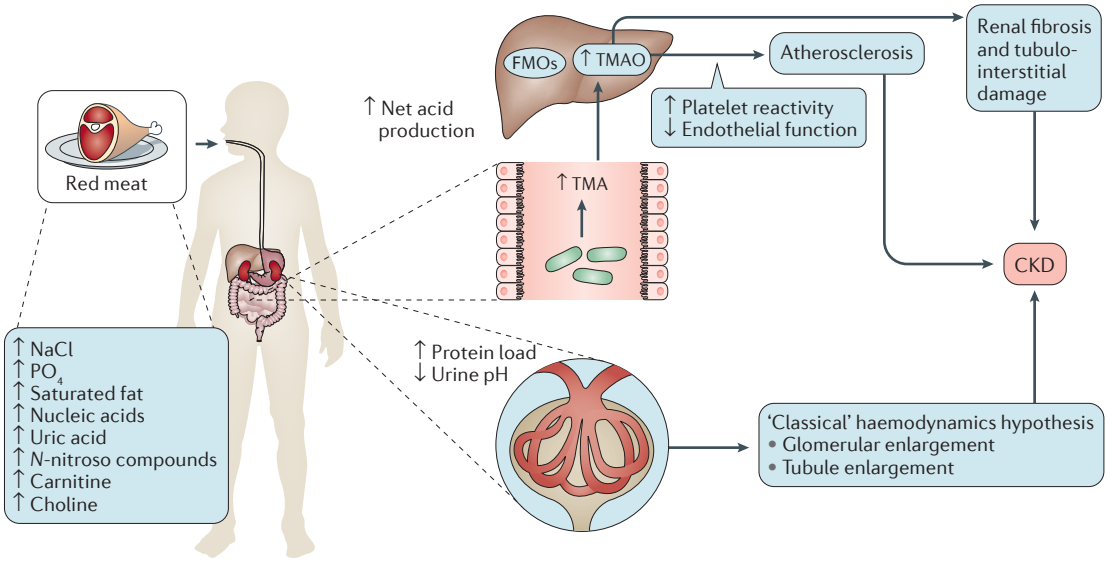


Figure 2 | **Effect of red meat intake on kidney functions.** Epidemiological studies suggest that red meat (but not other sources of protein) promotes chronic kidney disease (CKD). Several factors have been proposed to be implicated in the disease-promoting effects of a diet rich in red meat. In addition to hyperfiltration due to a high protein load (causing a haemodynamic insult), elevated levels of trimethylamine-*N*-oxide (TMAO) generated from gut microbiota and the metabolism of trimethylamine (TMA) in the liver via flavin-containing monooxygenases (FMOs) could contribute to CKD directly via renal fibrosis and indirectly via atherosclerosis. Additional pathophysiological mechanisms linking a high intake of red meat to cardiovascular disease, cancer and CKD have been reported. Increased intake of salt (NaCl), phosphate (PO_4), saturated fats, nucleic acids, uric acid, *N*-nitroso compounds, haeme iron, carnitine, choline and acid production with a high consumption of red meat may also contribute to the observed associations between increased red meat consumption and CKD. The intestinal microbiome represents a new potential therapeutic target for the prevention of CKD and for treatment of cardio-metabolic complications in CKD.

renal fibrosis in animal models[49] and inflammation in endothelial cells[50]. Although diminished renal function impairs the ability to eliminate TMAO, it predicts outcomes in patients with CKD even after adjustment for other risk factors[51]. Inhibition of gut microbial trimethylamine (TMA) production prevented the development of atherosclerotic lesions in *Apoe*$^{-/-}$ mice[52]. Moreover, exposure to carnitine (a major nutrient in red meat) in mice affects the composition of gut microbiota via the proatherogenic intermediate γ-butyrobetaine, which is converted into TMA and TMAO[53]. Alterations in gut microbiota might also affect processes, such as haem-induced lipoperoxidation[54]. Red meat consumption is also associated with increased intake of phosphate, which is associated with decreased renal function, inflammation and premature ageing[55]. Moreover, phosphate activates nuclear factor-κB (NF-κB) signalling and promotes the generation of reactive oxygen species (ROS) in vascular smooth muscle cells (VSMCs)[56]. This observation implies that the putative protective effects of antioxidative factors, such as nuclear factor erythroid 2-related factor 2 (NRF2) (BOX 1), on renal function should be investigated in the context of a diet rich in red meat.

The high content of nucleic acids in animal proteins probably also contributes to the nephrotoxic effects of red meat diets in humans and felids. Animal proteins are much more likely to raise serum uric acid levels than are proteins from vegetable and dairy sources[57]. In domestic cats, a transient (up to 50-fold) increase in urine uric acid occurs following the ingestion of purine-rich animal proteins compared with a purine-free diet, despite the presence of a uric acid-degrading enzyme (uricase)[58]. In humans, consumption of animal proteins and/or purines also results in an acute rise in serum and urine uric acid levels[59,60], which is accompanied by a substantial acid load in urine that leads to a decrease in urine pH[13]. A urine pH of <5 is extremely common in cats with uraemic manifestations[22], and a low urine pH (5.0–5.5) predicts stage 3 CKD in humans[61]. Although urate stones are relatively rare in cats[62], urate crystalluria is a common problem in felids[63]. Coupled with dehydration and heat exposure, we propose that urate crystalluria and/or uricosuria resulting from high protein intake could facilitate tubulointerstitial injury. Both soluble and crystalline forms of urate have been shown to induce inflammation in rat tubular cells *in vitro*[64]. Indeed, signs of dehydration in felids with CKD are common[22] and predictive for the development of CKD in domestic cats[65]. In humans, although the aetiology of CKD in populations from Central America and Sri Lanka remains a subject of debate[66], we propose a role for heat stress and recurrent dehydration in the presence of high uric acid levels in disease pathophysiology[67].

Protein metabolism in vampire bats

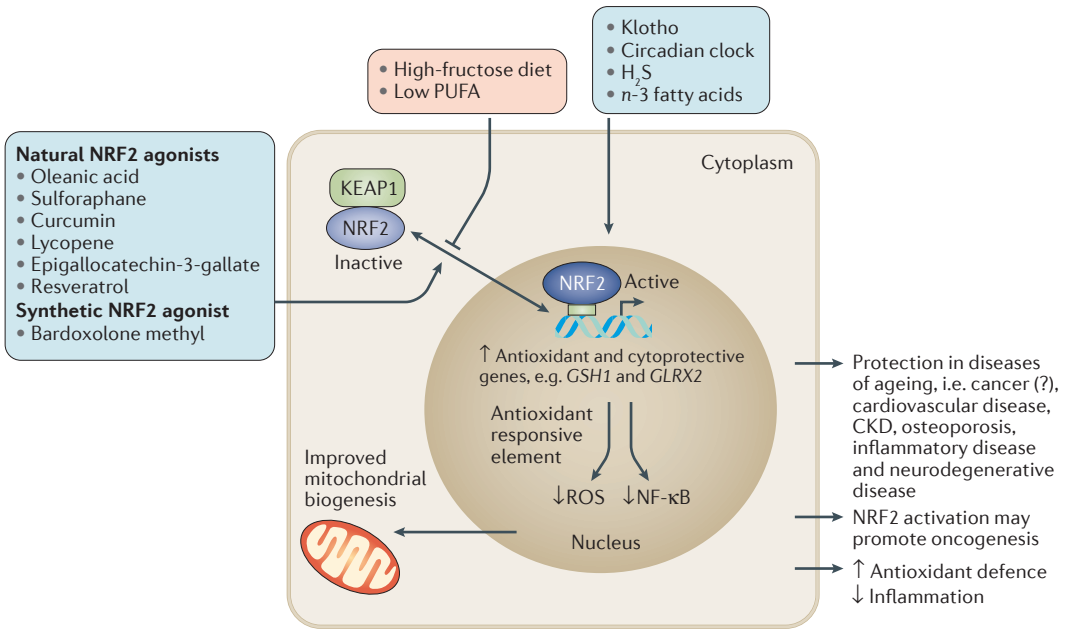
Vampire bats (*Desmodus rotundus*) feed mostly on the blood of warm-blooded mammals. However, in contrast to humans and felids, they seem to be resistant to the detrimental metabolic effects of a high-protein intake. Their protein intake would be comparable to

a daily intake of approximately 6 kg protein in a 70 kg man (as compared to a normal daily intake of 50–120 g in humans). As the consumption of >20 g of blood in a 20 min feed increases the body weight of vampire bats by 20–30%, they rapidly absorb the blood plasma and start urine production within 2 min of feeding[68]. The blood urea concentration of vampire bats is 27–57 mmol/l (compared with 3–8 mmol/l in healthy humans), depending on the time point after feeding[69]. Despite this high protein intake, the vampire bat does not have larger kidneys than mammals of similar size[70], which suggests no difference in glomerular number and glomerular capillary surface area. Indeed, indirect allometric calculations indicate that the vampire bat's GFR is not greater than that of similarly sized mammals[69]; however, to our knowledge, GFR measurements have not been performed. Of interest, mammalian blood has a lower relative purine content than does red meat[71]. Whether this difference accounts for the differential risk of CKD between felids and vampire bats is speculative.

Box 1 | **The cytoprotective effects of the transcription factor NRF2**

The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) upregulates the expression of cell-detoxifying enzymes in response to oxidative stress. Activators of NRF2 induce structural changes in Kelch-like ECH-associated protein 1 (KEAP1), which allows nuclear translocation of NRF2. In the nucleus, NRF2 initiates the transcription of >250 target genes, such as haemoxygenase, catalase and glucose-6-phosphate 1-dehydrogenase, which are important for antioxidant defences, through binding to antioxidant response elements (see the figure).

Nrf2-knockout mice have increased susceptibility to kidney damage. As impaired NRF2 activation is observed in renal fibrosis, focal segmental glomerulosclerosis and hypertensive kidney disease, NRF2-targeting therapies should be of interest for the study of chronic kidney disease (CKD) progression. Patients on haemodialysis have downregulated levels of NRF2 coupled with an upregulation of nuclear factor-κB (NF-κB)[276] and display a phenotype characterized by persistent systemic inflammation[79] and increased oxidative stress[277]. Given the potential contribution of a repressed NRF2 system in premature ageing, both synthetic compounds, such as the potent NRF2 agonist bardoxolone methyl[278], and natural nutrigenomic compounds, such as sulforaphane[279], pomegranate polyphenols[280], curcumin[281], ethanol extract of *Alisma orientale* tubers[282] and cinnamon polyphenols[283], that restore NRF2 expression could slow progression and ageing-related CKD[284]. Indeed, as sulforaphane (found in broccoli) inhibits restenosis by suppressing inflammation and proliferation of vascular smooth muscle cells (VSMCs) in a carotid injury model[285], it has been suggested that dietary activators of NRF2 inhibit atherogenesis[286]. Moreover, sulforaphane suppresses NRF2-mediated hepatic glucose production and attenuates exaggerated glucose intolerance by an order of magnitude similar to that of metformin in patients with type 2 diabetes mellitus (T2DM)[279]. However, forced overexpression of NRF2 might not always be enough to restore adaptive responses[287]. For example, bardoxolone methyl increased the risk of heart failure compared with placebo in a clinical trial with patients with T2DM and stage 4 CKD[288], which highlights potential limitations of manipulating transcription factors. Although activation of NRF2 leads to improved antioxidant defences, whether this effect is independent of any influence on mitochondrial dynamics remains to be determined. Sulforaphane, for example, modulates the KEAP1–NRF2 antioxidant element response signalling pathway yet is a NRF2-independent inhibitor of mitochondrial fission[289]. Whether such an effect for bardoxolone methyl contributed to its failure owing to excess mortality[288] remains to be proven. In future clinical trials of this compound, attention should be given to the dose-dependent effects on CKD progression[290]. Whereas too little NRF2 activity can result in loss of cytoprotection, diminished β-oxidation of fatty acids and lower antioxidant capacity, too much NRF2 activity may perturb the homeostatic balance and promote overproduction of reduced glutathione and NADPH[291]. H_2S, hydrogen sulfide; PUFA; polyunsaturated fatty acids; ROS, reactive oxygen species.



Nutrigenomic compounds
Bioactive nutrients that have an effect on or interact with the genome. Nutrigenomics also encompasses the effect of genetic variations on the absorption, metabolism, elimination or biological effects of various nutrients.

Ageing and longevity

Ageing has been defined as an accumulation of deficits occurring in different individuals in different ways and with varied rates in different organs[72]. Ageing is an actively regulated process influenced by genetics, epigenetics, lifestyle, nutrition and psychosocial factors[73], which may act synergistically, independently or cumulatively. The ageing process is characterized by a series of hallmarks, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, stem cell exhaustion, mitochondrial dysfunction, altered intercellular communication and cellular senescence[74], which are common across different taxa and affected by the uraemic milieu[73,75,76].

Ageing and kidney disease

In addition to the progressive loss of renal function, ageing in humans, rats and many other mammals is associated with the development of glomerulosclerosis and interstitial fibrosis[77,78], which are linked to impaired autoregulation of renal blood flow and impaired angiogenesis, epigenetic modifications, endothelial dysfunction, oxidative stress and inflammation[73]. Chronic inflammation (also known as inflammageing) is an important driver of premature uraemic ageing[79] and manifests with an increased frequency of age-related complications, such as vascular stiffening, osteoporosis, muscle wasting, depression, cognitive dysfunction and frailty[79]. In addition, persistent mitochondrial dysfunction with increased generation of ROS features in both normative ageing[80] and progressive CKD[81].

Whether ageing-associated renal disease is inevitable[82] or modifiable[83] remains controversial. The use of senolytic agents, which selectively remove senescent cells, in preclinical models suggests that ageing-associated renal disease is modifiable[75], and direct improvement of physiological function following removal of these cells indicates causality. These cells are non-proliferative, are resistant to apoptosis and are generated in response to genotoxic stress and resulting DNA damage as part of normative ageing. Loss of age-related regenerative capacity in tissues and organs occurs as a direct consequence, and a senescence-associated pro-inflammatory milieu subsequently develops. The selective removal of senescent cells from tissues and organs via immune-mediated clearance is dysregulated during normative ageing and contributes to inflammageing[84]. The accumulation of these cells has been observed across a broad spectrum of non-communicable diseases.

Ageing in the animal kingdom

One way to improve our understanding of ageing processes and senescence is to study animals with unusual longevity. Long-lived animals are found across the taxonomic spectrum, such as in certain mammals, birds, sea turtles and fish. For example, extreme longevity is observed in the ocean quahog (*Arctica islandica*; >500 years)[85] and the Greenland shark (*Somniosus microcephalus*; ~400 years)[86]. The study on the ocean quahog supports the notion that chronic low-grade inflammation in the cardiovascular system is a ubiquitous feature of ageing[85]. Other interesting candidates for studies of reduced senescence include the rougheye rockfish (*Sebastes aleutianus*) and the bowhead whale (*Balaena mysticetus*), both with documented lifespans of >200 years. Interestingly, ageing rockfish do not show signs of organ degeneration or a decline in liver lysosomal function[87], which are typically observed in normative ageing. By contrast, examples of exceptionally short-lived species that exhibit an accelerated expression of ageing biomarkers are found in the family of Cyprinodontidae (killifish), which have a maximal lifespan of only 13 weeks[88]. Thus, a better understanding of the mechanisms by which some animals have delayed or accelerated ageing processes[87,89] may provide insights into not only the process of ageing in humans but also ageing-related kidney disease.

Insights from the naked mole rat. Naked mole rats (*Heterocephalus glaber*) have emerged as a good model organism to study ageing and ageing-related diseases. These subterranean rodents are rarely exposed to sunlight and have no obvious dietary source of vitamin D[90]. However, despite having undetectable calcifediol (25(OH)D) levels (the precursor of vitamin D), their calcium phosphate homeostasis is adequately maintained[91]. Although they have a small body size and are constantly exposed to hypoxia, oxidative stress and hypercapnia, they can live >30 years and maintain a healthy cardiovascular and reproductive status as well as body composition throughout their life[5]. Interestingly, the structure and function of their proteins are not affected by their substantial exposure to oxidative stress[92], and they display high levels of autophagy and efficient removal of stress-damaged proteins throughout life[93]. In contrast to humans and other rodents,[94] these animals preserve normal vascular and cardiac function with ageing[95,96] and are resistant to the development of cancer[97]. Moreover, their bone mineral density, articular cartilage and nitric oxide sensitivity of VSMCs are not affected by ageing[98]. Whereas most nephropathologies seem to be absent in naked mole rats, cases of nephrocalcinosis have been reported[99].

NRF2-mediated antioxidant activity. Some of the molecular pathways that protect these animals from cancer have been elucidated. For example, one study reported that the fivefold higher production of high-molecular-weight hyaluronan in fibroblasts protects naked mole rats from cancer[100]. High expression levels of the transcription factor NRF2, which stimulates intracellular antioxidant activity by regulating the expression of many target genes involved in the antioxidant response (BOX 1), may also protect the naked mole rat from cellular damage. In addition to antioxidative activities, NRF2 has other important functions, such as regulating NF-κB activity, which may play a part in mitochondrial homeostasis[101] and may decelerate the ageing process[102]. As NRF2 expression correlates positively with maximum lifespan in long-lived rodents[103], diminished NRF2 activity may be important for the ageing phenotype of organisms as diverse as worms, flies and mammals[104].

Telomere attrition
Telomeres are the protective endcaps of chromosomes. Attrition, or shortening, of telomeres is a form of tumour suppression and may be due to inflammation and oxidative stress as well as exposure to infectious agents, resulting in limited stem cell function, regeneration and organ maintenance during ageing.

Uraemic milieu
Toxic internal milieu in patients with uraemia that is characterized by accumulation of uraemic toxins and waste products that promote inflammation, oxidative stress, carbonylation, calcification and endothelial dysfunction.

Senescent cells
Cellular senescence is an irreversible cell cycle arrest mechanism that acts to protect against cancer. Senescent cells also have a role in complex biological processes, such as development, tissue repair and age-related disorders.

Hypercapnia
Abnormally elevated carbon dioxide (CO_2) levels in the blood.

High-molecular-weight hyaluronan
A high-molecular-weight polysaccharide found in the extracellular matrix, especially in soft connective tissues.

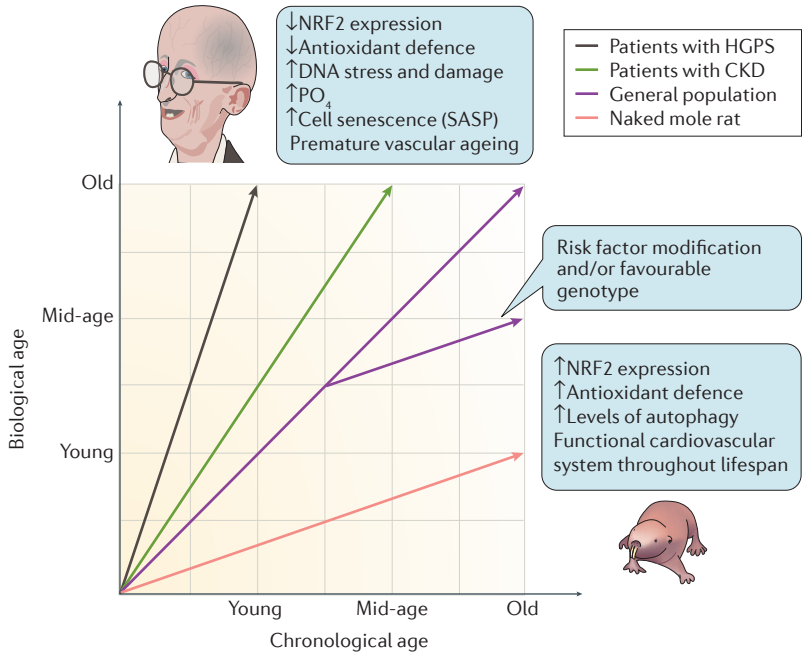


Figure 3 | **Extreme models of ageing with a marked discrepancy between chronological and biological age can be used to learn more about progeric processes in CKD.** Children with the rare Hutchinson–Gilford progeria syndrome (HGPS) express truncated lamin (progerin) that mediates premature ageing, especially in the cardiovascular system, resulting in premature death from stroke or myocardial infarction. On the other hand, naked mole rats undergo negligible senescence and can live for >30 years without signs of cardiovascular ageing. Integration of data from these two models of ageing can reveal detailed mechanisms of the progeric phenotype. A high biological age in chronic kidney disease (CKD) is characterized by a premature ageing phenotype, which includes vascular stiffness, frailty, osteoporosis and sarcopenia, as well as high levels of inflammation, carbonylation and oxidative stress. NRF2, nuclear factor erythroid 2-related factor 2; SASP, senescence-associated secretory phenotype.

Evidence for a role of NRF2 in ageing has also been reported in humans. For example, children with the rare Hutchinson–Gilford progeria Syndrome (HGPS), which is caused by a mutation in prelamin A/C, age extremely prematurely, are subject to increased oxidative stress and have a repressed NRF2 pathway[105]. As reactivation of NRF2 reversed the cellular ageing defects in cells from patients with HGPS and in an animal model of HGPS repression, NRF2-mediated transcription seems to have a pathogenic role in the progeric phenotype[105]. As HGPS shares many features common to age-associated diseases, it has been regarded as a model system to better understand ageing processes in chronic diseases[106]. For unknown reasons at present, children with HGPS do not seem to have an increased risk of CKD despite a prematurely aged phenotype, which may reflect a feature of antagonistic pleiotropy[106]. Despite apparent differences in the pathways underlying HGPS and CKD, we suggest that models of ageing and longevity, such as HGPS and the naked mole rat, can be used to study factors that underlie progeric processes in CKD (FIG. 3).

Vascular calcification and phosphate

Phosphate and calcification in vertebrates. The composition of sea water is similar to that of the human body in regard to the abundance of elements[107] (Supplementary information S3 (table)), consistent with the view that life originated from the sea[108]. Of the ten most abundant elements in the human body, only phosphorous is not among the ten most abundant elements present in sea water[109], indicating that organisms selectively accumulated phosphorus (in form of phosphate within cells) at some point in time during evolution (Supplementary information S4 (figure)). Phosphate is a major component of nucleic acids and membrane phospholipids and has a key role in numerous intracellular functions, including ATP synthesis and function and kinase-mediated signal transduction[110]. Phosphate is so fundamental to life that its deficiency can be fatal, which may be a reason for the evolution of phosphate appetite[111].

Although intracellular phosphate is essential to all forms of life, accumulation of extracellular phosphate first emerged in bony fish during the evolution of skeletons[112]. Unlike invertebrates, which have a calcium carbonate ($CaCO_3$)-based exoskeleton, most skeletons of vertebrates consist of calcium and phosphate, especially in the form of calcium hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$)[113]. This acquisition was likely required for terrestrial vertebrates to support their body weight on land. The extracellular fluid of vertebrates consists of a highly saturated solution of calcium and phosphate[114], which enables bone formation simply by controlling where to provide a cue for nucleation of calcium phosphate, such as production and secretion of bone matrix proteins by osteoblast lineage cells. Undesired nucleation within the extraosseous tissues is achieved by maintaining an extracellular phosphate concentration within a narrow range, in a process that is partially controlled by fibroblast growth factor 23 (FGF23) and its obligate co-receptor Klotho (encoded by *Kl*)[112]. Interestingly, *Kl*-knockout mice have a 12-fold reduction in lifespan and a 2-fold increase in extracellular phosphate concentration compared with wild-type mice[115]. Secreted Klotho also exerts multiple functions independently of FGF23, such as inhibition of insulin-like growth factor 1 activity and upregulation of antioxidant enzyme expression levels. These additional functions may contribute to the anti-ageing properties of Klotho[116]. Furthermore, Klotho induces NRF2 expression and subsequent antioxidant defence mechanisms[117], which links altered NRF2 expression to bone mineral metabolism and phosphate homeostasis[118].

Phosphate in ageing and calcification. Vascular calcification is a common feature of the progeric uraemic phenotype[119] and is linked to senescence[120]. High extracellular phosphate levels, which often occur in combination with elevated calcium levels, increase the risk of calcium phosphate deposition in the vasculature and vascular calcification[119]. Cell culture studies have shown that a high phosphate concentration induces cellular senescence[121] and leads to the conversion of VSMC to osteoblastic cells[122,123], a process that can be prevented by inhibiting calcium phosphate precipitation using pyrophosphate, phosphonoformic acid[124,125] and phosphate binders[126]. Consistent with the observation that a high phosphate concentration induces cellular senescence and that accumulation of senescent

Antagonistic pleiotropy
Scenarios in which one gene contributes to multiple traits, whereby at least one of these traits is beneficial and at least one is detrimental to the organism's health.

Phosphate appetite
A well-documented behaviour in animals that is induced by phosphate deficiency, which is especially common among herbivores.

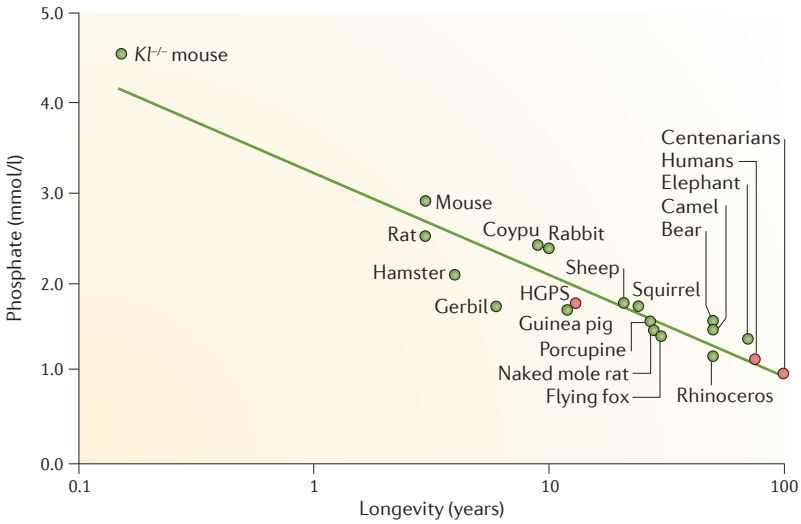


Figure 4 | **The role of phosphate in ageing.** Extracellular serum phosphate levels and maximum lifespan in different mammals, including humans (general population, centenarians and children with Hutchinson–Gilford progeria syndrome (HGPS); red circles), are inversely correlated. This inverse correlation indirectly suggests that high phosphate levels promote progeria and cellular senescence. α-Klotho-deficient (*Kl*$^{-/-}$) mice have high phosphate levels and a shortened lifespan compared to that of wild-type mice. In addition, dietary phosphate shortens the lifespan of *Kl*$^{-/-}$ mice further, which is likely mediated by the AKT–mTORC1 pathway (RAC-α serine/threonine-protein kinase–mechanistic target of rapamycin complex 1) [140]. Mouse (*Mus musculus*), rat (*Rattus*), hamster (Cricetinae), coypu (or nutria) (Myocastoridae), rabbit (Leporidae), gerbil (Rodentia), guinea pig (*Cavia porcellus*), sheep (*Ovis aries*), squirrel (Sciuridae), porcupine (Hystricidae and Erethizontidae), naked mole rat (*Heterocephalus glaber*), flying fox (*Pteropus*), bear (Ursidae), camel (*Camelus*), rhinoceros (Rhinocerotidae), elephant (Elephantidae), human (*Homo sapiens*). Adapted with permission from REF. 128, Elsevier.

cells accelerates ageing of the organism[127], a negative correlation exists between extracellular phosphate levels and longevity across mammalian species[128] (FIG. 4). For example, children with HGPS have elevated phosphate levels, develop rapid vascular calcification and typically die of stroke or myocardial infarction as teenagers[129]. Furthermore, expression of progerin (the mutated form of prelamin A associated with HGPS) in VSMCs leads to a decrease in extracellular pyrophosphate[130]. As pyrophosphate protects VSMCs from calcification, high serum phosphate and low extracellular pyrophosphate may contribute to accelerated vascular calcification in HGPS. In the general population, high phosphate levels are associated with premature vascular ageing[131], shortened telomere length, reduced DNA methylation content and elevated IL-6 (REF. 55), which are all biological markers of ageing.

Studies from the past few years have provided insights into the mechanisms by which high extracellular phosphate levels lead to vascular calcification. Under conditions of inflammation, oxidative stress and high extracellular phosphate levels, nanoparticle calcium phosphate precipitates can develop in the vasculature, despite the presence of multiple endogenous inhibitors of calcium phosphate deposition[132,133] and can grow to form calciprotein particles (CPPs). CPPs are aggregates of α2-HS-glycoprotein (AHSG) loaded with calcium phosphate precipitates and dispersed as colloids in the blood. These CPPs may play a part in CKD progression, as recent clinical studies showed that serum CPP levels correlated with vascular calcification and/or stiffness[132,134] and predicted mortality in patients on dialysis[135]. Of interest, tigers have particularly high levels of phosphate (1.7 ± 0.3 mmol/l) and serum creatinine (265 ± 62 μmol/l), suggesting it would be of interest to determine levels of serum CPP and FGF23 in these animals[136].

Therapeutic strategies to prevent vascular calcification in CKD. The best current approach to prevent vascular calcification in CKD is dietary phosphate restriction or chelation through the use of phosphate binders[137]. However, a consequence of dietary phosphate restriction is reduced protein intake, which can lead to protein–energy wasting and inadvertently increased mortality[138]. A major problem with phosphate binder therapies is patient non-adherence due to the high pill burden and gastrointestinal adverse effects[139]. The high risk for gastrointestinal adverse effects imply that phosphate binders may alter the gut microbiota. Alternative treatment strategies to prevent vascular calcification could potentially be derived from comparative physiology studies. For example, agents that stimulate NRF2 (BOX 1), block mechanistic target of rapamycin complex 1 (mTORC1) signalling[140] or reduce phosphate absorption, such as by inducing calcium phosphate precipitation in the gut with magnesium[141], should be tested for their ability to decrease extracellular phosphate levels.

Of interest, a diet of highly fermentable carbohydrates (for example, starch) in captive wild ruminants, such as giraffes (*Giraffa camelopardalis*) — in combination with low calcium, high phosphate and low magnesium levels in the serum — is associated with premature death in these animals[142]. Because introduction of a diet with lower starch content led to higher magnesium and lower phosphate levels[142], one potential approach would be to use resistant starch, which is a complex carbohydrate fermented by gut microbiota that increases colonic absorption of minerals in animals. Indeed, resistant starch has been suggested to be a novel dietary method to prevent diabetic CKD[143].

Caloric restriction and ageing

Although dietary phosphate restriction is one mechanism to slow vascular calcification and ageing, a more effective approach to extend the lifespan of animals is by caloric restriction[144], which has demonstrated effectiveness in both short-lived species, including flies, worms, rats and mice[145], and more long-lived species, such as primates[146]. Fat stores, especially those generated during fructose metabolism, result in fructose-induced oxidative stress, which is associated with increased translocation of NRF2 to the nucleus, decreases in mitochondrial DNA content and mitochondrial dysfunction, with subsequent cellular apoptosis[147,148]. In most animals, excess fat stores are maintained as a protective mechanism for periods of food shortage[149]. Thus, as long as food is available on a daily basis, caloric restriction would be expected to reduce mitochondrial oxidative stress and preserve mitochondrial metabolism. Other ways to

Protein–energy wasting
A process characterized by a decline in body protein mass and energy reserves, including muscle and fat wasting and loss of visceral proteins. Protein energy wasting is often associated with inflammation and is a strong predictor of mortality.

Caloric restriction
A reduction in calorie intake without incurring malnutrition or a reduction in essential nutrients. In a variety of species, such yeast, fish, rodents and dogs, calorie restriction has been shown to slow the biological ageing process.

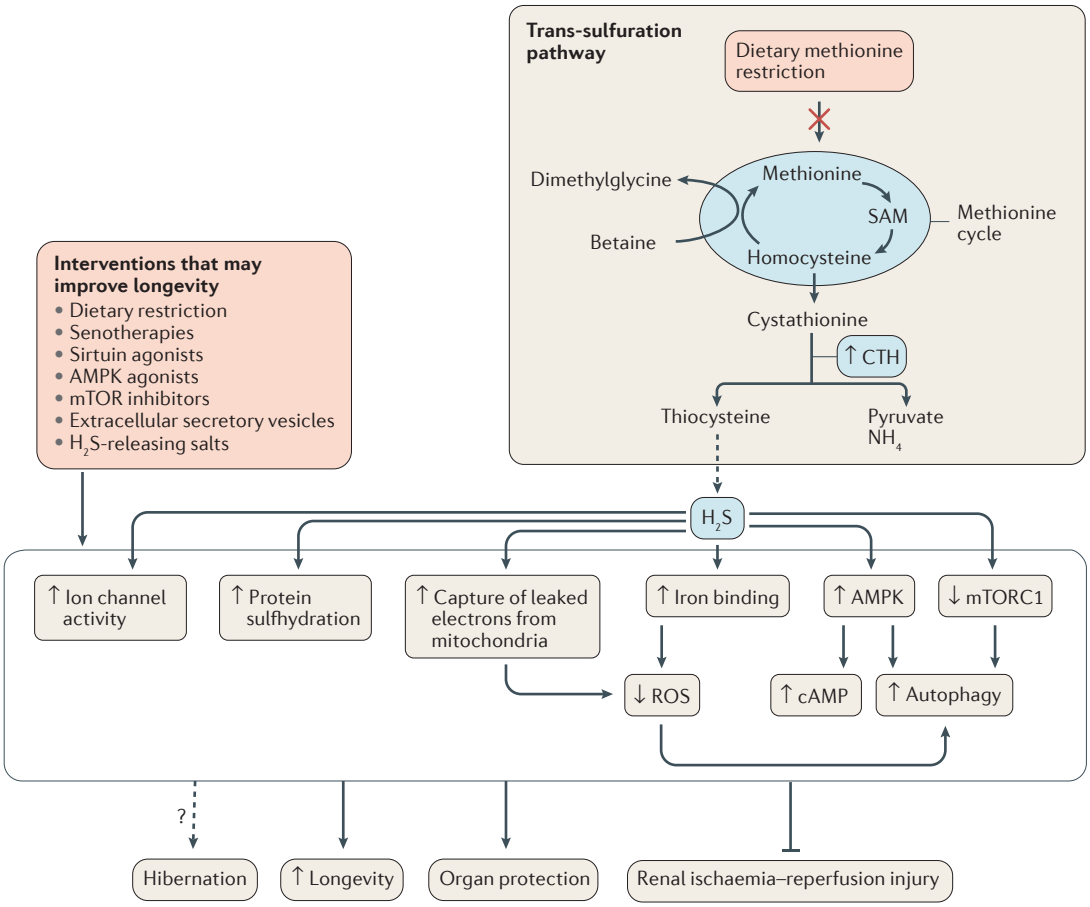


Figure 5 | **Strategies to increase lifespan, protect organs and avoid renal ischaemia–reperfusion injury.** Premature cardiovascular death and vascular progeria are prominent features of chronic kidney disease (CKD). On the basis of insights from long-lived animals and basic research, several treatment strategies have been identified that could be tested for their effect on longevity. Activation of the cytoprotectant functions of hydrogen sulfide (H_2S) via restriction of the sulfur-containing amino acid methionine is of major interest. Other potential treatment strategies that activate anti-inflammatory and antioxidant pathways include dietary restriction, senotherapies, sirtuin (NAD^+-dependent protein deacetylases) agonists, 5′-AMP-activated protein kinase (AMPK) agonists, mechanistic target of rapamycin (mTOR) inhibitors, extracellular secretory vesicles and H_2S-releasing salts. Studies suggest that inhibition of mTOR and activation of nuclear factor erythroid 2-related factor 2 (NRF2) signalling by such therapies increases longevity, aids organ protection and decreases the risk of renal ischaemia and reperfusion injuries. Because hibernation shares features and pathways associated with longevity, it can be speculated that successful hibernation depends on these pathways. CTH, cystathionine γ-lyase; mTORC1, mTOR complex 1; NH_4, ammonia; ROS; reactive oxygen species; SAM, S-adenosyl-L-methionine.

Sirtuin
Sirtuins (or NAD^+-dependent histone deacetylases) are a class of proteins that possess deacylase activity and regulate important biological pathways and cellular processes, including ageing, inflammation, transcription and apoptosis. Sirtuin agonists include pterostilbene and resveratrol.

Trans-sulfuration pathway
A metabolic pathway that involves the interconversion of homocysteine and cysteine via the intermediate cystathionine.

S-Sulfhydration
A post-translational modification that increases the catalytic activity of proteins. Physiological actions of sulfhydration include the regulation of endoplasmic reticulum stress signalling, inflammation and vascular tension.

mimic caloric restriction would be to administer agents that modulate cellular metabolism, including sirtuin agonists[150,151] and 5′-AMP-activated protein kinase (AMPK) agonists[152], the effects of which are mediated in part by the activities of the forkhead box protein (FOXO) family and the insulin signalling pathways[153]. For example, resveratrol prolongs lifespan in the extremely short-lived killifish[88]. We found that mice that cannot generate fructose, which are therefore protected from mitochondrial oxidative stress, were also protected from developing age-related renal disease[83]. In theory, elevated expression of NRF2 also mimics caloric restriction, as knockdown of Kelch-like ECH-associated protein 1 (KEAP1) in mice results in accumulation of NRF2 and thus augments the activation of cellular stress responses, including fatty acid oxidation and lipogenesis[154].

Methionine restriction and ageing. In addition to caloric restriction, dietary restriction of proteins — especially the sulfur-containing amino acid methionine — also promotes longevity in various animal models[155] (FIG. 5). This effect is likely to be mediated through the cytoprotectant hydrogen sulfide (H_2S) gas and increased activation of the trans-sulfuration pathway, prevention of electron leakage from mitochondria and possible hermetic effects on the mTOR pathway and NRF2 activity[156]. Under conditions of cellular stress, H_2S-mediated *S*-sulfhydration of KEAP1 leads to its disassociation from NRF2 and increased NRF2 nuclear translocation (BOX 1). This increases mRNA expression of NRF2-targeted downstream genes, such as GS homeobox 1 (*GSH1*; also known as *GSX1*) and glutathione reductase, and upregulates a range of cellular defences. In addition, methionine

restriction increases expression of the trans-sulfuration pathway enzyme cystathionine γ-lyase (CTH), resulting in increased H_2S production, which leads to AMPK activation and mTORC1 repression, thus reducing cellular stress and promoting physiological longevity[157]. H_2S also binds iron and captures electrons leaked from mitochondria, which reduces mitochondrion-mediated ROS formation[158,159]. In support of a role for H_2S activity in longevity, lower circulating methionine levels have been reported in naked mole rats than in shorter-lived laboratory rodents[160]. The finding of low sulfide levels in naked mole rats and the inverse correlation between circulating sulfide levels and maximum longevity in six different species[161] add to the complexity of understanding the role of H_2S in ageing. Thus, for prolonging lifespan, interconnections between methionine and caloric restriction in the context of comparative biology need to be investigated further.

Methionine restriction might be particularly important in preventing ageing and age-associated renal dysfunction[55]. For example, an inverse correlation between methionine content in tissue proteins and longevity was reported in eight different species[162]. Although circulating methionine levels do not differ between patients with CKD and healthy controls[163], oral methionine loading in patients on haemodialysis leads to an accumulation of homocysteine and other methionine metabolites in plasma and red blood cells[164], indicating impairment of the trans-sulfuration pathway. High doses of vitamin B_6 and folic acid failed to mitigate this phenotype, indicating that it most probably was not due to a lack of these cofactors[164]. Methionine restriction also increases the replicative lifespan and decelerates the accumulation of senescent cells across taxa from yeast to man[165]. Consistent with these observations, we reported lower methionine levels in wild hibernating brown bears (*Ursus arctos*)[8] and observed a fourfold increase in the methyl donor betaine during hibernation (P.G.S. and J.P., unpublished observations). Thus, it could be speculated that an increased production of H_2S protects the bears from ROS-mediated DNA damage. Moreover, dietary supplementation of H_2S in mice alleviates inflammation, aberrant methylation and dysfunction in a model of hypertensive kidney disease[166], suggesting that the use of this cytoprotective gas should be investigated further as a novel treatment strategy in CKD. A diet rich in one-carbon methyl donor units relative to calories, such as betaine (found in fruits, cereals and vegetables), can be used as an epigenetic switch and, via DNA hypermethylation and transmethylation in the methionine cycle, can promote longevity[167]. This mechanism merits further investigation, as low betaine levels have been observed in humans with poor renal function and accelerated biological ageing (P.G.S., unpublished observations).

Hypoxia and ischaemia

Naked mole rats survive constant exposure to hypoxic conditions by generating ATP through glycolysis. This process is mediated in part by using endogenously produced fructose, which preferentially stimulates glycolysis and lactate production[168]. We have found that fructose metabolism commonly leads to glycogen accumulation in the liver in mice and rats (R.J.J. and M.L., unpublished observations). This metabolic mechanism might also protect the kidneys of diving marine mammals that are subject to periods of prolonged hypoxia during deep dives. Harbour seals (*Phoca vitulina*) and whales (Cetacea), for example, have large amounts of glycogen in their proximal tubules, along with high levels of glycolytic enzymes to generate ATP during hypoxia[169,170]. The kidneys of Weddell seals (*Leptonychotes weddellii*) are protected from hypoxia despite severe renal vasoconstriction upon diving[6]. Likewise, kidneys of hibernating squirrels are protected from ischaemic injury, in a process that is probably mediated via an absence of caspase-3-like mediated activity[171].

One potential mechanism by which glycolysis protects against hypoxia could occur through the upregulation of antioxidants. Fasting seals have high expression levels of NRF2 (REF. 172), antioxidant enzymes[173] and glutathione levels[174] compared with non-fasting state levels. In support of a protective role for antioxidants, hyperactivation of NRF2 prevents progression of tubular damage after renal ischaemic injury in mice[175]. Thus, NRF2 might be a therapeutic target to prevent acute kidney injury and could activate a hypoxia survival pathway (BOX 1). By contrast, very high intracellular concentrations of dietary or endogenously produced fructose lead to rapid and transient ATP depletion, resulting in a strong pro-inflammatory response and substantial oxidative stress in human proximal tubular cells[176]. Indeed, a high-fructose diet inhibits KEAP1–NRF2 antioxidant signalling and increases the risk of non-alcoholic hepatosteatosis in mice[177]. Thus, high concentrations of fructose may be injurious, whereas low concentrations may carry survival functions.

Lastly, although hypoxia and ischaemia usually occur in conjunction, some species, such as the turtle, are tolerant to hypoxia but still sensitive to brain ischaemia[178]. A better understanding of hypoxic tolerance in turtles and naked mole rats may provide novel therapeutic interventions to combat the harmful effects of cerebral, renal and cardiac ischaemia in humans.

Seasonal acclimatization and hibernation

Seasonal acclimatization of metabolic activity

Many small mammals escape food shortage during winter by hibernation or daily torpor[179]. Other species that do not hibernate or go into daily torpor in the classical sense, such as red deer (*Cervus elaphus*) or Alpine ibex (*Capra ibex*), adopt a similar hypometabolic state during winter. The reduction in energy expenditure is, therefore, similarly to hibernators and species undergoing daily torpor, mainly accomplished by lowering endogenous heat production and increasing the tolerance to a lower body temperature. Although the 2–3 °C change in core body temperature is only moderate[180,181], a substantially lower body temperature down to 15 °C is present at the body's periphery[182], which is indicative of a substantial reduction in the mean temperature of the entire body mass. The winter phenotype of mammals

One-carbon methyl donor units
DNA methylation influences the expression of some genes and depends upon the availability of methyl groups. Dietary methyl groups are derived from food sources that contain methionine, one-carbon units, choline or betaine (a choline metabolite).

Torpor
A state of reduced body temperature and metabolic rate in animals that enables them to survive periods of reduced food availability.

further includes a shift from an anabolic metabolism during summer to the use of body fat reserves to fuel metabolism during winter[183,184]. As a result, many hibernators do not eat during winter[183], and non-hibernating species such as red deer reduce their food intake substantially, even when fed *ad libitum*[185]. The endogenous nature of the seasonal cycle of appetite and its entrainment by photoperiod have been shown experimentally for many wild species[186]. Decreased food intake during winter leads to a reduction in the size of the gut and visceral organs, such as the kidney[185,187], which further contributes to lower energy expenditure.

Major differences exist in the levels of serum biomarkers of microbiota metabolites between wild bears and bears in captivity (P.G.S. and J.P., unpublished observations), suggesting that nutrients and feeding patterns contribute to the metabolic changes required for hibernation. A transition in energy metabolism from carbohydrates during summer to lipids during winter is facilitated by a switch from insulin sensitivity in the summer to insulin resistance during hibernation[188]. The observation that central administration of leptin to captive grizzly bears leads to reduced food intake in October but not in August implies that seasonal variations exist in the sensitivity of the bear brain to the anorexic effects of leptin[188]. In addition, seasonal variations in gut microbiota might also contribute to changes in energy metabolism in hibernating bears, as transplantation of summer gut microbiota from wild bears promoted adiposity without affecting glucose tolerance in germ-free mice[189]. Although humans do not hibernate, investigating the processes that trigger fat accumulation in the summer followed by the switch to reduced energy intake and a fat-burning state occurring immediately before animals hibernate[190] may help to understand the mechanisms driving obesity.

Seasonal changes in membrane composition

Seasonal variation in body temperature is preceded by changes in the composition of cellular membranes, which consists of the integration of nutritionally acquired polyunsaturated fatty acids (PUFAs) into phospholipids during periods of cold acclimatization[191]. In addition to seasonal changes, even daily rhythmic changes in the phospholipid fatty acid composition of membranes have been found in humans along with changes in body temperature[192]. Furthermore, physical exercise can alter the lipid composition of membranes, for example, by increasing the concentration of docosahexaenoic acid (DHA) in skeletal muscle phospholipids[193] and by enhancing insulin sensitivity, probably through increasing insulin receptor expression levels. Of interest, the composition of membrane phospholipids has also been reported to contribute to the outstanding longevity in naked mole rats[194].

The composition of membrane lipids influences the activity of membrane-bound enzymes, for example, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity is increased in membranes that are rich in linoleic acid. Therefore, incorporation of linoleic acid into phospholipids of cardiac myocytes can compensate for reduced SERCA activity owing to low temperatures and enables adequate Ca^{2+} handling in cardiac myocytes even at body temperatures close to freezing point[191,195]. High concentrations of linoleic acid in membranes also improve muscle performance at a high body temperature, as suggested by the positive relationship between linoleic acid content of membrane phospholipids of muscle cells and maximum running speed found in a comparative study of 36 mammal species[196]. By contrast, DHA incorporation into phospholipids decreases SERCA activity[195] but seems to increase the activity of key enzymes of the Krebs cycle and fatty acid β-oxidation[197]. Accordingly, an increase of the DHA content into phospholipids during hibernation in Alpine marmots is paralleled by an increase of thermogenic capacity[191].

As all PUFAs are of dietary origin in mammals and birds, uptake influences the fatty acid composition of membranes. However, the balance of ω-6 to ω-3 PUFA in phospholipids seems to be regulated more by deacylation–reacylation processes, that is, membrane remodelling, rather than directly by dietary intake[185,198]. The different effects of ω-6 and ω-3 PUFA on membrane-bound enzymes hint at intriguing molecular conflicts. There probably is no optimal all-purpose PUFA composition in tissues, which creates a trade-off between costs and benefits of each fatty acid that is influenced by metabolic state, for example, fasting or fattening, and hence is subject to seasonal and even daily variations[185].

In rats with adenine-induced CKD, a pro-inflammatory fatty acid pattern (low PUFA and high saturated fatty acid concentrations) was associated with downregulation of NRF2 activity and increased activation of NF-κB and its downstream cytoprotective and antioxidant proteins[199]. As oxidation of eicosapentaenoic acid and DHA generate concentrations high enough to induce NRF2-directed gene expression[200]; this may explain the antioxidative and anti-inflammatory properties of ω-3 PUFAs. Burmese pythons (*Python molurus*) were reported to display 40% cardiac hypertrophy with increased cardiac output 48–72 hours after large meals[201]. Because consumption of these meals activates expression of fatty acid transport pathways and cardioprotective enzymes, and because injection of a combination of python fatty acids found in plasma promotes physiological hypertrophy in mammalian cardiomyocytes[202], targeted fatty acid supplementation may be a novel strategy to modulate cardiac gene expression and function in heart failure.

Circadian clock and kidney functions

Oscillating molecules that regulate circadian clocks are common in most if not all animal species[203]. Disruptions of the circadian clock lead to metabolic syndrome with dyslipidaemia, hyperleptinaemia, hyperglycaemia and hepatic steatosis in *Clock*$^{-/-}$mice[204]. As the circadian clock activates NRF2–glutathione-mediated antioxidant defence pathways and as arrhythmic *Clock*$^{\Delta 19}$ mice have low NRF2 expression[205], this network might have an important role in regulating energy balance and antioxidative protection. Circadian fluctuations are also known to affect renal blood flow, glomerular filtration,

Circadian clock
The circadian clock regulates the internal and external activities of organisms, such as sleep and changes in metabolism, based on the day–night cycle.

blood pressure and water and sodium excretion[206]. Thus, whether CKD progression is affected by circadian disruption and the potential benefits of chronotherapy should be investigated[207]. In addition, further investigations are warranted into the reasons for seasonal variations in the incidence, progression and mortality of ESRD[208].

Insights from hibernating bears

Osteoporosis, poor wound healing, vascular disease, inflammation and muscle loss, together with substantial metabolic dysfunction (FIG. 1), are common features of the uraemic phenotype[10]. The metabolism of bears is suppressed to approximately 25% of basal rates during hibernation[190]. Nevertheless, hibernating bears tolerate extended periods of an extremely low heart rate (~10 beats/min)[209] without developing congestive heart failure, atherosclerosis[210] thromboembolic events or cardiac dilation, which are common features in CKD. The protection against vascular disease may in part be mediated by changes in the coagulation pathway, in which traditionally intrinsic cascades (initiated when blood comes in contact with exposed collagen from damaged endothelial cells) are suppressed and extrinsic tissue factor pathways (initiated by vascular wall trauma) are maintained, to prevent thromboembolic events while enabling external injuries to be healed[211].

The fact that hibernating bears do not develop azotaemia or uraemic complications[8] is remarkable, considering that they have a 90% reduction in renal blood flow, anuria (70–180 ml of urine per day is reabsorbed through the urinary bladder wall[212]), mild hypothermia (30–36 °C) and a 50–70% reduction in GFR, and experience fasting and immobilization for 5–6 months of winter sleep. It is even more intriguing that females are able to give birth to cubs and nurse them during hibernation. Although a histological study in Romanian brown bears reported signs of glomerular fibrosis after awakening from winter sleep[213], the reduced renal function was normalized within weeks[8]. Thus, studies of the profound metabolic changes that occur in bears from summer to winter may provide clues that point towards novel therapeutic strategies for patients with CKD[7] (FIG. 1). Bears and marine mammals have a reniculated kidney system (renal lobulation) (Supplementary information S5 (figure)). Proximal convoluted tubules in multilobulated and reniculated kidneys are comparatively short, which decreases the resistance to intraluminal flow. The large body size in combination with the limitation of length of the proximal convoluted tubules[214] seems to be the most likely explanation for multilobulation of large terrestrial and marine mammalian kidneys. Similar to the protection from hypoxia during deep dives of seals, bears might benefit from reniculated kidneys during hibernation when their blood flow is reduced.

Applications for transplantation. Kidneys are particularly susceptible to ischaemic injury because of their high metabolic rate and oxygen consumption. Ischaemia–reperfusion injury is common in donor organs used for renal transplantation, in part owing to mitochondrial dysfunction, oxidative stress, ATP depletion and apoptosis following rewarming of the donor kidney. Despite extensive and repetitive periods of low metabolism, starvation and low cardiac output[215], bears return from hibernation without signs of persisting organ damage. Hence, studying the molecular changes in hibernating bears may lead to novel pharmacological approaches that could mimic hibernation and limit organ damage during renal transplantation[215]. As active suppression of metabolism during hibernation precedes the lowering of the body temperature, it can be speculated that lowering the basal metabolic rate may be more effective at preventing ischaemia–reperfusion injury to the donor organ than would therapeutic hypothermia[190]. Intriguingly, the metabolic switches that occur in preparation for hibernation share features with the metabolic changes associated with longevity in the animal kingdom[216]. Indeed, hibernating species have an approximately 15% higher annual survival rate than non-hibernators of similar size[217]. The observation that animals initiate hibernation owing to a lack of food (or other environmental cues) and not because of a lower body temperature[218] and terminate hibernation owing to physiological factors[209] can guide future research on the metabolic switches that induce and terminate hibernation.

On the basis of metabolic pathways that are altered in hibernation and associated with longevity, approaches that might preserve organ function during transplantation could be proposed: for example, the cytoprotective gas H_2S induces a torpor-like state in mice[219], protects against lethal hypoxia[220] and, as mentioned earlier, activates anti-inflammatory and antioxidant pathways via mTOR and NRF2 (REF. 221). Thus, H_2S treatment might confer organ cytoprotection via creation of a hibernation-like environment[222]. Furthermore, injection of the AMPK agonist 5′-AMP induces torpor independently of H_2S[223], although the mechanism underpinning this observation remains to be defined. Therefore, pretreatment of donor organs with agents that inhibit inflammatory responses and activate antioxidant pathways, such as H_2S gas, sirtuin agonists, mTOR inhibitors and AMPK agonists, might prevent renal ischaemia–reperfusion injury more effectively than current approaches[224,225].

Applications for muscle wasting. The loss of skeletal muscle mass that can occur in patients with CKD is caused by a combination of sedentary behaviour, anorexia and the activation of catabolic pathways in the uraemic milieu. In contrast to humans, whose muscle mass and strength may be reduced by >90% during extended periods of immobilization, hibernating black bears show minor loss in skeletal muscle cell number or size[226]. One mechanism by which bears retain muscle strength is by *de novo* amino acid and protein synthesis from urea[227], coupled with a unique ability to recycle urea during hibernation that has not yet been observed in other hibernating animals[7]. Metabolic recycling of nitrogenous waste products seems to be a conceivable mechanism to prevent loss of muscle protein (FIG. 6). In addition, the skeletal muscle of hibernating bears seems more resistant to denervation than skeletal muscle of non-hibernating

Chronotherapy
The science of timing drugs according to the circadian clock. This approach is used in various clinical conditions, such as cancer, hypertension, seasonal affective disorder and bipolar disorder.

Renal lobulation
Carnivores and most small mammals have smooth-surfaced and uni-pyramidal kidneys, whereas primates and Suidae (hogs and pigs) have a smooth-surfaced and multi-pyramidal kidney system. Large terrestrial mammals have multi-lobulated and multi-pyramidal kidneys to keep the proximal convoluted tubules short. Most marine mammals and bears have each lobe separated into renules (reniculated kidney system).

Therapeutic hypothermia
(also known as targeted temperature management). The induction of mild hypothermia (32–35 °C) after cardiac arrest for neuroprotection.

Sedentary behaviour
A type of behaviour that is characterized by an energy expenditure ≤1.5 metabolic equivalents while in a lying, reclining or sitting posture. Typical sedentary behaviours include watching TV, computer work, driving and reading.

Denervation
Loss of nerve supply to a part of the body, which can be due to multiple causes, such as surgery, physical injury, chemical toxicity or diseases.

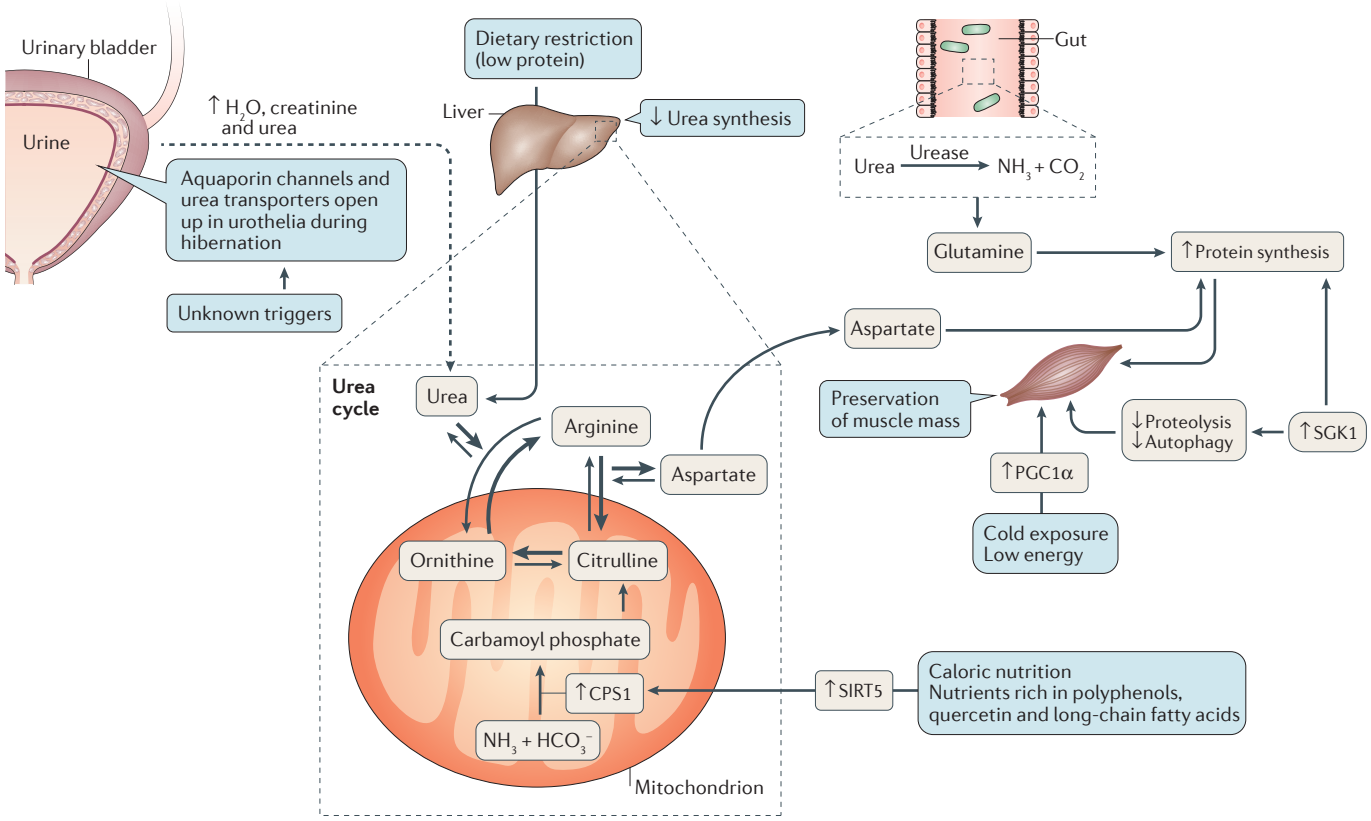


Figure 6 | **Nitrogen metabolism in hibernating bears.** To conserve mobility and muscle strength, hibernating bears must minimize muscle protein loss and re-utilize the vast majority of urea produced, which is mediated by microbial ureolysis and urea-N resorption. Multiple mechanisms are responsible for the reduction in serum urea levels during hibernation. Lower urea production during hibernation leads to reduced amino acid degradation. Moreover, urea is reabsorbed from urine via solute and water channels, such as urea transporters and aquaporin channels, in a leaky bladder wall. The reabsorbed urea is believed to be recycled back into skeletal muscle. Urea is also hydrolysed by urease-expressing gut bacteria into ammonia (NH_3), which is used by the host to synthetize glutamine for incorporation into proteins. Other factors that may prevent muscle loss in hibernating animals include activation of peroxisome proliferator-activated receptor γ-co-activator 1α (PGC1α), for example, by cold environmental temperature and the low-energy state, and serum–glucocorticoid-regulated kinase 1 (SGK1). Urea levels decrease in the autumn when food is still available, and the metabolic changes that determine urea metabolism may already occur before the bear enters hibernation. Because sirtuin (SIRT) stimulators, such as polyphenols in berries and plants, stimulate carbamoyl phosphate synthase 1 (CPS1), which is the first and rate-limiting step of the urea cycle, this may decrease urea generation and prepare the animal for low urine output during hibernation. Because urea recycling in bears has been insufficiently studied, the proposed pathways are mainly speculative. CO_2, carbon dioxide; HCO_3^-, bicarbonate ion; H_2O, water.

Disuse atrophy
A type of muscle atrophy that occurs when a muscle is less active than usual. Disuse atrophy is a common feature in chronic debilitating diseases and immobility.

Mechanical unloading
A mechanical manoeuvre or therapy that decreases tissue growth and regeneration. Whereas mechanical loading of mammalian tissues is a potent promoter of tissue growth and regeneration, mechanical unloading in microgravity causes reduced tissue regeneration via stem cell tissue progenitors.

bears[228], suggesting that hibernation is associated with changes in the neural regulation of skeletal muscle catabolic pathways and that targeting these pathways could offer novel solutions for the treatment of disuse atrophy.

The plasma of hibernating bears has an anti-proteolytic effect that inhibits wasting of isolated skeletal muscle[229]. Serum–glucocorticoid-regulated kinase 1 (SGK1) is activated by insulin and growth factors and helps to prevent loss of muscle mass via downregulation of proteolysis and autophagy and increased protein synthesis[230]. As high SGK1 expression levels have been reported in hibernating ground squirrels[231], mice lacking SGK1 have muscle atrophy[230] and low SGK1 expression levels are found in patients with CKD[232], this serine/threonine kinase may be a novel therapeutic target to prevent uraemic muscle loss. Moreover, expression levels of peroxisome proliferator-activated receptor γ-co-activator 1α (PGC1α), which activates metabolic pathways associated with endurance exercise (such as running), are induced by cold exposure[233] and are elevated in hibernating squirrels[222]. This master regulator plays a major part in renal recovery from acute kidney injury through regulation of NADH synthesis[234]. Hence, stimulation of PGC1α, such as through exercise[235], might also promote skeletal muscle homeostasis in CKD. Because activation of NRF2 by sulforaphane also increases endurance exercise capacity[236], multiple targets and pathways to prevent uraemic muscle loss exist.

Applications for bone loss. In addition to being protected from muscle wasting, hibernating bears are protected from poor wound healing and osteoporosis. Unlike humans and other mammals, hibernating bears can withstand physical inactivity (mechanical unloading)

and nutritional deprivation for ≤6 months without any negative effects on bone strength[237]. Maintenance of calcium homeostasis is considered the most important contributing factor in bone health, but many other factors, such as growth hormones and cytokines, also have a role. Hibernating bears maintain eucalcaemia during immobilization[8] and have decreased markers of bone resorption and formation[238], which indicates precise balancing of bone remodelling activity. The suppression of bone remodelling during hibernation is likely an important mechanism to conserve energy during a long period of inactivity, decreased renal function and fasting[199]. Other contributing factors probably include the differential regulation of gene expression and hypothalamic control of hormones involved in bone remodelling, as higher expression levels of hormones that reduce bone formation, such as cocaine- and amphetamine-regulated transcript protein (CARTPT)[238]. An elevated expression of anabolic genes but not bone resorption genes[239] has also been reported.

Changes in vitamin D metabolism may also preserve bone mass during hibernation[240]. In contrast to humans, 25(OH)D vitamin levels do not change between seasons in bears[241], and bear kidneys continue to produce calcitriol ($1,25(OH)_2D_3$; the active metabolite of vitamin D) despite a marked reduction in renal function during hibernation[240]. Black bear parathyroid hormone activates cAMP, mitigates apoptosis in osteoblast cultures and increases trabecular bone volume[242]; hence, the anabolic effects of bear parathyroid hormone might also prevent disuse osteoporosis. In addition, NRF2 was reported to have a role in bone microarchitecture in a mouse model of osteoporosis[243] and inhibited tumour necrosis factor ligand superfamily member 11 (TNFSF11)-mediated osteoclastogenesis in osteolysis-induced mice[244]. Given that increased NRF2 expression plays a major part in the antioxidant defences that are required for hibernation success in ground squirrels[245], the potential role of NRF2 in maintaining skeletal mass in hibernating bears warrants investigation. Taken together, studies of hibernating bears can provide novel therapeutic approaches for the treatment of intracellular calcium disorders and prevention of bone loss during immobilization in humans.

Applications for wound healing. Bears also have the ability to heal wounds despite immobilization, hypothermia and anuria — conditions that are usually unfavourable for wound healing[246]. Elevated levels of δ-opioid receptor agonists and ursodeoxycholic acid have been linked to the wound-healing capabilities of hibernating bears[246], but further insights into the underlying mechanisms involved might provide strategies to enhance wound healing. Changes in the coagulation pathways that occur during hibernation[211] may also contribute to better wound healing.

Applications for azotaemia. The unique ability of hibernating bears to recycle urea back into proteins protects the bear not only from muscle wasting but also from azotaemia (FIG. 5). Because little urea is generated during hibernation[247], minimal amounts of urine need to be excreted[227]. When ^{14}C urea and heavy water (D_2O) were administered into the bladder of hibernating bears, reabsorption of both isotopes occurred across urothelia with rapid appearance in plasma[248]. Although small quantities of solute and water transport across urinary tract urothelia are features of most mammalian species[249], the mechanism(s) by which bears accomplish this transport during hibernation remains unknown[249]. One hypothesis is that the passage of recycled urea from the intestine contributes to *de novo* amino acid synthesis, as urease-expressing gut bacteria release ammonia that can be used by the host to synthetize glutamine for protein synthesis[247]. In contrast to bears, humans cannot recycle urea, and urea degradation in the human gut does not stimulate the conservation of nitrogen[250]. In addition, glycerol prevents azotaemia in hibernating black bears by serving as a carbon source for *de novo* amino acid synthesis[251]. As urea levels decrease in the autumn before hibernation[252], a dietary shift may contribute to this change. The metabolic regulation of fasting is, in part, mediated by the activities of sirtuin 5 (SIRT5). SIRT5 exhibits deacetylase, desuccinylase and demalonylase activities and regulates the urea cycle enzyme carbamoyl-phosphate synthase 1 (CPS1) in liver mitochondria. Because *Sirt5*$^{-/-}$ mice fail to upregulate CPS1 and exhibit hyperammonaemia during fasting[253], this implies a role for SIRT5 in urea metabolism and the metabolic regulation of fasting. Thus, the long-term effects of sirtuin activators, such as resveratrol, on urea handling should be tested in patients with CKD.

Protective compounds in berries. Bears can ingest up to 200,000 berries per day in peak season, which occurs in late summer[254]. There is a synchronous timing of food resources that triggers the switch from salmon to berries during the summer[255]. Blueberries have potent anti-inflammatory and antioxidant properties (for example, through the actions of phenol-like antioxidants) and contain anthocyanins. Berries are also an important source of sirtuin agonists (such as pterostilbene and resveratrol), quercetin, vitamin K, vitamin C and fibres. In addition, berries contain fructose and linoleic acid that may stimulate fat storage in preparation for hibernation. Polyphenols are secondary metabolites in plants that are needed not only for plant growth but also as a defence mechanism against UVB exposure and aggression by insects and fungal pathogens[256]. In a mouse model of polygenic obesity, consumption of berries results in a shift in gut microbiota towards obligate anaerobes, which correlates with a decrease in gastrointestinal luminal oxygen and oxidative stress[257]. Potential implications on human health of the nearly anoxic conditions observed in the mouse gut lumen after berry consumption should be investigated.

In addition, resveratrol preserves bone mass in old male rats[258], anthocyanins in berries increase serum alkaline phosphatase levels in obese male mice[259], and the anthocyanin delphinidin inhibits excessive osteoclastogenesis in a mouse model of osteoporosis[260]. Notably, delphinidin also prevents muscle atrophy in mice[261] and lowers fasting glycaemia in individuals with prediabetes[262]. Moreover, dietary supplementation

Eucalcaemia
The maintenance of normal and constant serum calcium levels.

Blueberries
Blueberries comprise all blue-coloured berries of the *Vaccinium* genus, of which the most common is bilberries. Blueberries have a low glycaemic index and are a rich source of fibres, vitamin K, manganese, >15 different anthocyanins (especially delphinidin and malvidin), quercetin, myricetin and resveratrol.

Anthocyanins
Anthocyanins (>600 molecular structures) belong to a class of molecules called flavonoids that are universal plant colourants responsible for the red, purple and blue colours in many fruits, berries, vegetables and flowers. Due to their contribution in multiple physiological activities, the consumption of these molecules is believed to have a substantial role in preventing lifestyle-related diseases.

Senolytic effects
Senolytic compounds selectively induce the death of senescent cells.

with anthocyanins isolated from roselle (*Hibiscus sabdariffa*) attenuated progression of adenine-induced CKD in rats[263]. Because a causal role for senescent cells in ageing-related bone loss has been demonstrated in mice[264], nutritional compounds with senolytic effects, such as quercetin and fisetin[265] — found in fruits, capers, vegetables and berries — may also contribute to the capacity of bears to maintain their bone mass[237]. Quercetin also blocks phosphate-induced apoptosis and VSMC calcification via inhibition of mitochondrial fission and oxidative stress[266]. As polyphenols that stimulate sirtuins and PGC1α prevent muscle wasting induced by mechanical unloading[267] or in streptozotocin-induced diabetes in rats[268], their long-term effects should be tested in patients with CKD who experience muscle wasting. Resveratrol and grape seed proanthocyanidin extract facilitate vascular endothelial growth factor A (VEGFA) expression and angiogenesis in different wound models[269]. Hence, the long-term effects of sirtuin activators and anthocyanins on wound healing require further investigation. In healthy humans and patients with the metabolic syndrome, blueberry supplementation decreases cardiovascular risk factors[270], increases HDL cholesterol[271] and improves insulin sensitivity[272]. Moreover, a study based on validated food-frequency questionnaires in 93,600 women (Nurses Health Study) showed that a high intake of anthocyanins (highest versus lowest quintile) was associated with a decreased risk of myocardial infarction[273]. A diet rich in fermentable carbohydrates, such as berries, has been reported to have arisen in a basal ursine bear (*Protarctos abstrusus*) during the Pliocene period (~2.6–5.3 million years ago), enabling bears to occupy cold habitats, accumulate fat and hibernate[274]. Finally, because many plants that are consumed by bears contain melatonin[275], the effect of plants, such as tall fescue (*Festuca arundinacea*), on the metabolic changes that occur between seasons in hibernating bears should be investigated further. Taken together, the potential beneficial effects of berries and other plant nutrients on the uraemic phenotype should be assessed.

Conclusions

Species living in extreme habitats have acquired adaptive mutations through natural selection and epigenetic calibration to survive in challenging environments. Environmental factors and stressors — such as infections, toxins, starvation, climate change and psychosocial factors — have modified the epigenetic landscape throughout evolution to enable dynamically responsive changes in gene expression and associated biochemical networks to help mitigate the effects of these changes[73]. Although humans have a common ancestry with mammals and share the same vulnerability to infections, environmental toxins and illnesses, most physicians have regarded animal diseases as different and of minor interest in the understanding of complex human diseases. In fact, almost all diseases that affect humans have an equivalent in the animal kingdom, although treatment options may differ. Thus, we propose a multidisciplinary approach to improve health care of patients with CKD by sharing new discoveries and tools from the fields of zoology, botany, ecology, veterinary medicine, anthropology and biology.

1. Stenvinkel, P. & Johnson, R. J. Kidney biomimicry — a rediscovered scientific field that could provide hope to patients with kidney disease. *Arch. Med. Res.* **44**, 584–590 (2013).
2. Krogh, A. The progress of physiology. *Am. J. Physiol.* **90**, 243–251 (1929).
3. Smith, H. W. Comparative physiology of the kidney. *JAMA* **153**, 1512–1514 (1953).
4. Sperber, I. Studies on the mammalian kidney. *Zool. Bidrag Uppsala* **22**, 249–432 (1944).
5. O'Connor, T. P., Lee, A., Jarvis, J. U. & Buffenstein, R. Prolonged longevity in naked mole-rats: age-related changes in metabolism, body composition and gastrointestinal function. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **133**, 835–842 (2002).
6. Davis, R. W., Castellini, M. A., Kooyman, G. L. & Maue, R. Renal glomerular filtration rate and hepatic blood flow during voluntary diving in Weddell seals. *Am. J. Physiol.* **245**, R743–R748 (1983).
7. Stenvinkel, P., Jani, A. H. & Johnson, R. J. Hibernating bears (Ursidae): metabolic magicians of definite interest for the nephrologist. *Kidney Int.* **83**, 207–212 (2013).
8. Stenvinkel, P. *et al.* Metabolic changes in summer active and anuric hibernating free-ranging brown bears (*Ursus arctos*). *PLOS One* **8**, e72934 (2013).
9. Levin, A. *et al.* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet* **390**, 1888–1917 (2017).
10. Stenvinkel, P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. *J. Intern. Med.* **268**, 456–467 (2010).
11. Kooman, J. P., Kotanko, P., Schols, A. M., Shiels, P. G. & Stenvinkel, P. Chronic kidney disease and premature ageing. *Nat. Rev. Nephrol.* **10**, 732–742 (2014).
12. Lew, Q. J. *et al.* Red meat intake and risk of ESRD. *J. Am. Soc. Nephrol.* **28**, 304–312 (2017).
13. Goraya, N. & Wesson, D. E. Is dietary red meat kidney toxic? *J. Am. Soc. Nephrol.* **28**, 5–7 (2017).
14. Reynolds, B. S. & Lefebvre, H. P. Feline CKD: pathophysiology and risk factors — what do we know? *J. Feline Med. Surg.* **15** (Suppl. 1), 3–14 (2013).
15. Jiménez, A. *et al.* Membranous glomerulonephritis in the Iberian lynx (*Lynx pardinus*). *Vet. Immunol. Immunopathol.* **121**, 34–43 (2008).
16. Chetboul, V. *et al.* Spontaneous feline hypertension: clinical and echocardiographic abnormalities, and survival rate. *J. Vet. Intern. Med.* **17**, 89–95 (2003).
17. Cannon, A. B., Westropp, J. L., Ruby, A. L. & Kass, P. H. Evaluation of trends in urolith composition in cats: 5,230 cases *J. Am. Vet. Assoc.* **231**, 570–576 (2007).
18. Brown, C. A., Elliott, J., Schmiedt, C. W. & Brown, S. A. Chronic kidney disease in aged cats: clinical features, morphology, and proposed pathogeneses. *Vet. Pathol.* **53**, 309–326 (2016).
19. Munson, L. *et al.* Extrinsic factors significantly affect patterns of disease in free-ranging and captive cheetah (*Acinonyx jubatus*) populations. *J. Wildl. Dis.* **41**, 542–548 (2005).
20. Waki, M. F., Martorelli, C. R., Mosko, P. E., Erdmann, P. & Kogika, M. M. Classification into stages of chronic kidney disease in dogs and cats — clinical, laboratorial and therapeutic approach (Portuguese). *Cienia Rural* **40**, 2226–2234 (2010).
21. Junginger, J. *et al.* Pathology in captive wild felids at German zoological gardens. *PLOS One* **10**, e0130573 (2015).
22. Elliott, J. & Barber, P. J. Feline chronic renal failure: clinical findings in 80 cases diagnosed between 1992 and 1995. *J. Small Anim. Pract.* **39**, 78–85 (1998).
23. Zini, E. *et al.* Renal morphology in cats with diabetes mellitus. *Vet. Pathol.* **51**, 1143–1150 (2014).
24. Bolton, L. A. & Munson, L. Glomerulosclerosis in captive cheetahs (*Acinonyx jubatus*). *Vet. Pathol.* **36**, 14–22 (1999).
25. Oaks, J. L. *et al.* Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature* **427**, 630–633 (2004).
26. Eisert, R. Hypercarnivory and the brain: protein requirements of cats reconsidered. *J. Comp. Physiol. B* **181**, 1–17 (2011).
27. Meyer, T. W., Lawrence, W. E. & Brenner, B. M. Dietary protein and the progression of renal disease. *Kidney Int. Suppl.* **16**, S243–S247 (1983).
28. Kramer, H. Kidney disease and the westernization and industrialization of food. *Am. J. Kidney Dis.* **70**, 111–121 (2017).
29. DiBartola, S. P., Buffington, C. A., Chew, D. J., McLoughlin, M. A. & Sparks, R. A. Development of chronic renal disease in cats fed a commercial diet. *J. Am. Vet. Med. Assoc.* **202**, 744–751 (1993).
30. Juraschek, S. P., Appel, L. J., Anderson, C. A. & Miller, E. R. Effect of a high-protein diet on kidney function in healthy adults: results from the OmniHeart trial. *Am. J. Kidney Dis.* **61**, 547–554 (2013).
31. Brenner, B. M., Meyer, T. W. & Hostetter, T. H. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N. Engl. J. Med.* **307**, 652–659 (1982).
32. Mafra, D. *et al.* Red meat intake in chronic kidney disease patients: two sides of the coin. *Nutrition* **46**, 26–32 (2018).
33. Haring, B. *et al.* Dietary protein sources and risk for incident chronic kidney disease: results from the atherosclerosis risk in communities (ARIC) study. *J. Ren Nutr.* **4**, 233–242 (2017).
34. Rebholz, C. M. *et al.* DASH (Dietary Approaches to Stop Hypertension) diet and risk of subsequent kidney disease. *Am. J. Kidney Dis.* **68**, 853–861 (2016).
35. Lin, C. K. *et al.* Comparison of renal function and other health outcomes in vegetarians versus omnivores in Taiwan. *J. Health Popul. Nutr.* **28**, 470–475 (2010).
36. Kontessis, P. *et al.* Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. *Kidney Int.* **38**, 136–144 (1990).
37. Azadbakht, L., Atabak, S. & Esmaillzadeh, A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy: a longitudinal randomized clinical trial. *Diabetes Care* **31**, 648–654 (2008).

38. Nongouch, A. & Davenport, A. The effect of vegetarian diet on skin autofluorescence measurements in haemodialysis patients. *Br. J. Nutr.* **113**, 1040–1043 (2015).
39. Gluba-Brzózka, A., Franczyk, B. & Rysz, J. Vegetarian diet in chronic kidney disease — a friend or foe. *Nutrients* **9**, 374 (2017).
40. Larsson, S. C. & Orsini, N. Red meat and processed meat consumption and all-cause mortality: a meta-analysis. *Am. J. Epidemiol.* **179**, 282–289 (2014).
41. Crippa, A., Larsson, S. C., Discacciati, A., Wolk, A. & Orsini, N. Red and processed meat consumption and risk of bladder cancer: a dose-response meta-analysis of epidemiological studies. *Eur. J. Nutr.* http://dx.doi.org/10.1007/s00394-016-1356-0 (2016).
42. Kaluza, J., Wolk, A. & Larsson, S. C. Red meat consumption and risk of stroke: a meta-analysis of prospective studies. *Stroke* **43**, 2556–2560 (2012).
43. Micha, R., Wallace, S. K. & Mozaffarian, D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation* **121**, 2271–2283 (2010).
44. Micha, R., Michas, G. & Mozaffarian, D. Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes — an updated review of the evidence. *Curr. Atheroscler Rep.* **14**, 515–524 (2012).
45. de Mello, V. D., Zelmanovitz, T., Perassolo, M. S., Azevedo, M. J. & Gross, J. L. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am. J. Clin. Nutr.* **83**, 1032–1038 (2006).
46. de Mello, V. D., Zelmanovitz, T., Azevedo, M. J., de Paula, T. P. & Gross, J. L. Long-term effect of a chicken-based diet versus enalapril on albuminuria in type 2 diabetic patients with microalbuminuria. *J. Renal Nutr.* **18**, 440–447 (2008).
47. Elliott, J., Rawlings, J. M., Markwell, P. J. & Barber, P. J. Survival of cats with naturally occurring chronic renal failure: effect of dietary management. *J. Small Anim. Pract.* **41**, 235–242 (2000).
48. Alisson-Silva, F., Kawanishi, K. & Varki, A. Human risk of diseases associated with red meat intake: analysis of current theories and proposed role for metabolic incorporation of a non-human sialic acid. *Mol. Aspects Med.* **51**, 16–30 (2016).
49. Tang, W. H. *et al.* Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ. Res.* **116**, 448–455 (2015).
50. Sun, X. *et al.* Trimethylamine N-oxide induces inflammation and endothelial dysfunction in human umbilical vein endothelial cells via activating ROS-TXNIP-NLRP3 inflammasome. *Biochem. Biophys. Res. Commun.* **481**, 63–70 (2016).
51. Missailidis, C. *et al.* Serum trimethylamine-N-oxide is strongly related to renal function and predicts outcome in chronic kidney disease. *PLOS One* **11**, e0141738 (2016).
52. Wang, Z. *et al.* Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell* **163**, 1585–1595 (2015).
53. Koeth, R. A. *et al.* γ-Butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO. *Cell Metab.* **20**, 799–812 (2014).
54. Martin, O. C. *et al.* Antibiotic suppression of intestinal microbiota reduces heme-induced lipoperoxidation associated with colon carcinogenesis in rats. *Nutr. Cancer* **67**, 119–125 (2015).
55. McClelland, R. *et al.* Accelerated ageing and renal dysfunction links lower socioeconomic status and dietary phosphate intake. *Aging* **8**, 1135–1149 (2016).
56. Martínez-Moreno, J. M. *et al.* High phosphate induces a pro-inflammatory response by vascular smooth muscle cells and modulation by vitamin D derivatives. *Clin. Sci.* **131**, 1449–1463 (2017).
57. Choi H. K., Atkinson K., Karlson E. W., Willett W., & Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N. Engl. J. Med.* 350, 1093–1103 (2004).
58. Hammett, F. S. The nitrogen excretion of the cat during a purine-free and a purine-rich diet. *J. Biol. Chem.* **22**, 551–558 (1915).
59. Villegas, R. *et al.* Purine-rich foods, protein intake, and the prevalence of hyperuricemia: the Shanghai Men's Health Study. *Nutr. Metab. Cardiovasc. Dis.* **22**, 409–416 (2012).
60. Clifford, A. J., Riumallo, J. A., Youn, V. R. & Scrimshaw, N. S. Effect of oral purines on serum and urinary uric acid of normal, hyperuricemic and gouty humans. *J. Nutr.* **106**, 428–450 (1976).
61. Nakanishi, N. *et al.* Low urine pH Is a predictor of chronic kidney disease. *Kidney Blood Press Res.* **35**, 77–81 (2012).
62. Appel, S. L., Houston, D. M., Moore, A. E. & Weese, J. S. Feline urate urolithiasis. *Can. Vet. J.* **51**, 493–496 (2010).
63. Osborne C. A., Lulich J. P., Ulrich L. K., & Bird K. A. Feline crystalluria. Detection and interpretation. *Vet. Clin. North Am. Small Anim. Pract.* 26, 369–391 (1996).
64. Ryu, E. S. *et al.* Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease. *Am. J. Physiol. Renal Physiol.* **304**, F471–F480 (2013).
65. Greene, J. P. *et al.* Risk factors associated with the development of chronic kidney disease in cats evaluated at primary care veterinary hospitals. *J. Am. Vet. Med. Assoc.* **244**, 320–327 (2014).
66. Campese, V. M. Con: Mesoamerican nephropathy: is the problem dehydration or rehydration? *Nephrol. Dial Transplant* **32**, 603–606 (2017).
67. Johnson, R. J. Heat stress as a potential etiology of Mesoamerican and Sri Lankan nephropathy: a late night consult with Sherlock Holmes. *Nephrol. Dial Transplant* **32**, 598–602 (2017).
68. McFarland, W. N., Wimsatt, W., A. Urine flow and composition in the vampire bat. *Am. Zool.* **5**, 662–667 (1965).
69. Singer M. A. Vampire, bat, shrew, and bear: comparative physiology and chronic renal failure. *Am. J. Physiol. Regulatory Integrative Comp. Physiol.* **282**, R1583–R1592 (2002).
70. Hoff, C. C. & Reidesel, M. L. (eds) *Physiological Systems in Semiarid Environments*. (University of New Mexico Press, 1969).
71. Holloway, B. W. & Ripley, S. H. Nucleic acid content of reticulocytes and its relation to uptake of radioactive leucine *in vitro*. *J. Biol. Chem.* **196**, 695–701 (1952).
72. Fulop, T. *et al.* Aging, frailty and age-related diseases. *Biogerontology* **11**, 547–563 (2010).
73. Shiels P. G., McGuiness D., Eriksson M., Kooman J. P. & Stenvinkel P. The role of epigenetics in renal ageing. *Nat. Rev. Nephrol.* **13**, 471–482 (2017).
74. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The hallmarks of aging. *Cell Metab.* **153**, 1194–1217 (2013).
75. Sturmlechner, I., Durik, M., Sieben, C. J., Baker, D. J. & van Deursen, J. M. Cellular senescence in renal ageing and disease. *Nat. Rev. Nephrol.* **13**, 77–89 (2017).
76. Stenvinkel, P. & Larsson, T. Chronic kidney disease: a clinical model of premature aging. *Am. J. Kidney Dis.* **62**, 339–351 (2013).
77. Karam, Z. & Tuazon, J. Anatomic and physiologic changes of the aging kidney. *Clin. Geriatr. Med.* **29**, 555–564 (2013).
78. Kaplan, C., Pasternack, B., Shah, H. & Gallo, G. Age-related incidence of sclerotic glomeruli in human kidneys. *Am. J. Pathol.* **80**, 227–234 (1975).
79. Kooman, J. *et al.* Inflammation and premature aging in advanced chronic kidney disease. *Am. J. Physiol. Renal Physiol.* **313**, F938–F950 (2017).
80. Schriner, S. E. *et al.* Extension of murine life span by overexpression of catalase targeted to mitochondria. *Science* **308**, 1909–1911 (2005).
81. Bhargava, P. & Schnellmann, R. G. Mitochondrial energetics in the kidney. *Nat. Rev. Nephrol.* **13**, 629–646 (2017).
82. Glassock, R. J. & Rule, A. D. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int.* **82**, 270–277 (2012).
83. Roncal-Jimenez, C. A. *et al.* Aging-associated renal disease in mice is fructokinase dependent. *Am. J. Physiol. Renal Physiol.* **311**, F722–F730 (2016).
84. Childs, B. G. *et al.* Senescent cells: an emerging target for diseases of ageing. *Nat. Rev. Drug Discov.* **16**, 718–735 (2017).
85. Sosnowska, D. *et al.* A heart that beats for 500 years: age-related changes in cardiac proteasome activity, oxidative protein damage and expression of heat shock proteins, inflammatory factors, and mitochondrial complexes in Arctica islandica, the longest-living noncolonial animal. *J. Gerontol. A Biol. Sci. Med. Sci.* **69**, 1448–1461 (2014).
86. Nielsen, J. *et al.* Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (*Somniosus microcephalus*). *Science* **353**, 702–704 (2016).
87. Finch, C. E. Update on slow aging and negligible senescence — a mini-review. *Gerontology* **55**, 307–313 (2009).
88. Valenzano, D. R. *et al.* Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. *Curr. Biol.* **16**, 296–300 (2006).
89. Buffenstein, R. Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. *J. Comp. Physiol. B* **4**, 439–445 (2008).
90. Jarvis, J. U. M. & Bennet, N. C. in *The Biology of the Naked Mole-Rat*. (eds Sherman, P. W., Jarvis, J. U. M. & Alexander, R. D.) 66–96 (Princeton University Press, 1991).
91. Yahav, S., Buffenstein, R. & Pettifor, J. M. Calcium and inorganic phosphorus metabolism in naked mole rats *Hetercephalus glaber* is only indirectly affected by cholecalciferol. *Gen. Comp. Endocrinol.* **89**, 161–166 (1993).
92. De Waal, E. M. *et al.* Elevated protein carbonylation and oxidative stress do not affect protein structure and function in the long-living naked-mole rat: a proteomic approach. *Biochem. Biophys. Res. Commun.* **434**, 815–819 (2013).
93. Triplett, J. C. *et al.* Age-related changes in the proteostasis network in the brain of the naked mole-rat: implications promoting healthy longevity. *Biochim. Biophys. Acta* **1852**, 2213–2224 (2015).
94. Dai, D. F., Wessells, R. J., Bodmer, R. & Rabinovitch, P. S. in *The Comparative Biology of Aging*. (ed Wolf N. S.) 259–286 (Springer, 2010).
95. Grimes, K. M., Lindsey, M. L., Gelfond, J. A. & Buffenstein, R. Getting to the heart of the matter: age-related changes in diastolic heart function in the longest-lived rodent, the naked mole rat. *J. Gerontol. A Biol. Sci. Med. Sci.* **67**, 384–394 (2012).
96. Grimes, K. M., Reddy, A. K., Lindsey, M. L. & Buffenstein, R. And the beat goes on: maintained cardiovascular function during aging in the longest-lived rodent, the naked mole-rat. *Am. J. Physiol. Heart Circ. Physiol.* **307**, H284–291 (2014).
97. Lagunas-Rangel, F. A. & Chávez-Valencia, V. Learning of nature: the curious case of the naked mole rat. *Mech. Ageing Dev.* **164**, 76–81 (2017).
98. Skulachev, V. P. *et al.* Neoteny, prolongation of youth: from naked mole rats to "naked apes" (humans). *Physiol. Rev.* **97**, 699–720 (2017).
99. Comfort, A. *The biology of senescence*. 3rd edn (Elsevier, 1979).
100. Tian, X. *et al.* High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. *Nature* **499**, 346–349 (2013).
101. Itoh, K., Ye, P., Matsumiya, T., Tanji, K., & Ozaki, T. Emerging functional cross-talk between the Keap1–Nrf2 system and mitochondria. *J. Clin. Biochem. Nutr.* 56, 91–97 (2015).
102. Lewis, K. N., Mele, J., Hayes, J. D., & Buffenstein, R. Nrf2, a guardian of healthspan and gatekeeper of species longevity. *Integr. Comp. Biol.* 50, 829–843 (2010).
103. Lewis, K. N. *et al.* Regulation of Nrf2 signaling and longevity in naturally long-lived rodents. *Proc. Natl Acad. Sci. USA* **112**, 3722–3727 (2015).
104. Pomatto, L. C. D., Tower, J. & Davies, K. J. A. Sexual dimorphism and aging differentially regulate adaptive homeostasis. *J. Gerontol. A Biol. Sci. Med. Sci.* http://dx.doi.org/10.1093/gerona/glx083 (2017).
105. Kubben, N. *et al.* Repression of the antioxidant Nrf2 pathway in premature aging. *Cell* **165**, 1361–1374 (2016).
106. Kubben, N. & Misteli, T. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. *Nat. Rev. Mol. Cell Biol.* **18**, 595–609 (2017).
107. Chopra, A. & Lineweaver, C. H. in *Proceedings of the 8th Australian Space Science Conference*. 1st edn (eds Short, W. & Cairns, I.) 49–55 (National Space Society of Australia Ltd, 2008).
108. Ohno, S. The reason for as well as the consequence of the cambrian explosion in animal evolution. *J. Mol. Evol.* **44**, S23–S27 (1997).
109. Bowen, H. J. M. *Environmental Chemistry of the Elements*. (Academic Press, 1979).
110. Benner, S. A., Ellington, A. D. & Tauer, A. Modern metabolism as a palimpsest of the RNA world. *Proc. Natl Acad. Sci. USA* **86**, 7054–7058 (1989).

111. Blair-West, J. R. *et al.* Behavioral and tissue responses to severe phosphorus depletion in cattle. *Am. J. Physiol.* **263**, R656–R663 (1992).
112. Hu, M. C., Shiizaki, K., Kuro-o M. & Moe, O. W. Fibroblast growth factor 23 and klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. *Annu. Rev. Physiol.* **75**, 503–533 (2013).
113. Swapna, M. *Applied Mineralogy: Applications in Industry and Environment*. (Springer, 2011).
114. Lenton, S., Nylander, T., Teixeira, S. C. & Holt, C. A review of the biology of calcium phosphate sequestration with special reference to milk. *Dairy Sci. Technol.* **95**, 3–14 (2015).
115. Kuro-o, M., Matsumura, Y. *et al.* Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* **390**, 45–51 (1997).
116. Kuro-o, M. The FGF23 and Klotho system beyond mineral metabolism. *Clin. Exp. Nephrol.* **21**, 64–69 (2017).
117. Maltese, G. *et al.* The anti-ageing hormone klotho induces Nrf2-mediated antioxidant defences in human aortic smooth muscle cells. *J. Cell. Mol. Med.* **21**, 621–627 (2017).
118. Beck, G. R., Moran, E. & Knecht, N. Inorganic phosphate regulates multiple genes during osteoblast differentiation, including Nrf2. *Exp. Cell Res.* **288**, 288–300 (2003).
119. Shanahan, C. M. Mechanisms of vascular calcification in CKD — evidence for premature ageing? *Nat. Rev. Nephrol.* **9**, 661–670 (2013).
120. Stenvinkel, P. *et al.* CDKN2A/p16INK4a expression is associated with vascular progeria in chronic kidney disease. *Aging* **9**, 494–507 (2017).
121. Troyano, N. *et al.* Hyperphosphatemia induces cellular senescence in human aorta smooth muscle cells through integrin linked kinase (ILK) up-regulation. *Mech. Ageing Dev.* **152**, 43–55 (2015).
122. Di Marco, G. S. *et al.* Increased inorganic phosphate induces human endothelial cell apoptosis *in vitro*. *Am. J. Physiol. Renal Physiol.* **294**, F1381–F1387 (2008).
123. Jono, S. *et al.* Phosphate regulation of vascular smooth muscle cell calcification. *Circ. Res.* **87**, E10–E17 (2000).
124. Sage, A. P., Lu, J., Tintut, Y. & Demer, L. L. Hyperphosphatemia-induced nanocrystals upregulate the expression of bone morphogenetic protein-2 and osteopontin genes in mouse smooth muscle cells *in vitro*. *Kidney Int.* **79**, 414–422 (2011).
125. Villa-Bellosta, R. & Sorribas, V. Phosphonoformic acid prevents vascular smooth muscle cell calcification by inhibiting calcium-phosphate deposition. *Arterioscler. Thromb. Vasc. Biol.* **29**, 761–766 (2009).
126. Yamada, S. *et al.* Phosphate binders prevent phosphate-induced cellular senescence of vascular smooth muscle cells and vascular calcification in a modified, adenine-based uremic rat model. *Calcif. Tissue Int.* **96**, 347–358 (2015).
127. Jeyapalan, J. C. & Sedivy, J. M. Cellular senescence and organismal aging. *Mech. Ageing Dev.* **129**, 467–474 (2008).
128. Kuro-o, M. A potential link between phosphate and aging — lessons from Klotho-deficient mice. *Mech. Ageing Dev.* **131**, 270–275 (2010).
129. Merideth, M. A. *et al.* Phenotype and course of Hutchinson-Gilford progeria syndrome. *N. Engl. J. Med.* **358**, 592–604 (2008).
130. Villa-Bellosta, R. *et al.* Defective extracellular pyrophosphate metabolism promotes vascular calcification in a mouse model of Hutchinson-Gilford progeria syndrome that is ameliorated on pyrophosphate treatment. *Circulation* **127**, 2442–2451 (2013).
131. Chang, A. R., Lazo, M., Appel, L. J., Gutierrez, O. M. & Grams, M. E. High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. *Am. J. Clin. Nutr.* **99**, 320–327 (2014).
132. Hamano, T. *et al.* Fetuin-mineral complex reflects extraosseous calcification stress in CKD. *J. Am. Soc. Nephrol.* **21**, 1998–2007 (2010).
133. Smith, E. R., Ford, M. L., Tomlinson, L. A., Rajkumar, C., McMahon, L. P., & Holt, S. G. Phosphorylated fetuin-A-containing calciprotein particles are associated with aortic stiffness and a procalcific milieu in patients with pre-dialysis CKD. *Nephrol. Dial. Transplant.* **27**, 1957–1966 (2012).
134. Smith, E. R., Hanssen, E., McMahon, L. P. & Holt, S. G. Fetuin-A-containing calciprotein particles reduce mineral stress in the macrophage. *PLOS One* **8**, e60904 (2013).
135. Smith, E. R. *et al.* Serum calcification propensity predicts all-cause mortality in predialysis CKD. *J. Am. Soc. Nephrol.* **25**, 339–348 (2014).
136. Teare, J. A. *ISIS Reference Ranges for Physiological Values in Captive Wildlife (Electronic Resource)*. (International Species Information System, 2002).
137. Moe, S. M. *et al.* KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). *Kidney Int. Suppl.* **113**, S1–S130 (2009).
138. Fouque, D., Horne, R., Cozzolino, M. & Kalantar-Zadeh, K. Balancing nutrition and serum phosphorus in maintenance dialysis. *Am. J. Kidney Dis.* **64**, 143–150 (2014).
139. Peter, W. L. S., Wazny, L. D., Weinhandl, E., Cardone, K. E. & Hudson, J. Q. A. Review of phosphate binders in chronic kidney fisease: incremental progress or just higher costs? *Drugs* **14**, 329–345 (2016).
140. Kawai, M., Kinoshita, S., Ozono, K. & Michigami, T. Inorganic phosphate activates the AKT/mTORC1 pathway and shortens the life span of an α-Klotho-deficient model. *J. Am. Soc. Nephrol.* **27**, 2810–2824 (2016).
141. ter Braake, A. D., Shanahan, C. M. & de Baaij, J. H. F. Magnesium counteracts vascular calcification: passive interference or active modulation? *Arterioscler. Thromb. Vasc. Biol.* **37**, 1431–1445 (2017).
142. Miller, M. *et al.* Changes in serum calcium, phosphorus, and magnesium levels in captive ruminants affected by diet manipulation. *J. Zoo Wildl. Med.* **41**, 404–408 (2010).
143. Koh, G. Y. & Rowling, M. J. Resistant starch as a novel dietary strategy to maintain kidney health in diabetes mellitus. *Nutr. Rev.* **75**, 350–360 (2017).
144. Bilinski, T., Paszkiewicz, T. & Zadrag-Ecza, R. Energy excess is the main cause of accelerated aging of mammals. *Oncotarget* **6**, 12090–12919 (2016).
145. Stenvinkel, P., Kooman, J. P. & Shiels, P. G. Nutrients and ageing: what can we learn about ageing interactions from animal biology? *Curr. Opin. Clin. Nutr. Metab. Care* **19**, 19–25 (2016).
146. Mattison, J. A. *et al.* Caloric restriction improves health and survival of rhesus monkeys. *Nat. Commun.* **8**, 14603 (2017).
147. Lanaspa, M. A. *et al.* Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J. Biol. Chem.* **287**, 40732–40744 (2012).
148. Sanchez-Lozada, L. G. *et al.* Uric Acid-Induced Endothelial Dysfunction Is Associated with Mitochondrial Alterations and Decreased Intracellular ATP Concentrations. *Nephron. Exp. Nephrol.* **121**, e71–e78 (2012).
149. Johnson, R. J. The Fat Switch. (Mercola.com, 2012).
150. Dolinsky, V. W. *et al.* Improvements in skeletal muscle strength and cardiac function induced by resveratrol during exercise training contribute to enhanced exercise performance in rats. *J. Physiol.* **590**, 2783–2799 (2012).
151. Hall, J. A., Dominy, J. E., Lee, Y. & Puigserver, P. The sirtuin family's role in aging and age-associated pathologies. *J. Clin. Invest.* **123**, 973–979 (2013).
152. Narkar, V. A. *et al.* AMPK and PPARδ agonists are exercise mimetics. *Cell* **134**, 405–415 (2008).
153. Cantó, C. & Auwerx, J. Caloric restriction, SIRT1 and longevity. *Trends Endocrinol. Metab.* **20**, 325–331 (2009).
154. Kulkarni, S. R., Armstrong, L. E. & Slitt, A. Caloric restriction-mediated induction of lipid metabolism gene expression in liver is enhanced by Keap1-knockdown. *Pharm. Res.* **30**, 2221–2231 (2013).
155. Sanchez-Roman, I. & Barja, G. Regulation of longevity and oxidative stress by nutritional interventions: role of methionine restriction. *Exp. Gerontol.* **48**, 1030–1042 (2013).
156. Yang, G. *et al.* Hydrogen sulfide protects against cellular senescence via S-sulfhydration of Keap1 and activation of Nrf2. *Antioxid. Redox Signal* **18**, 1906–1919 (2013).
157. Hine, C. *et al.* Endogenous hydrogen sulfide production is essential for dietary restriction benefits. *Cell* **160**, 132–144 (2015).
158. Pietri, R., Román-Morales, E. & López-Garriga, J. Hydrogen sulfide and hemeproteins: knowledge and mysteries. *Antioxid. Redox Signal* **15**, 393–404 (2011).
159. Wallace, J. L. & Wang, R. Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. *Nat. Rev. Drug Discov.* **14**, 329–345 (2015).
160. McIsaac, R. S., Lewis, K. N., Gibney, P. A. & Buffenstein, R. From yeast to human: exploring the comparative biology of methionine restriction in extending eukaryotic life span. *Ann. NY Acad. Sci.* **1363**, 155–170 (2016).
161. Dziegelewska, M. *et al.* Low sulfide levels and a high degree of cystathionine β-synthase (CBS) activation by S-adenosylmethionine (SAM) in the long-lived naked mole-rat. *Redox Biol.* **8**, 192–198 (2016).
162. Pamplona, R. & Barja, G. Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine conenction. *Biochim. et Biophys. Acta* **1757**, 496–508 (2006).
163. Valli, A. *et al.* Elevated serum levels of S-adenosylhomocysteine, but not homocysteine, are associated with cardiovascular disease in stage 5 chronic kidney disease patients. *Clin. Chim. Acta* **395**, 106–110 (2008).
164. Suliman, M. E., Filho, J. C., Bárány, P., Lindholm, B. & Bergström, J. Effects of methionine loading on plasma and erythrocyte sulphur amino acids and sulph-hydryls before and after co-factor supplementation in haemodialysis patients. *Nephrol. Dial Transplant* **16**, 102–110 (2001).
165. Brown-Borg, H. M. & Buffenstein, R. Cutting back on the essentials: can manipulating intake of specific amino acids modulate health and lifespan? *Aging Res. Rev.* **39**, 87–95 (2017).
166. Weber, G. J., Pushpakumar, S. B. & Sen, U. Hydrogen sulfide alleviates hypertensive kidney dysfunction through an epigenetic mechanism. *Am. J. Physiol. Heart Circ. Physiol.* **312**, H874–H885 (2017).
167. Cooney, C. A. Are somatic cells inherently deficient in methylation metabolism? A proposed mechanism for DNA methylation loss, senescence and aging. *Growth Dev. Aging* **57**, 261–273 (1993).
168. Park, T. J. *et al.* Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. *Science* **356**, 307–311 (2017).
169. Pfeiffer, C. J. Renal cellular and tissue specializations in the bottlenose dolphin (*Tursiops truncatus*) and the beluga whale (*Delphinapteras leucas*). *Aquatic Mammals* **23**, 75–84 (1997).
170. Andrews, M. T., Russeth, K. P., Drewes, L. R. & Henry, P. G. Adaptive mechanisms regulate preferred utilization of ketones in the heart and brain of a hibernating mammal during arousal from torpor. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **296**, R383–393 (2009).
171. Jani, A. *et al.* Renal protection from prolonged cold ischemia and warm reperfusion in hibernating squirrels. *Transplantation* **92**, 1215–1221 (2011).
172. Vázquez-Medina, J. P. *et al.* Prolonged fasting activates Nrf2 in post-weaned elephant seals. *J. Exp. Biol.* **216**, 2870–2878 (2013).
173. Vázquez-Medina, J. P., Zenteno-Savín, T., Elsner, R. & Ortiz, R. M. Coping with physiological oxidative stress: a review of antioxidant strategies in seals. *J. Comp. Physiol. B* **182**, 741–750 (2012).
174. Vázquez-Medina, J. P., Zenteno-Savín, T., Forman, H. J., Crocker, D. E. & Ortiz, R. M. Prolonged fasting increases glutathione biosynthesis in postweaned northern elephant seals. *J. Exp. Biol.* **214**, 1294–1299 (2011).
175. Nezu, M. *et al.* Transcription factor Nrf2 hyperactivation in early-phase renal ischemia-reperfusion injury prevents tubular damage progression. *Kidney Int.* **91**, 387–401 (2017).
176. Cirillo, P. *et al.* Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. *J. Am. Soc. Nephrol.* **20**, 545–553 (2009).
177. Nigro, D. *et al.* Chronic administration of saturated fats and fructose differently affect SREBP activity resulting in different modulation of Nrf2 and Nlrp3 inflammasome pathways in mice liver. *J. Nutr. Biochem.* **42**, 160–171 (2017).
178. Perez-Pinzon, M. A. Mechanisms of neuroprotection during ischemic preconditioning: lessons from anoxic tolerance. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **147**, 291–299 (2007).
179. Geiser, F. & Ruf, T. Hibernation versus daily torpor in mammals and birds: physiological variables and classification of torpor patterns. *Physiol. Zool.* **68**, 935–966 (1995).
180. Turbill, C., Ruf, T., Mang, T. & Arnold, W. Regulation of heart rate and rumen temperature in red deer: effects of season and food intake. *J. Exp. Biol.* **214**, 963–970 (2011).

181. Signer, C., Ruf, T. & Arnold, W. Hypometabolism and basking: the strategies of alpine ibex to endure harsh over-wintering conditions. *Funct. Ecol.* **25**, 537–547 (2011).
182. Arnold, W. *et al.* Nocturnal hypometabolism as an overwintering strategy of red deer (*Cervus elaphus*). *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **286**, R174–R181 (2004).
183. Arnold, W. in *Life in the Cold: Ecological, Physiological, and Molecular Mechanisms*. (eds Carey, C., Florant, G. L., Wunder, B. A. & Horwitz, B.) 65–80. (Westview Press, 1993).
184. Parker, K. L., Barboza, P. S. & Gillingham, M. P. Nutrition integrates environmental responses of ungulates. *Funct. Ecol.* **23**, 57–69 (2009).
185. Arnold, W. *et al.* Contrary seasonal changes of rates of nutrient uptake, organ mass, and voluntary food intake in red deer (*Cervus elaphus*). *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **309**, R277–R285 (2015).
186. Loudon, A. S. I. Photoperiod and the regulation of annual and circannual cycles of food intake. *Proc. Nutr. Soc.* **53**, 495–507 (1994).
187. Hume, D. *et al.* Seasonal changes in morphology and function of the gastrointestinal tract of free-living alpine marmots (*Marmota marmota*). *J. Comp. Physiol. B* **172**, 197–207 (2002).
188. Rigano, K. S. *et al.* Life in the fat lane: seasonal regulation of insulin sensitivity, food intake, and adipose biology in brown bears. *J. Comp. Physiol. B* **187**, 649–676 (2017).
189. Sommer, F. *et al.* The gut microbiota modulates energy metabolism in the hibernating brown bear *Ursus arctos*. *Cell Rep.* **14**, 1655–1661 (2016).
190. Toien, O. *et al.* Hibernation in black bears: independence of metabolic suppression from body temperature. *Science* **331**, 906–909 (2011).
191. Arnold, W., Ruf, T., Frey-Roos, F. & Bruns, U. Diet-independent remodeling of cellular membranes precedes seasonally changing body temperature in a hibernator. *PLOS One* **6**, e18641 (2011).
192. Arnold, W., Giroud, S., Valencak, T. G. & Ruf, T. Ecophysiology of omega fatty acids: a lid for every jar. *Physiology* **30**, 232–240 (2015).
193. Helge, J. W. *et al.* Training affects muscle phospholipid fatty acid composition in humans. *J. Appl. Physiol.* **90**, 670–677 (2001).
194. Mitchell, T. W., Buffenstein, R. & Hulbert, A. J. Membrane phospholipid composition may contribute to exceptional longevity of the naked mole-rat (*Heterocephalus glaber*): a comparative study using shotgun lipidomics. *Exp. Gerontol.* **42**, 1053–1062 (2007).
195. Giroud, S. *et al.* Membrane phospholipid fatty acid composition regulates cardiac SERCA activity in a hibernator, the Syrian hamster (*Mesocricetus auratus*). *PLOS One* **8**, e63111 (2013).
196. Arnold, W., Ruf, T. & Kuntz, R. Seasonal adjustment of energy budget in a large wild mammal, the Przewalski horse (Equus ferus przewalskii) II. Energy expenditure. *J. Exp. Biol.* **209**, 4566–4573 (2006).
197. Maillet, D. & Weber, J. M. Relationship between n-3 PUFA content and energy metabolism in the flight muscles of a migrating shorebird: evidence for natural doping. *J. Exp. Biol.* **210**, 413–420 (2007).
198. Hulbert, A. J., Kelly, M. A. & Abbott, S. K. Polyunsaturated fats, membrane lipids and animal longevity. *J. Comp. Physiol. B* 184, 149–166 (2014).
199. Chen, D. Q. *et al.* The link between phenotype and fatty acid metabolism in advanced chronic kidney disease. *Nephrol. Dial Transplant.* **32**, 1154–1166 (2017).
200. Gao, L. *et al.* Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3. *J. Biol. Chem.* **282**, 2529–2537 (2007).
201. Andersen, J. B., Rourke, B. C., Caiozzo, V. J., Bennett, A. F. & Hicks, J. W. Postprandial cardiac hypertrophy in pythons. *Nature* **434**, 37 (2005).
202. Riquelme, C. A. *et al.* Fatty acids identified in the Burmese python promote beneficial cardiac growth. *Science* **334**, 528–531 (2011).
203. Hall, J. C. & Rosbash, M. Oscillating molecules and how they move corcadian clocks across evolutionary boundaries. *Proc. Natl Acad. Sci. USA* **90**, 5382–5383 (1993).
204. Turek, F. W. *et al.* Obesity and metabolic syndrome in circadian clock mutant mice. *Science* **308**, 1043–1045 (2005).
205. Pekovic-Vaughan, V. *et al.* The circadian clock regulates rhythmic activation of the NRF2/glutathione-mediated antioxidant defense pathway to modulate pulmonary fibrosis. *Genes Dev.* **28**, 548–560 (2014).
206. Gumz, M. L. Molecular basis of circadian rhythmicity in renal physiology and pathophysiology. *Exp. Physiol.* **101**, 1025–1029 (2016).
207. Smolensky, M. H., Hermida, R. C., Reinberg, A., Sackett-Lundeen, L. & Portaluppi, F. Circadian disruption: new clinical perspective of disease pathology and basis for chronotherapeutic intervention. *Chronobiol. Int.* **33**, 1101–1119 (2016).
208. Obi, Y. *et al.* Seasonal variations in transition, mortality and kidney transplantation among patients with end-stage renal disease in the USA. *Nephrol. Dial. Transplant.* **32**, 907 (2017).
209. Evans, A. L. *et al.* Drivers of hibernation in the brown bear. *Front. Zool.* **13**, 7 (2016).
210. Arinell, K. *et al.* Brown bears (*Ursus arctos*) seem resistant to atherosclerosis despite highly elevated plasma lipids during hibernation and active state. *Clin. Transl Sci.* **5**, 269–272 (2012).
211. Iles, T. L., Laske, T. G., Garschelis, D. L. & Iaizzo, P. A. Blood clotting behavior is innately modulated in *Ursus americanus* during early and late denning relative to summer months. *J. Exp. Biol.* **220**, 455–459 (2017).
212. Brown, D. C., Mulhausen, R. O., Andrew, D. J. & Seal, U. S. Renal function in anesthetized dormant and active bears. *Am. J. Physiol.* **220**, 293–298 (1971).
213. Prunescu, C., Serban-Parau, N., Brock, J. H., Vaughan, D. M. & Prunescu, P. Liver and kidney structure and iron content in romanian brown bears (*Ursus arctos*) before and after hibernation. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **134**, 21–26 (2003).
214. Ortiz, R. M. Osmoregulation in marine mammals. *J. Exp. Biol.* **204**, 1831–1844 (2001).
215. Dugbartey, G. J. *et al.* Renal mitochondrial response to low temperature in non-hibernating and hibernating species. *Antioxid. Redox Signal* **27**, 599–617 (2017).
216. Walford, R. L. & Spindler, S. R. The response to caloric restriction in mammals shows features also common to hibernation: a cross-adaption hypothesis. *J. Gerontol. A Biol. Sci. Med. Sci.* **52**, B179–B183 (1997).
217. Turbilli, C., Bieber, C. & Ruf, T. Hibernation is associated with increased survival and the evolution of slow life histories among mammals. *Proc. R. Soc.* **278**, 3355–3363 (2011).
218. Storey, K. B. & Storey, J. M. Metabolic rate depression and biochemical adaptation in anaerobiosis, hibernation and estivation. *Quarterly Rev. Biol.* **65**, 145–174 (1990).
219. Blackstone, E., Morrison, M. & Roth, M. B. H2S induces a suspended animation-like state in mice. *Science* **308**, 518 (2005).
220. Blackstone, E. & Roth, M. B. Suspended animation-like state protects mice from lethal hypoxia. *Shock* **27**, 370–372 (2007).
221. Shimada, S. *et al.* Hydrogen sulfide augments survival signals in warm ischemia and reperfusion of the mouse liver. *Surg. Today* **45**, 892–903 (2015).
222. Xu, R. *et al.* Hibernating squirrel muscle activates the endurance exercise pathway despite prolonged immobilization. *Exp. Neurol.* **247**, 392–401 (2013).
223. Dugbartey, G. J., Bouma, H. R., Strijkstra, A. M., Boerema, A. S. & Henning, R. H. Induction of a torpor-like state by 5′-AMP does not depend on H2S production. *PLOS One* **21**, e01366113 (2015).
224. Huang, L. *et al.* The AMPK agonist PT1 and mTOR Inhibitor 3HOI-BA-01 protect cardiomyocytes after ischemia through induction of autophagy. *J. Cardiovasc. Pharmacol. Ther.* **21**, 70–81 (2016).
225. Ratigan, E. D. & McKay, D. B. Exploring principles of hibernation for organ preservation. *Transpl. Rewiews* **30**, 13–19 (2016).
226. Harlow, H. J., Lohuis, T., Beck, T. D. I. & Iaizzo, P. A. Muscle strength in overwintering bears. *Nature* **409**, 997 (2001).
227. Nelson, R., Wahner, H. W., Jones, J. D., Ellefson, R. D. & Zollman, P. E. Metabolism of bears before, during, and after winter sleep. *Am. J. Physiol.* **224**, 491–496 (1973).
228. Lin, D. C., Hershey, J. D., Mattoon, J. S. & Robbins, C. T. Skeletal muscles of hibernating brown bears are unusually resistant to effects of denervation. *J. Exp. Biol.* **215**, 2081–2087 (2012).
229. Fuster, G., Busquets, S., Almendro, V., Lopez-Soriano, F. J. & Argilés, J.M. Antiproteolytic effects of plasma from hibernating bears: a new approach for muscle wasting therapy? *Clin. Nutr.* **26**, 658–661 (2007).
230. Andres-Mateos, E. *et al.* Activation of serum/glucocorticoid-induced kinase 1 (SGK1) is important to maintain skeletal muscle homeostasis and prevent atrophy. *EMBO Mol. Med.* **5**, 80–91 (2013).
231. Ivakine, E. A. & Cohn, R. D. Maintaining skeletal muscle mass: lessons learned from hibernation. *Exp. Physiol.* **99**, 632–637 (2014).
232. Luo, J. *et al.* Serum glucocorticoid-regulated kinase 1 blocks CKD-Induced muscle wasting via inactivation of FoxO3a and Smad2/3. *J. Am. Soc. Nephrol.* **27**, 2797–2808 (2016).
233. Chung, N., Park, J. & Lim, K. The effects of exercise and cold exposure on mitochondrial biogenesis in skeletal muscle and white adipose tissue. *J. Exerc. Nutr. Biochem.* **21**, 39–47 (2017).
234. Tran, M. T. *et al.* PGC1α drives NAD biosynthesis linking oxidative metabolism to renal protection. *Nature* **531**, 528–532 (2016).
235. Gidlund, E. K. *et al.* Rapidly elevated levels of PGC-1α-b protein in human skeletal muscle after exercise: exploring regulatory factors in a randomized controlled trial. *J. Appl. Physiol.* **119**, 374–384 (2015).
236. Oh, S. *et al.* Nuclear factor (erythroid derived 2)-like 2 activation increases exercise endurance capacity via redox modulation in skeletal muscles. *Sci. Rep.* **7**, 12902 (2017).
237. McGee Lawrence, M. E. *et al.* Six months of disuse during hibernation does not increase intracortical porosity or decrease cortical bone geometry, strength or mineralization in black bears (*Ursus americanus*) femurs. *J. Biomech.* **42**, 1378–1383 (2009).
238. McGee-Lawrence, M. *et al.* Suppressed bone remodeling in black bears conserves energy and bone mass during hibernation. *J. Exp. Biol.* **218**, 2067–2074 (2015).
239. Fedorov, V. B. *et al.* Preservation of bone mass and structure in hibernating black bears (*Ursus americanus*) through elevated expression of analoic genes. *Funct. Integr. Genom.* **12**, 357–365 (2012).
240. Seger, R. *et al.* Investigating the mechanisms for maintaing eucalcemia despite immobility and anuria in the hibernating American black bear (*Ursus americanus*). *Bone* **49**, 1205–1212 (2011).
241. Donahue, S. W. *et al.* Parathyroid hormone may maintain bone formation in hibernating black bears (*Ursus americanus*) to prevent disuse osteoporosis. *J. Exp. Biol.* **209**, 1630–1638 (2006).
242. Gray, S. K. *et al.* Black bear parathyroid hormone has greater anabolic effects on trabecular bone in dystrophin-deficient mice than in wild type mice. *Bone* **51**, 578–585 (2012).
243. Ibánez, L. *et al.* Effects of Nrf2 deficiency on bone microarchitecture in an experimental model of osteoporosis. *Oxid. Med. Cell. Longev.* **2014**, 726590 (2014).
244. Thummuri, D., Naidu, V. G. M. & Chaudhari, P. Carnosic acid attenuates RANKL-induced oxidative stress and osteoclastogenesis via induction of Nrf2 and suppression of NF-κB and MAPK signalling. *J. Mol. Med.* **95**, 1065–1076 (2017).
245. Ni, Z. & Storey, K. B. Heme oxygenase expression and Nrf2 signaling during hibernation in ground squirrels. *Can. J. Physiol. Pharmacol.* **88**, 379–387 (2010).
246. Iaizzo, P. A., Laske, T. G., Harlow, H. J., McClay, C. B. & Garshelis, D. L. Wound healing during hibernation by black bears (*Ursus americanus*) in the wild: elicitation of reduced scar formation. *Integr. Zool.* **7**, 48–60 (2012).
247. Barboza, P. S., Farley, S. D. & Robbins, C. T. Whole-body urea cycling and protein turnover during hyperphagia and dormancy in growing bears (*Ursus americanus* and *U. arctos*). *Canadian J. Zoology* **75**, 2129–2136 (1997).
248. Nelson, R. A., Jones, J. D., Wahner, H. W., McGill, D. B. & Code, C. F. Nitrogen metabolism in bears: urea metabolism in summer starvation and in winter sleep and role of urinary bladder in water and nitrogen conservation. *Mayo Clin. Proc.* **50**, 141–146 (1975).
249. Spector, D. A., Deng, J., Coleman, R. & Wade, J. B. The urothelium of a hibernator: the American black bear. *Physiol. Rep.* **3**, e12429 (2015).
250. Walser, M. Urea metabolism in chronic renal failure. *J. Am. Soc. Nephrol.* **9**, 1544–1551 (1998).
251. Ahlquist, D. A., Nelson, R. A., Steiger, D. L., Jones, J. D. & Ellefson, R. D. Glycerol metabolism in the hibernating black bear. *J. Comp. Physiol.* **155**, 75–79 (1984).
252. Nelson, R. A., Beck, T. D. I. & Steiger, D. L. Ratio of serum urea to serum creatinine in wild black bears. *Science* **226**, 841–842 (1984).

253. Nakagawa, T., Lomb, D. J., Haigis, M. C. & Guarente, L. SIRT5 Deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle. *Cell* **137**, 560–570 (2009).
254. Van Tighem, K. Food and Diet. *The Get Bear Smart Society* http://www.bearsmart.com/about-bears/food-diet/.
255. Carlson, S. M. Synchronous timing of food resources triggers bears to switch from salmon to berries. *Proc. Natl Acad. Sci. USA* **114**, 10309–10311 (2017).
256. Lattanzio, V., Lattanzio, V. M. T. & Cardinali, A. in *Phytochemistry: Advances in Research*. (ed Imperato, F.) 23–67 (Research Signpost, 2006).
257. Overall, J. *et al.* Metabolic effects of berries with structurally diverse anthocyanins. *Int. J. Mol. Sci.* **15**, E422 (2017).
258. Durbin, S. M. *et al.* Resveratrol supplementation preserves long bone mass, microstructure, and strength in hindlimb-suspended old male rats. *J. Bone Miner. Metab.* **32**, 38–47 (2014).
259. Lee, S. G. *et al.* Relationship between oxidative stress and bone mass in obesity and effects of berry supplementation on bone remodeling in obese male mice: an exploratory study. *J. Med. Food* **18**, 476–482 (2015).
260. Moriwaki, S. *et al.* Delphinidin, one of the major anthocyanidins, prevents bone loss through the inhibition of excessive osteoclastogenesis in osteoporosis model mice. *PLOS One* **13**, e97177 (2014).
261. Murata, M. *et al.* Delphinidin prevents muscle atrophy and upregulates miR-23a expression. *J. Agr. Food Chem.* **65**, 45–50 (2017).
262. Alvarado, J. L. *et al.* Delphinidin-rich maqui berry extract (Delphinol®) lowers fasting and postprandial glycemia and insulinemia in prediabetic individuals during oral glucose tolerance Tests. *Biomed. Res. Int.* **2016**, 9070537 (2016).
263. Ali, B. H. *et al.* Effect of aqueous extract and anthocyanins of calyces of *Hibiscus sabdariffa* (Malvaceae) in rats with adenine-induced chronic kidney disease. *J. Pharm. Pharmacol.* **69**, 1219–1229 (2017).
264. Farr, J. N. *et al.* Targeting cellular senescence prevents age-related bone loss in mice. *Nat. Med.* **23**, 1072–1079 (2017).
265. Zhu, Y. *et al.* The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell* **14**, 644–659 (2015).
266. Chang, X. Y. *et al.* Quercetin attenuates vascular calcification through suppressed oxidative stress in adenine-induced chronic renal failure rats. *Biomed. Res. Int.* **2017**, 5716204 (2017).
267. Momken, I. *et al.* Resveratrol prevents the wasting disorders of mechanical unloading by acting as a physical exercise mimetic in the rat. *FASEB J.* **10**, 3646–3660 (2011).
268. Cheng, K. H. *et al.* Resveratrol ameliorates metabolic disorders and muscle wasting in streptozotocin-induced diabetic rats. *Am. J. Physiol. Endocrinol. Metab.* **301**, E853–E863 (2011).
269. Sen, C. K., Khanna, S., Gordillo, G., Bagchi, D., Bagchi, M. & Roy, S. Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. *Ann. NY Acad. Sci.* **957**, 239–249 (2002).
270. Basu, A. *et al.* Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. *J. Nutr.* **140**, 1582–1587 (2010).
271. Erlund, I. *et al.* Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. *Am. J. Clin. Nutr.* **87**, 323–331 (2008).
272. Stull, A. J., Cash, K. C., Johnson, W. D., Champagne, C. M. & Cefalu, W. T. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. *J. Nutr.* **140**, 1764–1768 (2010).
273. Cassidy, A. *et al.* High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation* **127**, 188–196 (2013).
274. Wang, X., Rybczynski, N., Harington, C.R., White, S.C. & Tedford, R.H. A basal ursine bear (*Protarctos abstrusus*) from the pliocene high arctic reveals eurasian affinities and a diet rich in fermentable sugars. *Sci. Rep.* **7**, 17722 (2017).
275. Reiter, R. J. *et al.* Melatonin in edible plants (phytomelatonin): identification, concentrations, bioavailability and proposed functions. *World Rev. Nutr. Diet* **97**, 211–230 (2007).
276. Pedruzzi, L. M. *et al.* Systemic inflammation and oxidative stress in hemodialysis patients are associated with down-regulation of Nrf2. *J. Nephrol.* **28**, 495–501 (2015).
277. Himmelfarb, J., Stenvinkel, P., Ikizler, T. A. & Hakim, R. M. The elephant of uremia: oxidative stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int.* **62**, 1524–1538 (2002).
278. Noel, S., Hamad, A. R. & Rabb, H. Reviving the promise of transcription factor Nrf2-based therapeutics for kidney diseases. *Kidney Int.* **88**, 1217–1218 (2015).
279. Axelsson, A. S. *et al.* Sulforaphane reduces hepatic glucose production and improves glucose control in patients with type 2 diabetes. *Sci. Transl. Med.* **9**, eeah4477 (2017).
280. Sun, W. *et al.* Pomegranate extract decreases oxidative stress and alleviates mitochondrial impairment by activating AMPK-Nrf2 in hypothalamic paraventricular nucleus of spontaneously hypertensive rats. *Sci. Rep.* **6**, 34246 (2016).
281. Ali, B. H. *et al.* Curcumin ameliorates kidney function and oxidative stress in experimental chronic kidney disease. *Bas. Clin. Pharmacol. Toxicol.* **122**, 65–73 (2018).
282. Han, C. W. *et al.* Ethanol extract of *Alismatis Rhizoma* reduces acute lung inflammation by suppressing NF-κB and activating Nrf2. *J. Ethnopharmacol* **146**, 402–410 (2013).
283. Wondrak, G. T. *et al.* The cinnamon-derived dietary factor cinnamic aldehyde activates the Nrf2-dependent antioxidant response in human epithelial colon cells. *Molecules* **15**, 3338–3355 (2010).
284. Esgalhado, M., Stenvinkel, P. & Mafra, D. Nonpharmacologic strategies to modulate nuclear factor eryhroid 2-related factor 2 pathway in chronic kidney disease. *J. Ren. Nutr.* **27**, 282–291 (2017).
285. Kwon, J. S. *et al.* Sulforaphane inhibits restenosis by suppressing inflammation and the proliferation of vascular smooth muscle cells. *Atherosclerosis* **225**, 41–49 (2012).
286. Juurlink, B. H. Dietary Nrf2 activators inhibit atherogenic processes. *Atherosclerosis* **225**, 29–33 (2012).
287. Pomatto, L. C. D. *et al.* The age- and sex-specific decline of the 20s proteasome and the Nrf2/CncC signal transduction pathway in adaption and resistance to oxidative stress in *Drosophila melanogaster*. *Aging* **9**, 1153–1185 (2017).
288. de Zeeuw, D. *et al.* Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N. Engl. J. Med.* **369**, 2492–2503 (2013).
289. O'Mealey, G. B. *et al.* PGAM5-KEAP1-Nrf2 complex is required for stress-induced mitochondrial retrograde trafficking. *J. Cell Sci.* **130**, 3467–3480 (2017).
290. Vaziri, N. D. *et al.* Dose-dependent deleterious and salutary actions of the Nrf2 inducer dh404 in chronic kidney disease. *Free Radic. Biol. Med.* **86**, 374–381 (2015).
291. Tebay, L. E. *et al.* Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease. *Free Radic. Biol. Med.* **88**, 108–146 (2015).

Acknowledgements
The authors thank the Scandinavian Brown Bear Project (in particular, O. Fröbert, J. E. Swenson, S. Brunberg, J. M. Arnemo and A. Zedrosser). P.S.'s research benefits from support from the Swedish Medical Research Council, the Heart and Lung Foundation, Njurfonden and EU-funded INTRICARE projects. R.J.J. and M.L. benefit from research support from the Veterans Administration (BX002586), Department of Defense (PR130106), US National Institutes of Health (NIH) (DK108859 and DK109408), La Isla Foundation, Solidaridad and the Danone Research Foundation. M.K. is supported by the Japan Agency for Medical Research and Development (AMED) Core Research for Evolutionary Medical Science and Technology (CREST), AMED, and the Japan Society for the Promotion of Science (16H05302, 16K15470). W.A.'s research has benefited from the grant 'Polyunsaturated fatty acids and seasonal acclimatization' (30061-B25).

Author contributions
P.S. and R.J.J. launched the idea of studying renal biomimetics. P.S., J.P., M.K., M.L., W.A., T.R., P.G.S. and R.J.J. researched the literature, discussed the content of the article and wrote the text. All authors reviewed or edited the article before submission.

Competing interests statement
P.S. has received grants and honoraria from Baxter, Bayer, Astra Zeneca, Bristol-Myers Squibb, Pfizer, Akeiba and Corvidia. M.K. has received grants and honoraria from Bayer, Astellas, Bristol-Myers Squibb and Kissei Pharmaceuticals. R.J.J. has grants from the US National Institutes of Health (NIH), Department of Defense and the Veteran's Administration. He is also a member of Colorado Research Partners, LLC, which is developing inhibitors of fructose metabolism. The other authors declare no competing interests.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (figure) | S3 (table) | S4 (figure) | S5 (figure)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF