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Review

A potential link between phosphate and aging—Lessons from Klotho-deficient mice

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ABSTRACT

Phosphate homeostasis is maintained primarily by a bone–kidney endocrine axis. When phosphate is in excess, fibroblast growth factor-23 (FGF23) is secreted from bone and acts on kidney to promote phosphate excretion into urine. FGF23 also reduces serum vitamin D levels to suppress phosphate absorption from intestine. Thus, FGF23 functions as a hormone that induces negative phosphate balance. One critical feature of FGF23 is that it requires Klotho, a single-pass transmembrane protein expressed in renal tubules, as an obligate co-receptor to bind and activate cognate FGF receptors. Importantly, defects in either FGF23 or Klotho not only cause phosphate retention but also a premature-aging syndrome in mice, which can be rescued by resolving hyperphosphatemia. In addition, changes in extracellular and intracellular phosphate concentration affect glucose metabolism, insulin sensitivity, and oxidative stress *in vivo* and *in vitro*, which potentially affect aging processes. These findings suggest an unexpected link between inorganic phosphate and aging in mammals.

1. Introduction

Aging is one of the most potent risk factors for any age-related diseases, including cancer, cardiovascular disease, stroke, chronic kidney disease, and neurodegenerative disorders, which are leading causes of death and disability in aging society. Suppression of aging, if at all possible, would be the most effective way to prevent these diseases, reduce mortality, and improve quality of life. Aging processes can be accelerated or suppressed by various environmental factors. Diet restriction (a dietary regimen of 40–50% less food intake than the average diet) has been known to suppress aging and extend life span in diverse experimental organisms including nematodes, fruit flies, rodents, and non-human primates (Masoro, 2006). Thus, diet restriction very likely suppresses aging in humans as well. However, it is extremely difficult for anyone to reduce daily meals down to about one-half and continue this eating habit throughout life. The major challenge is to find a strategy for suppressing aging that is feasible in daily life. If one can identify a particular nutrient(s) responsible for the benefit of diet restriction, reducing intake of such nutrient(s) alone may be as effective as and more feasible than diet restriction. In addition, identification of such nutrient(s) is expected to provide new insights into the molecular mechanism of aging. As discussed below, recent animal studies and epidemiological studies have raised the possibility that phosphate may be one of such nutrients. The purpose of this review is to discuss potential link between aging and phosphate.

2. Endocrine regulation of phosphate metabolism

Serum mineral levels are maintained within narrow ranges. In humans, serum calcium and phosphate levels are normally 2.2–2.5 mM (8.8–10.2 mg/dL) and 0.81–1.45 mM (2.5–4.5 mg/dL), respectively (Ravel, 1994; Tonelli et al., 2005). Serum calcium and phosphate levels are determined by counterbalance between absorption from intestine, mobilization from bone (the major reservoir of calcium phosphate in the body), and excretion from kidney into urine (Berndt and Kumar, 2009; Schiavi and Kumar, 2004). These processes are coordinately regulated by several endocrine factors. Vitamin D and parathyroid hormone (PTH) have been extensively studied as hormones that regulate calcium and phosphate metabolism (Dusso et al., 2005). The active form of vitamin D (1,25-dihydroxyvitamin D_3) is synthesized in the kidney and acts on intestine to increase absorption of dietary calcium and phosphate. It also acts on bone to stimulate osteoclastogenesis and promote mobilization of calcium and phosphate from the reservoir, leading to increase in both calcium and phosphate levels in blood. PTH is secreted from parathyroid gland in response to low serum calcium levels and acts on kidney to promote vitamin D synthesis, thereby increasing intestinal absorption of calcium and phosphate. Unlike vitamin D, PTH has an activity that promotes phosphate excretion into urine (phosphaturia). Thus,

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PTH selectively increases blood calcium levels without concomitant increase in blood phosphate levels (Berndt and Kumar, 2007).

Recent studies have identified fibroblast growth factor-23 (FGF23) as a novel hormone that selectively lowers blood phosphate levels (Kuro-o, 2006; Quarles, 2003; White et al., 2000). When phosphate is in excess, FGF23 is secreted from bone and acts on kidney to induce phosphaturia and suppress vitamin D synthesis to induce a negative phosphate balance and maintain phosphate homeostasis (Liu et al., 2006, 2007; Quarles, 2003). FGF23 was originally identified as a gene mutated in patients with autosomal dominant hypophosphatemic rickets (ADHR), one of the rare hereditary disorders that exhibit renal phosphate wasting (White et al., 2000). Patients with ADHR carry missense mutations in the *FGF23* gene that confer resistance to proteolytic degradation of the FGF23 protein. Wild-type FGF23 protein is cleaved by an unknown protease at the ^{176}RXXR^{179} motif and inactivated (White et al., 2001). Missense mutations in this critical motif (R176Q, R179Q/W) make the protein resistant to the protease (Shimada et al., 2002). As a result, ADHR patients have high serum FGF23 levels and phosphate-wasting phenotypes including hypophosphatemia and defects in bone mineralization (rickets). In contrast, mice lacking FGF23 (*Fgf23*$^{-/-}$ mice) develop severe phosphate-retention phenotypes characterized by extensive soft tissue calcification and hyperphosphatemia (Shimada et al., 2004b). Furthermore, several mutations that affect expression and/or proteolytic degeneration of FGF23 have been identified in mice and humans, in which phosphate-wasting phenotypes or phosphate-retention phenotypes are associated with increased or decreased serum FGF23 levels, respectively (Kurosu and Kuro-o, 2009a; Quarles, 2008). These observations have established that FGF23 is a hormone indispensable for maintaining phosphate homeostasis.

3. Molecular basis of FGF23 action

Although FGF23 belongs to the FGF ligand superfamily (Yamashita et al., 2000), phylogenetic and sequence analyses have segregated FGF23 and two additional FGFs (FGF19 and FGF21) from the other FGF family members (Itoh and Ornitz, 2008). These three atypical FGFs, namely FGF19, FGF21, and FGF23, are also known as endocrine FGFs, because they function as endocrine factors unlike the other classical FGFs that primarily function as paracrine and/or autocrine factors (Kuro-o, 2008). The molecular basis behind the endocrine mode of action may lie in the fact that these endocrine FGFs have low affinity to heparan sulfate (HS). In general, FGF ligands have high affinity to heparin and HS, because they share a conserved HS-binding domain (Mohammadi et al., 2005a,b; Murzin et al., 1992). However, the HS-binding domain of endocrine FGFs deviates from that of the other paracrine-acting FGFs and prohibits formation of hydrogen bonding between HS and amino acid residues in the HS-binding domain, which is the basis of affinity to HS (Goetz et al., 2007; Harmer et al., 2004). This unique structural feature reduces affinity of endocrine FGFs to HS and allows them to escape from HS-rich extracellular matrices and enter systemic circulation. Although the low affinity to HS may help endocrine FGFs function as hormones, it may attenuate their ability to activate FGF receptors (FGFRs), because HS is required for high affinity binding of FGFs to FGFRs. FGFRs are receptor tyrosin kinases that dimerize upon binding FGFs. HS participates in the FGF–FGFR interaction and promotes formation of a 2:2:2 FGF–FGFR–HS signaling complex, which is essential for efficient activation of FGFR tyrosine kinase (Schlessinger et al., 2000). Thus, endocrine FGFs may require a co-factor(s) other than and/or in addition to HS to secure efficient dimerization and activation of FGFR. In fact, FGF23 cannot activate FGF signaling in most cultured cells even when they express FGFRs endogenously, whereas classical FGFs like FGF2 can activate FGF signaling in these cells (Kurosu et al., 2006).

Recent studies identified Klotho, a single-pass transmembrane protein expressed in the kidney, as a co-factor required for FGF23 to bind to FGFRs (Kurosu et al., 2006; Urakawa et al., 2006). Klotho protein forms a constitutive binary complex with several FGFRs (FGFR1c, 3c, and 4) and increases their affinity specifically to FGF23. In other words, Klotho functions as an obligate co-receptor for FGF23. In fact, Klotho-deficient mice are totally resistant to FGF23 and exhibit phosphate-retention phenotypes like FGF23-deficeint mice (Tsujikawa et al., 2003; Yoshida et al., 2002). Kidney-specific expression of Klotho explains why FGF23 recognizes kidney as its target organ among many organs that express FGFRs. Klotho protein may have evolved to compensate for the low affinity of FGF23 to heparan sulfate and specifically support FGFR activation with FGF23, which represents a novel mechanism for confining target organs in redundant ligand–receptor interactions. Thus, Klotho and FGF23 have emerged as important components of the bone–kidney endocrine axis that regulates phosphate metabolism (Kuro-o, 2006, 2008; Kurosu and Kuro-o, 2008, 2009b; Liu et al., 2007; Liu and Quarles, 2007).

The phosphaturic activity of FGF23 stems from its ability to suppress sodium-phosphate co-transporter type-2a (NaPi-2a) that mediates transepithelial phosphate reabsorption in renal tubules (Segawa et al., 2003, 2007; Shimada et al., 2004c). Injection of recombinant FGF23 protein reduces the number of NaPi-2a expressed on the apical brush border membrane of proximal tubules and induces phosphaturia within hours, although the precise signaling pathway through which FGF23 regulates NaPi-2a trafficking and/or expression in a Klotho-dependent manner remains to be determined. Importantly, negative phosphate balance reduces serum FGF23 levels, indicating the existence of a negative feedback loop in the regulation of phosphate excretion (Yu et al., 2005) (Fig. 1). This negative feedback loop is essential for phosphate homeostasis, because disruption of this loop by ablating FGF23 or Klotho expression results in hyperphosphatemia and severe phosphate retention in mice and humans. On the other hand, the activity of FGF23 as a counter-regulatory hormone for vitamin D originates from its ability to suppress synthesis and promote degradation of 1,25-dihydroxyvitamin D_3 in the kidney (Shimada et al., 2004a). FGF23 down-regulates expression of the *Cyp27b1* gene that encodes 1α-hydroxylase, the enzyme that synthesizes the active form of vitamin D (1,25-dihydroxyvitamin D_3) from its inactive precursor (25-hydroxyvitamin D_3). In addition, FGF23 up-regulates expression of the *Cyp24* gene that encodes 24-hydroxylase, the enzyme that hydrolyzes and inactivates 1,25-dihydroxyvitamin D_3 (Liu et al., 2006). Importantly, 1,25-dihydroxyvitamin D_3 up-regulates expression of the *FGF23* gene (Shimada et al., 2004a) and closes a negative feedback loop (Fig. 1). This negative feedback loop is essential for maintaining vitamin D homeostasis, because disruption of this loop results in high serum 1,25-dihydroxyvitamin D_3 levels as observed in Klotho-deficient mice (Tsujikawa et al., 2003) and FGF23-deficient mice (Shimada et al., 2004b).

4. Genetic evidence for phosphate toxicity

Defects in either Klotho or FGF23 disrupt the negative feedback loops that maintain phosphate and vitamin D homeostasis, resulting in high serum phosphate and vitamin D levels. High serum vitamin D promotes intestinal absorption of calcium and induces hypercalcemia as well. Of note, this metabolic state characterized by high serum phosphate, calcium, and vitamin D levels is associated with a premature-aging syndrome. In fact, the *klotho* gene was originally identified as a gene mutated in a mouse strain that inherited a premature-aging syndrome (Kuro-o et al., 1997). Mice lacking Klotho develop multiple aging-like phenotypes, including a shortened life span, growth retardation,

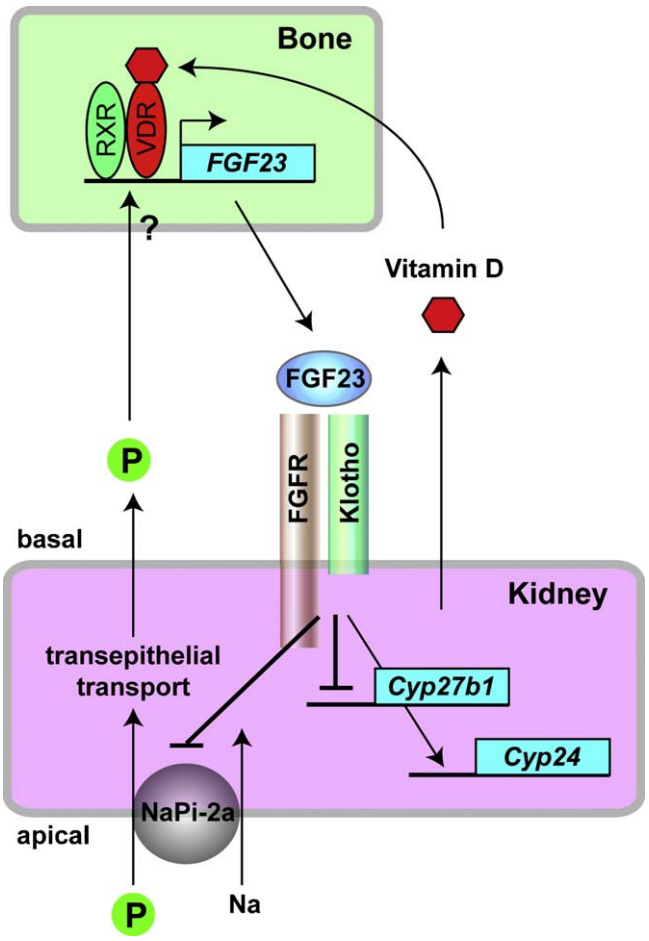

Fig. 1. The bone–kidney endocrine axes mediated by FGF23 and Klotho. In osteocytes, active form of vitamin D (1,25-dihydroxyvitamin D_3) binds to vitamin D receptor (VDR) and forms heterodimers with another nuclear receptor (RXR) to transactivate transcription of FGF23 gene. Phosphate (P) also increases expression of FGF23 in bone, but its mechanism remains to be determined. FGF23 secreted from bone acts on the Klotho–FGFR complex expressed in renal epithelium in the kidney. As a phosphaturic hormone, FGF23 inhibits transepithelial phosphate reabsorption by suppressing sodium-phosphate co-transporter type-IIa (NaPi-2a) on the apical brush-border membrane of renal tubules, thereby closing a negative feedback loop for phosphate homeostasis. As a counter-regulatory hormone for vitamin D, FGF23 reduces serum levels of 1,25-dihydroxyvitamin D_3 through suppressing its synthesis by down-regulating expression of the *Cyp27b1* gene and promoting its inactivation by up-regulating expression of the *Cyp24* gene, thereby closing a negative feedback loop for vitamin D homeostasis.

hypogonadotropic hypogonadism, rapid thymus atrophy (Min et al., 2007), skin atrophy, sarcopenia, vascular calcification, osteopenia (Kawaguchi et al., 1999), pulmonary emphysema (Ishii et al., 2008; Sato et al., 2007; Suga et al., 2000), cognition impairment (Nagai et al., 2003), hearing disturbance (Kamemori et al., 2002), and motor neuron degeneration (Anamizu et al., 2005). These phenotypes are also observed in mice lacking FGF23 (Razzaque et al., 2006).

These observations imply that phosphate, calcium, and/or vitamin D may be toxic when retained and accelerate aging. Several studies have supported this notion. First, vitamin D-deficient diet not only restored serum phosphate and calcium levels to normal but also rescued several aging-like phenotypes in both Klotho-deficient mice and FGF23-deficient mice (Stubbs et al., 2007; Tsujikawa et al., 2003). Second, ablation of vitamin D action in Klotho-deficient mice and FGF23-deficient mice by disrupting the *Cyp27b1* gene (Ohnishi et al., 2009; Razzaque et al., 2006) or vitamin D receptor gene (Hesse et al., 2007) also rescued hyperphosphatemia, hypercalcemia, and the premature-aging syndrome. Lastly, low phosphate diet rescued shortened life span and vascular calcification in both FGF23-deficient mice and Klotho-deficient mice (Morishita et al., 2001; Stubbs et al., 2007). These studies have provided unequivocal evidence that the premature-aging syndrome caused by defects in the Klotho–FGF23 endocrine axis is due to retention of phosphate, calcium, and/or vitamin D. It should be noted that low phosphate diet rescued multiple phenotypes of FGF23-deficient mice despite the fact that it further increased already high serum calcium and vitamin D levels (Stubbs et al., 2007), suggesting that phosphate, but not calcium or vitamin D, is primarily responsible for the aging-like phenotypes. It is likely that low vitamin D diet and ablation of vitamin D activity rescued accelerated aging through reducing serum phosphate levels, although it remains to be determined whether high serum vitamin D and/or calcium levels are required for phosphate to induce the premature-aging syndrome.

5. Phosphate and aging

Inorganic phosphate is not only an essential component of cell structure (DNA and membrane phospholipids) but also a key mediator of numerous cellular activities, including energy metabolism (ATP production) and kinase-mediated signal transduction. It is also involved in pathophysiology of various disorders such as bone diseases, vascular calcification, and chronic kidney disease among others. Although little is known about direct effects of phosphate on aging, accumulating evidence has demonstrated that inorganic phosphate has significant impacts on glucose metabolism and oxidative stress, which potentially affect aging processes of any organism from yeast to human.

In *Saccharomyces cerevisiae*, phosphate starvation, as well as glucose starvation, induces cell cycle arrest and extension of chronological life span (Boer et al., 2008; Brauer et al., 2008). Several phosphate-responsive genes have been identified, including the *PHO85* gene that encodes a cycline-dependent kinase whose activity is correlated with intracellular phosphate concentration. Pho85 is inactivated under low phosphate conditions, leading to a quiescent G_0-like state and prolonged survival (Wanke et al., 2005). Pho85 also functions as a negative regulator for a set of genes that are typically induced under glucose starvation (DeRisi et al., 1997; Mouillon and Persson, 2006). Thus, phosphate restriction causes metabolic changes similar to those induced by caloric (glucose) restriction in yeast.

In mammals, low phosphate diet causes changes in metabolism similar to those induced by diet restriction as discussed below. Animals under diet restriction reduce blood insulin levels to adapt reduced carbohydrate availability and alter expression of insulin-responsive genes, which leads to changes in glucose metabolism including increased gluconeogenesis and decreased glycolysis among others (Cao et al., 2001; Kayo et al., 2001; Lee et al., 1999; Masoro, 2006; Wetter et al., 1999). Although low phosphate diet does not reduce blood insulin levels, it indeed alters expression of insulin-responsive genes in a way similar to that induced by diet restriction (Xie et al., 1999, 2000), resulting in increased gluconeogenesis and decreased glycolysis as well. This may be partly explained by the fact that low phosphate diet induces moderate insulin resistance by unknown mechanisms (Haap et al., 2006; Paula et al., 1998). Thus, moderate insulin resistance induced by phosphate restriction, as well as hypoinsulinemia induced by diet restriction, attenuate intracellular insulin signaling activity and induce similar changes in insulin-responsive gene expression, resulting in a similar metabolic state.

Recent studies have shown that increased insulin resistance does not necessarily mean diabetes and short life span. Rather, it has become increasingly clear that adequate suppression of insulin-like signaling pathway is an evolutionarily conserved

mechanism for anti-aging and life span extension. Reduction-of-function mutations in the genes encoding orthologs of insulin receptor, insulin receptor substrates (IRS), and PI3-kinase has been known to extend life span in *Caenorhabditis elegans* and *Drosophila* (Clancy et al., 2001; Kenyon, 2005; Kenyon et al., 1993; Morris et al., 1996; Tatar et al., 2001). In mammals, increased longevity is reported in mice lacking insulin receptor in adipose tissues (Bluher et al., 2003), mice heterozygous for a null allele of the insulin-like growth factor-1 (IGF-1) receptor gene (Holzenberger et al., 2003), mice lacking IRS-1 (Selman et al., 2008), mice lacking IRS-2 in the brain (Taguchi et al., 2007), and *dwarf* mice with impaired growth hormone (GH)–IGF-1 endocrine axis (Bartke and Brown-Borg, 2004; Brown-Borg et al., 1996; Flurkey et al., 2002). In humans, some centenarians show resistance to IGF-1, short statue, and high serum IGF-1 associated with loss-of-function mutations in the IGF-1 receptor gene (Suh et al., 2008). Importantly, some long-lived animals exhibit insulin resistance (Kurosu et al., 2005; Selman et al., 2008), indicating that increased insulin sensitivity is not a prerequisite for long life span and anti-aging. Although many long-lived animals indeed exhibit increased insulin sensitivity, it is always associated with hypoinsulinemia and attenuated insulin/IGF-1 signaling activity in tissues. Thus, attenuated insulin/IGF-1 signaling activity in tissues shows closer association with life span extension than increased insulin sensitivity.

In addition to its involvement in glucose metabolism and insulin sensitivity, inorganic phosphate is shown to increase oxidative stress both *in vivo* and *in vitro*. Phosphate retention caused by Klotho deficiency in mice results in cognition impairment due to increased oxidative damage and apoptosis in hippocampus neurons, which can be rescued by administration of an antioxidant (Nagai et al., 2003). Furthermore, human vascular endothelial cells cultured in high phosphate medium (2.5 mM) have higher levels of cellular reactive oxygen species (ROS) than those cultured in normal phosphate medium (1.0 mM) (Di Marco et al., 2008). These observations have raised the possibility that hyperphosphatemia by itself may play a causative role in pathogenesis of endothelial dysfunction and cardiovascular disease in chronic kidney disease (CKD) patients, because phosphate retention is universally observed in CKD patients and blood phosphate levels higher than 2.5 mM are often observed in this population. In fact, recent studies have identified hyperphosphatemia as a potent risk of death in CKD patients, even when the blood phosphate levels are within the normal range (Goodman et al., 2000; Tonelli et al., 2005). Thus, controlling blood phosphate levels below 2.0 mM by prescribing low phosphate diet and/or phosphate binders has become an important therapeutic goal for CKD patients (Ganesh et al., 2001). Of note, the National Kidney Foundation task force has indicated that the cardiovascular mortality of a 35-year-old patient on dialysis is equivalent to that of an 80-year-old "healthy" individual, rendering CKD to be the most potent accelerator of vascular senescence (Meyer and Levey, 1998). Furthermore, the American Heart Association announced that CKD should be included in the highest risk group for cardiovascular disease (Sarnak et al., 2003). Importantly, Klotho expression is significantly reduced in kidneys of CKD patients (Koh et al., 2001). Thus, CKD may be viewed as a segmental progeroid syndrome associated with a state of Klotho deficiency and phosphate retention. Interestingly, patients with Hutchinson-Gilford progeria syndrome (HGPS) exhibit hyperphosphatemia and reduced fractional excretion of phosphate (Merideth et al., 2008; Ortiz, 2008), which are characteristic features of mice lacking Klotho or FGF23. Although hyperphosphatemia is not primarily responsible for the HGPS phenotypes, it may increase the cardiovascular mortality in HGPS patients.

Inorganic phosphate entered into the cell is transported into mitochondria, where it functions not only as a substrate of ATP synthase but also as a key regulator of oxidative phosphorylation. In fact, mitochondrial membrane potential ($\Delta\Psi$), NADH concentration, and oxygen consumption in isolated mitochondria increase in a hyperbolic manner as extra-mitochondrial phosphate concentration increases (Bose et al., 2003). $\Delta\Psi$ is known to positively correlate ROS production in the electron transport chain (Papa and Skulachev, 1997). In addition, high phosphate concentration enhances delivery of reducing equivalent to cytochrome *c* in Complex III in the electron transport chain, which also increases ROS production (Bose et al., 2003). Thus, changes in mitochondrial function induced by high phosphate can increase ROS generation in mitochondria. The effects of inorganic phosphate on mitochondrial ROS generation likely have physiological significance, because cytoplasmic phosphate levels in mouse and human tissues as determined by ^{31}P nuclear magnetic resonance (NMR) indeed change from $<$1 mM to $>$10 mM depending on tissue types and their metabolic states (Katz et al., 1988, 1989). Furthermore, inorganic phosphate induces mitochondrial permeability transition (the inner membrane becomes non-selectively permeable to small solutes) in Ca^{2+}-loaded mitochondria, which occurs under pathological settings including ischemia/reperfusion and triggers cell death (Kowaltowski et al., 2001). Thus, inorganic phosphate plays multiple roles in the regulation of oxidative stress and mitochondrial function in health and disease, which potentially affect aging processes.

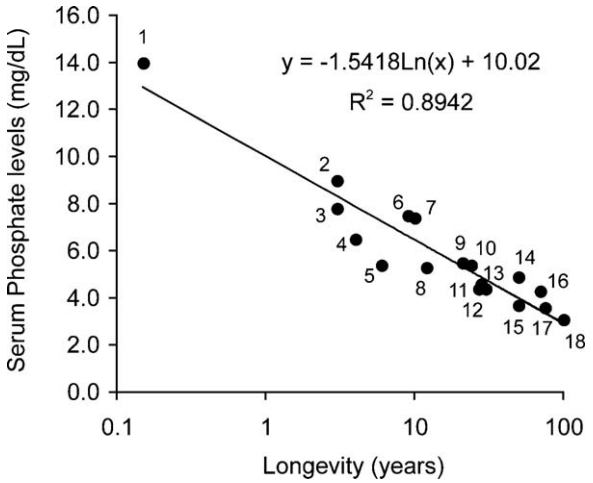

Fig. 2. Relation between longevity and serum phosphate in mammals. 1: *Klotho*$^{-/-}$ mouse, 2: Mouse, 3: Rat, 4: Hamster, 5: Gerbil, 6: Nutria, 7: Rabbit, 8: Guinea pig, 9: Sheep, 10: Squirrel, 11: Porcupine, 12: Naked mole rat, 13: Flying fox, 14: Bear, 15: Rhinoceros, 16: Elephant, 17: Human, 18: Human (centenarian). Serum phosphate levels are average or median values, whichever available in literatures (Asadi et al., 2007; Feldhamer et al., 2003; Field et al., 1998; Gorbunova et al., 2008; Heard et al., 2006; Holliday, 1995; Kuro-o et al., 1997; Moreau et al., 2003; Munson et al., 1998; Passeri et al., 2008; Pugh, 2002; Ramsay, 2003; Segawa et al., 2007; Thrall et al., 2004; Tuntasuvan et al., 2002; Yahav et al., 1993).

Another piece of evidence in support of the notion that phosphate affects aging processes is an inverse correlation between longevity and serum phosphate levels in mammals (Fig. 2). Although there are difficulties in precisely estimating the longevities and "normal" serum phosphate levels, a close relationship is clearly observed between longevity and serum phosphate throughout diverse species.

6. Perspective

When compared with endocrine regulation of calcium metabolism, that of phosphate metabolism was poorly understood until quite recently. Identification of the bone–kidney endocrine axis mediated by FGF23 and Klotho has greatly promoted our

understanding on phosphate metabolism. Since disruption of phosphate homeostasis is universally observed in patients with chronic kidney disease and identified as a potent risk for death, the FGF23–Klotho endocrine axis has emerged as a novel therapeutic target of chronic kidney disease (CKD), which nearly 26 million adult Americans, or 13% of the US population, suffer from and is increasingly recognized as a global public health problem in aging society (Coresh et al., 2007). In addition, animal studies on FGF23- and Klotho-deficient mice have revealed a potential link between phosphate and aging in mammals. If phosphate retention not only increases mortality of CKD patients but also accelerates aging processes in general, several important hypotheses may be drawn. First, CKD may be viewed as a state of accelerated aging or a segmental progeroid syndrome caused by phosphate retention. Second, prescription of low phosphate diet and/or phosphate binders may be considered not only for CKD patients but also for various common age-related diseases. Lastly, prescription of low phosphate diet and/or phosphate binders may be considered even for healthy individuals to prevent aging and age-related diseases. Further studies are required to prove or disprove a novel concept that phosphate accelerates aging.

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