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**Aging and uremia: Is there cellular and molecular crossover?**

White WE *et al.* Aging and uremia crossover

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**Abstract**

Many observers have noted that the morphological changes that occur in CKD patients resemble those seen in the geriatric population, with strikingly similar morbidity and mortality profiles and rates of frailty in the two groups, and shared characteristics at a pathophysiological level especially in respect to the changes seen in their vascular and immune systems. However, whilst much has been documented about the shared physical characteristics of aging and uremia, the molecular and cellular similarities between the two have received less attention. In order to bridge this perceived gap we have reviewed published research concerning the common molecular processes seen in aging subjects and CKD patients, with specific attention to altered proteostasis, mitochondrial dysfunction, post-translational protein modification, and senescence and telomere attrition. We have also sought to illustrate how the cell death and survival pathways apoptosis, necroptosis and autophagy are closely interrelated, and how an understanding of these overlapping pathways is helpful in order to appreciate the shared molecular basis behind the pathophysiology of aging and uremia. This analysis revealed many common molecular characteristics and showed similar patterns of cellular dysfunction. We conclude that the accelerated aging seen in patients with CKD is underpinned at the molecular level, and that a greater understanding of these molecular processes might eventually lead to new much needed therapeutic strategies of benefit to patients with renal disease.

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**Key words:** Aging; Uremia; Apoptosis; Autophagy; Senescence; Telomeres; Mitochondria; Post-translational protein modification; Klotho

**Core tip:** This review presents evidence that suggests that the morphological similarities between uremia and physiological aging are underpinned by similarities at a cellular and molecular level. Several of the classical cellular features of aging such as mitochondrial dysfunction and altered proteostasis have been observed in the cells and tissues of uremic humans and animals, and in *in vitro* models of uremia. There are also many shared features between aging and uremia in terms of cell death and survival pathways. These commonalities may present new targets for the future management of patients with CKD.

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**INTRODUCTION**

Observation alone suggests that patients with end stage kidney disease (ESKD) are biologically older than their unaffected peers. As a group, ESKD patients have a morbidity and mortality profile similar to that of the geriatric population, and the pathophysiology of the uremic syndrome has interesting parallels with the aging process. Based on these thoughts it has been posited that kidney failure results in accelerated, pathological aging[1]. Indeed there are striking analogies between the effects of aging and uremia on the structure and function of the heart and vasculature, with similar changes seen in pulse contour, pulse wave velocity, and impedance, and similar structural abnormalities with wall thickening, decreased elastin, and increased collagen content[2].

Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death[3]. Dialysis dependent patients of any age have an increased risk of mortality when compared to those with a functioning transplant and healthy controls of the same age[4], and are more susceptible to disease, particularly that of the cardiovascular system: a 25-34-year-old dialysis patient has a relative risk of cardiovascular mortality similar to that of a > 75-year-old in the general population[5]. Furthermore, the prognosis for CKD patients is still extremely poor and has not improved greatly despite many treatment advances: CKD patients receiving dialysis aged 50 and under are likely to live 30 years less than age-matched people without CKD[5]. Whilst survival rates have slightly improved they have not kept pace with the rises seen in the normal population without CKD, with the result that relative survival in age-specific patients with CKD actually decreased between 1977 and 2007[6]. There is thus a need to identify if CKD is inducing an aging-like cellular and molecular dysfunction, and if so whether any novel potential therapy might be derived from an increased understanding of the pathways that are induced by both CKD and aging.

ESKD confers a greatly increased risk of infectious morbidity and mortality, whilst simultaneously being a chronic inflammatory state, a pattern of immune dysfunction also associated with aging[7]. These abnormalities also seem to be reflected at a cellular level, with preferential loss of cells belonging to the lymphoid cell lineage, and inflammation and expansion of proinflammatory immune cells[8].

There is a high prevalence of the frailty syndrome amongst dialysis patients, a phenotype partly defined by weight loss, muscle weakness, and fatigue, which is associated with adverse outcomes in geriatric patients[9]. In the original study that developed this definition, 6.9% of participants ≥ 65-year-old were classified as frail; in a more recent study of dialysis patients 44% of those under 40-year-old were found to be frail[10]. Cognitive impairment is also highly prevalent in the dialysis-dependent population and occurs in comparatively young patients[1,11].

Whilst much has already been written about the intriguing similarities that appear to exist between the aging process and CKD[1,8,12,13],comparatively little work has been undertaken looking at the cellular and molecular hallmarks of aging in the context of the known evidence concerning uremia-induced cellular and molecular pathways.Therefore in this review, in order to try and fill this perceived gap in the literature, we have first briefly outlined what the main cell death pathways are and by what means these processes interact with each other, followed by an analysis of published research concerning the mechanisms of aging and uremia-induced cell death and their common molecular pathways and cellular characteristics. Lastly we provide an assessment of how this knowledge may lead to benefits in both nephrology and gerontology.

**CELL DEATH AND SURVIVAL PATHWAYS**

***An outline of cell death***

Since the first descriptions of apoptotic cell death appeared more than 40 years ago[14] the study of cell death has become a substantial and important area of study. The main cell death pathways have been reviewed exhaustively in the literature and it is not the aim of this review to repeat this information. What is pertinent here is how much our understanding of cell death has changed and evolved in recent years. This is because cell death and survival pathways are now being assessed more as molecular processes and less as a series of morphological characteristics. One of the most fundamental changes is that each death pathway is no longer considered in isolation and there is an appreciation that cell death can no longer be considered as a choice between apoptotic, autophagic or necrotic death. Pathways once thought of as discreet have been found to be closely interconnected with others whilst some pathways have needed to be recategorized. In addition several completely novel pathways have been described. An example of reclassification is that necrosis is now subdivided into two distinct forms, one being programmed necrosis that is usually termed necroptosis or regulated necrosis, and accidental or non-regulated necrosis which is more in line with the original concept of necrosis. Another example of recent developments is that apoptosis has now been split into four different classes whilst a total of 13 functional classes of regulated cell death have been described[15]. So whilst this review is focusing on the most established and described death and survival pathways they must not be considered as being complete. Lastly, the role of autophagy in cell death has been recently challenged[16,17] whilst its role in cell survival[18] asserted.

***Uremia induced apoptosis***

Whist apoptosis and uremia have been studied extensively both separately and collectively, a clear picture of how uremia induces apoptosis has yet to be established. Instead a large number of studies using experimental models and human subjects have shown that uremia is associated with apoptosis in a wide range of cells and tissues such as skeletal muscle[19,20], myocardium[21], platelets[22,23], monocytes[24], neutrophils[25], lymphocytes[26], leukocytes[27] and vascular endothelial cells[28]. The kidney has also been shown as a target for apoptosis in uremia with both podocytes[29] and proximal tubular cells identified as having increased apoptotic cell death[30]. Furthermore, it has become known that it certain circumstances dialysis itself can be an activator of apoptosis[20,26]. It is unclear if the apoptosis seen in the kidney is the cause or the effect of CKD. However, it does seem probable that AKI induced apoptosis can subsequently lead to the activation of interstitial fibroblasts *via* TGF-β resulting in CKD[31,32]. In fact expression of TGF-β has been found to be elevated in nearly all human and experimental forms of CKD{33]. TGF-β expression has also been demonstrated to be directly associated with age in healthy human subjects[34].

***Uremia induced necroptosis***

Uremia induced necroptosis (or programmed necrosis) has yet to feature prominently in the literature although this is possibly due, at least in part to previous cell death descriptions not being classified correctly according to current definitions (see Aging induced apoptosis below).

***Aging induced apoptosis and necroptosis***

The induction of apoptosis in aging in most tissues awaits clarification. However, in skeletal muscle at least there is clear evidence that muscle mass decreases with age[35-37] with apoptosis being known to be elevated in the skeletal muscle of aged subjects[38-41]. It has been suggested that aging increases cell death by caspase-independent mechanisms. There is also some evidence that TUNEL staining is greater the kidneys of aged in mice[42] but TUNEL staining has been shown not to be specific for apoptosis[43]. It seems plausible that at least some of the examples for age induced apoptosis in the literature reflect instead increases in necroptosis.

***Apoptosis and necroptosis crosstalk***

It is now appreciated how significantly involved the apoptosis machinery is in other cell death and survival pathways. Many of the described apoptotic death receptors such as TNFR1 and FAS are now also known to be able to induce necroptotic cell death[44,45]. Caspase-8, a key component of receptor mediated apoptosis is now thought to regulate the activation of necroptosis[45]. Inhibitor of apoptosis (IAP) are endogenous caspase inhibitors and therefore play a role in controlling apoptosis. When IAP levels are reduced this leads to caspases being activated which results in apoptotic cell death. Another IAP, X-Chromosome-linked IAP (XIAP) has been shown to be reduced in the muscle of CKD mice and *in vitro* in muscle cells treated with serum obtained from CKD mice[46].

The activation of autophagy is known to breakdown IAPs and lead subsequently to the induction of necroptosis. Furthermore, in conditions where IAPs are suppressed or absent and caspase activity is inhibited can lead to the activation of necroptosis *via* receptor-interacting protein1 RIP1 and its downstream kinase (RIPK1)[47]. It has been postulated that RIP1 together with RIP3, cIAP, Caspase-8 and cFlip act as essential components of the ripotosome, a signalling platform that can switch modes between apoptotic and necroptotic cell death[48]. Recent work indicates that it is RIPK3 activity that determines whether cells die by necroptosis, or in its absence, by caspase-8 mediated apoptosis[49] whilst another group have suggested that necroptosis can be induced in the absence of RIPK1 and without the formation of a functioning ripotosome[50], the complex considered essential for necroptosis to occur.

***Autophagy***

Autophagy is the dynamic, multistep cellular process wherein portions of cytoplasm, including organelles, are sequestered into double-membrane vesicles (termed autophagosomes) and delivered to lysosomes where they are degraded, with eventual recycling of the resultant macromolecules[51]. By removing excessive and aberrant organelles and proteins, autophagy contributes to cellular homeostasis and protein quality control, and functions as a source of energy for the cell[52]. Autophagy is up-regulated and has a protective function in the face of cellular stressors such as starvation[53] and ischemia[54].

***Autophagy and apoptosis crosstalk***

It is perhaps not surprising that autophagy and apoptosis exhibit crosstalk as both pathways play such significant roles in development, homeostasis and pathology[55]. Evidence of this crosstalk has been plentiful[56-60] and indicates that the pathways can interact in an additive or antagonistic fashion and that the molecular machinery for both can combine *via* p27[56], p38[57], p53[58] and beclin-1[59,60]. It is likely that these overlapping pathways are involved in uremia and aging induced dysfunction. For example in autophagy-deficient mice the onset of ischemia/reperfusion injury resulted in greater proximal tubular apoptotic injury with significantly elevations in serum urea and creatinine compared to wild type animals. This indicates that autophagy maintains proximal tubular homeostasis and protects against ischemic injury[61]. In another study using a dietary adenine-induced chronic renal failure model a high phosphate diet was found to increase apoptosis in VSMC and that this rise could be reduced by autophagy inhibition. However, reducing autophagy was associated with an increase in calcium deposition in VSMC. The study concluded that autophagy might be an endogenous protective mechanism against phosphate-induced vascular calcification[62].

***Autophagy and necroptosis***

In addition to necroptosis crosstalking with apoptosis *via* IAP (see apoptosis and necroptosis crosstalk) there is also evidence of autophagy and necroptosis crosstalk interacting in a similar fashion. Using a novel chalcone derivative as an anti-cancer agent they found that JNK-mediated autophagy was able to cause IAP degradation followed by necroptosis[63]. It seems likely therefore that there is a therapeutic potential for autophagy to be exploited by anticancer agents to provoke cancer cell death. However, it should be noted that the molecular interactions between the two processes is still largely unknown and indeed there is evidence that autophagy activation can block necroptosis in several cell lines[64,65].

***Autophagy in aging***

Beyond its function at a cellular and organ level, autophagy has been heavily implicated in the aging process and the determination of life span. Normal and pathological aging are associated with failing proteostasis and reduced autophagic activity[3], and genetic inhibition of autophagy produces degenerative changes in mammalian tissue resembling those seen in aging. Caloric restriction, which has been shown to promote longevity in model organisms, stimulates autophagy, as do some pharmacological interventions and genetic manipulations that increase life span in model organisms, and inhibiting autophagy attenuates this effect[66].

***Autophagy in uremia***

Much work has been published describing the role of autophagy in the pathophysiology of AKI and CKD, but very little has been published looking at the effects of uremia on autophagy in other tissues. Chen *et al*[67] assessed autophagy activation in leukocytes isolated from peripheral blood samples, which had been taken from stage 5 CKD patients and healthy controls after overnight fasting and 2 h after breakfast. Overnight fasting induced conversion of microtubule-associated protein light chain 3 (LC3) I to II (as detected by western blot as increased quantities of the latter, and signifying autophagosome formation) in healthy subjects. mRNA levels of autophagy-related gene 5 (*Atg5*) and beclin-1 also increased in fasted healthy subjects but not in CKD patients. Interestingly there was no difference between CKD patients receiving or not receiving hemodialysis. Furthermore, a negative association was found between LC3II and left atrium size, Atg5 transcription and left ventricular end-diastolic diameter, and beclin-1 transcription and mitral inflow E- and A-wave sizes. The authors conclude that autophagic activation is impaired in CKD patients and is not reversed with hemodialysis, and that this impairment is related to cardiac abnormalities.

Siedlecki *et al*[68] assessed the effect of rapamycin administration in a murine model of normotensive uremic cardiomyopathy. Treatment of surgically induced renal injury (SIRI) mice with rapamycin blocked the development of cardiac hypertrophy and fibrosis when compared with vehicle-treated animals. The experimenters suggest that this protective effect is mediated by the extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) pathways. They do not speculate on the possible involvement of autophagy, but rapamycin is known to stimulate autophagy *via* mTOR, and has been shown to have anti-aging effects in mammals[69]. The authors raise the interesting question of whether renal transplant recipients taking rapamycin as an immunosuppressant exhibit reversal of uremia-induced cardiac changes beyond that associated with successful transplantation.

In summary, the principle cell death and survival molecular pathways consisting of apoptosis, necroptosis and autophagy are strongly interrelated and crossover at many points. Whilst our current knowledge on how these interacting pathways are controlled and regulated is far from complete our appreciation of how similar many of the molecular signalling induced by uremia and aging appears to be growing.

**SHARED CELLULAR CHARACTERISTICS OF AGING AND UREMIA**

***Cell senescence, telomere shortening and stem cell exhaustion***

Cellular senescence can be defined as stable arrest of the cell cycle coupled to classic phenotypic changes[70]. This was originally described by Hayflick[71] in serially passaged human fibroblasts, which undergo a certain number of divisions before entering a senescent phase (the “Hayflick limit”). This phenomenon was subsequently shown to be due to telomere shortening[72], but can be triggered by non-telomeric aging-associated stimuli such as DNA damage and excessive mitogenic signaling[3].

Senescent cells accumulate in aged organisms, although senescence *per se* does not cause aging, having a protective effect by preventing the propagation and causing the removal of damaged and potentially oncogenic cells from tissues. A failure to clear senescent cells and replace these with new ones may, however lead to their accumulation[3]. Senescent cells are known to possess large amounts of proinflammatory cytokines and matrix metalloproteinases (the “senescence-associated secretory phenotype”) which may in themselves contribute to aging[73].

Senescent cells have a flattened and enlarged morphology, and express a different set of genes such as p16, p21, p53, and retinoblastoma protein (pRb)[74].Senescence-associated β-galactosidase (SA-β-gal) is a frequently used biomarker of cell senescence *in vivo* and *in vitro*[75].

Jiminez *et al*[76] looked at markers of senescence in circulating immune cells in uremic pre-dialysis, hemodialysis-dependent and transplanted patients. Abnormal telomere shortening was seen in a subpopulation of lymphocytes in pre-dialysis patients. In hemodialysis patients who dialyzed with cellulosic membranes, a subset of mononuclear cells demonstrated telomere shortening and exhibited increased levels of intracytoplasmic proinflammatory cytokines, which were released in response to substimulatory doses of lipopolysaccharide (LPS) and bacterial DNA *in vitro*. The authors postulate that these senescent mononuclear cells both result from and contribute to chronic inflammation in such patients. A subpopulation of lymphocytes with shortened telomeres was also found in transplant patients with near normal renal function. It was suggested that these resulted from chronic activation due to major histocompatibility complex (MHC) incompatibility and immunosuppressive therapy.

Tsirpanlis *et al*[77] measured the activity of telomerase (the enzyme that preserves telomere length and structure and thus prevents senescence[78]) in peripheral blood mononuclear cells (PBMCs) in hemodialysis-dependent patients and non-renal failure subjects. Telomerase activity was reduced in hemodialysis patients compared to healthy controls, and was lower in long-term than in short-term dialysis patients. These findings indicate that defence against senescence is reduced in this cell type and associated with chronicity in hemodialysis patients.

Several groups have looked at the role of senescence in the endothelial dysfunction associated with cardiovascular disease in uremia. Adijiang *et al*[79] administered indoxyl sulphate, a uremic toxin, to hypertensive and normotensive rats, and examined their aorta for histological and immunohistochemical evidence of senescence. The indoxyl sulphate-treated animals showed significantly increased aortic calcification and wall thickness, and significantly increased expression of SA- β-gal, p16, p21, p53 and pRb in cells embedded in the calcification area. The same group went on to demonstrate that indoxyl sulphate stimulated senescence of cultured human aortic smooth muscle cells *via* an oxidative stress mechanism[74].

Carracedo *et al*[80] evaluated the effects of uremia on LDL carbamylation and the effect of carbamylated LDL (cLDL) and oxidized LDL (oxLDL) on the number, function, and genomic stability of endothelial progenitor cells (EPCs) obtained from healthy volunteers. EPCs were exposed to cLDL generated after incubation of native LDL (nLDL) with uremic serum from patients with CKD stages 2-4. Compared with cLDL, nLDL induced an increase in oxidative stress, depolarization and senescence in EPCs, and a decrease in EPC proliferation and angiogenesis. The authors hypothesize that cLDL triggers genomic damage in EPCs resulting in premature senescence, and that this contributes to atherosclerotic disease in uremia.

Klinkhammer *et al*[81] demonstrated that bone marrow mesenchymal stem cells (MSCs) isolated from uremic rats (both surgically induced and adenine diet) showed signs of premature senescence, and failed to accelerate healing of glomerular lesions when injected into the left renal artery of rats with acute anti-Thy1.1-nephritis when compared to MSCs obtained from control rats. The authors conclude that CKD leads to a sustained loss of *in vitro* and *in vivo* functionality in MSCs, possibly due to premature senescence. Stem cell exhaustion and the resultant decline in tissue regenerative potential has been noted as one of the hallmarks of aging[3].

In summary, aging and uremia share many important cellular characteristics such as increases in cell senescence, telomere shortening and exhaustion of stem cells. This provides further evidence that supports the contention that uremia can be considered as a form of accelerated aging[1].

***Klotho***

The *KLOTHO* gene was originally identified as being involved in the suppression of aging in transgenic mouse studies[82]. Defective klotho expression resulted in mice having a premature aging phenotype, which had striking similarities to that of CKD patients, including reduced life span, arteriosclerosis, hyperphosphataemia and high concentrations of plasma fibroblast growth factor-23 (FGF23, a bone derived hormone that promotes renal phosphate excretion and reduces serum levels of 1,25-dihydroxyvitamin D3 (1,25-(OH)2VD3)[83]).This observation, coupled with the fact that, although found in multiple tissues, klotho expression is highest in the kidney (predominantly in the distal convoluted tubules[84]), suggested that CKD might be a state of klotho deficiency, and this might contribute to the accelerated aging phenotype of uremia[85].

Through alternative splicing klotho exists in membrane-anchored and soluble, secreted forms, the latter being found in mammalian cerebrospinal fluid, blood and urine[84]. These forms have distinct functions. Membrane klotho forms a complex with fibroblast growth factor (FGF) receptors and functions as a co-receptor for FGF23.Soluble klotho functions as an endocrine factor, and has a role in a number of processes including modulation of ion transport[86] and counteraction of the renin-angiotensin system[87]. Klotho suppresses 1α-hydroxylase in the kidney to regulate calcium metabolism[88], and participates in in the regulation of PTH synthesis in the parathyroid gland by FGF23[84,89].

Both physiological aging and CKD are associated with reduced klotho levels. Lower renal klotho protein expression has been shown in aging rodents compared to young ones[90], and plasma klotho concentrations were found to be two-fold higher in normal children than in adults[91]. Renal klotho RNA has been shown to be reduced in CKD kidneys[92], as have urinary klotho levels[85]. Klotho concentrations in plasma, urine and kidney are decreased in parallel in a rodent CKD model[85].

Klotho may influence cell death and survival pathways *via* its anti-senescence and oxidation effects. Liu *et al*[93] analysed various tissues and organs from klotho -/- mice and demonstrated a decrease in stem cell number and an increase in progenitor cell senescence. Tissues from klotho-deficient animals showed evidence of increased Wnt signalling. *In vivo* and *in vitro* Wnt exposure triggered by the absence of klotho accelerated cellular senescence. The authors conclude that klotho might act as a secreted Wnt antagonist and that a decrease in klotho concentration leads to an increase in Wnt signalling and this may play a role in aging.

de Oliveira *et al*[94] generated a klotho-knockdown human fibroblast, in which premature senescence was seen alongside an increase in p21 expression. p53 knockdown in klotho attenuated cells restored normal growth and replicative potential. These results suggest that klotho regulates cell senescence by suppressing the p53/p21 pathway. Ikushima *et al*[95] demonstrated that purified recombinant klotho protein could attenuate apoptosis and senescence in human umbilical vein endothelial cells (HUVEC). The same group went on to show that this occurred *via* mitogen-activated kinase and extracellular signal-related kinase pathways[96].

Klotho may exert an anti-aging effect by suppressing the inflammatory effect of substances secreted by senescent cells. Liu *et al*[97] have shown that cellular klotho interacts with retinoic acid-inducible gene-I (RIG-I) and that this interaction inhibits the RIG-I induced expression of IL-6 and IL-8 both *in vivo* and *in vitro*.

Thus the deficiency in klotho seen in uremia and aging might underpin the enhanced cell senescence, apoptosis and stem cell depletion common to both states[81]. Given that tissue klotho expression is greatest in the kidneys a common mechanism is perhaps to be expected. Indeed recent data indicate that kidney tissue klotho expression greatly effects systemic concentrations and they concluded that the kidney is the prime mediator of klotho function[98]. Therefore klotho, a recognised anti-aging factor, is under the control of the kidney and thus lends further support to there being a molecular basis for the observed shared phenotype between uremia and aging.

***Post-translational protein modification***

Spontaneous post-translational protein modifications result from the non-enzymatic attachment of reactive molecules to protein functional groups. This process occurs in healthy individuals with aging, but is increased in certain disease states. Alterations to protein structure may result in functional changes, which can be pathogenetic[99]. Carbamylation is one form of post-translational protein modification specifically associated with CKD and uremia. Cyanate, a dissociation product of urea, binds to proteins and free amino acids, resulting in abnormal cellular responses that may contribute to inflammation and atherosclerosis. As carbamylation results from a direct product of uremia it may serve as a quantitative biomarker of time-averaged urea concentrations in addition to its potential use in risk assessment[99].

One of the most widely studied and publicised forms of post-translational protein modification is glycation. Advanced glycation end products (AGEs) are formed by the non-enzymatic modification of tissue proteins by physiologic sugars. AGEs accumulate in tissues as a function of increased production (*e.g.*, in diabetes mellitus), decreased renal removal of AGE precursors (*e.g.,* in advanced CKD) and time (as occurs in physiological aging)[100]. Covalent cross-linking occurs in affected proteins, leading to increased stiffness of the protein matrix, thus impeding function, and increased resistance to proteolytic removal, thus affecting tissue remodeling[101]. This contributes, for instance, to the histological and functional changes seen in diabetic glomerulosclerosis and atherosclerosis[102]. AGE accumulation also stimulates cytokine and reactive oxygen species (ROS) production through AGE-specific receptors, modifies intracellular proteins[100], and has been shown to promote senescence[103] and apoptosis[104] in the cells of affected tissues, contributing to cell death and tissue dysfunction.

Significantly elevated serum levels of AGEs are present in ESKD, with no differences between patients with and without diabetes[105], and uremic patients are known to be exposed to high levels of oxidative stress[106]. Taki *et al*[107] demonstrated that plasma levels of pentosidine, an AGE, was correlated and independently associated with coronary artery calcification score (CACS) in hemodialysis patients. Pentosidine formation is accelerated by oxidative stress[108], and in this study was correlated with indoxyl sulphate. The authors thus conclude that indoxyl sulphate may enhance oxidative stress, which in turn enhances AGE generation.

Increased oxidative stress and AGE generation are known to play a role in the pathophysiology of aging[100], and both of these events are present in patients with CKD[105,106] and therefore represent two further potential crossovers between uremia and the aging process.

***Mitochondrial dysfunction***

According to the mitochondrial free radical theory of aging, progressive, age-related mitochondrial dysfunction results in increased production of ROS, which causes further mitochondrial deterioration and cellular damage[109]. Recent data has questioned the idea that ROS have an entirely deleterious effect in aging, suggesting that they represent a stress-induced survival signal which acts to activate homeostatic responses to cellular stress and damage. As these accumulate with aging ROS eventually pass a threshold and aggravate the damage[110].

Dysfunctional mitochondria can contribute to aging independently of ROS[3]. Damaged mitochondria have an increased tendency to permeabilize in response to stress, leading to apoptotic cell death[111] and inflammation[112]. Aging associated mitochondrial dysfunction arises *via* several mechanisms[3]. For example, mitochondrial decline occurs as a consequence of telomere attrition in telomerase-deficient mice with subsequent p53-mediated repression of PGC1a and PGC-1b[113], and can be partially reversed in wild-type mice by telomerase activation[114]. Sirtuins, a group of NAD-dependent protein deacetylases[115] , also play a role in controlling mitochondrial function. SIRT1 modulates mitochondrial biogenesis *via* the transcriptional co-activator PGC-1a[116] and the removal of damaged mitochondria by autophagy[117]. SIRT3 targets many enzymes involved in energy metabolism[118], and may directly control ROS production by deacetylating manganese superoxide dismutase, a mitochondrial antioxidant enzyme[119].

Mutations and deletions in mitochondrial DNA are known to accumulate with aging[3]. One of the most common and abundant mitochondrial DNA mutations is a 4977 base pair deletion between nucleotide positions 8470 to 13,477 (mtDNA4977)[120],which is known to accumulate in a variety of human tissues with age and has been demonstrated to be associated with several neurodegenerative diseases (including Alzheimer’s) and atherosclerosis[121,122]. Defective quality control by mitophagy (organelle-specific autophagy that targets abnormal or worn out mitochondria for degradation) leads to reduced clearance and turnover of ineffective and toxic mitochondria[123]. The net result of these processes is that there is a reduction in the formation of healthy mitochondria, an increased incidence of mitochondrial damage, and a failure to clear and recycle abnormal organelles, with consequently increasing bio-inefficiency, inflammation and cell death with aging.

Patients with advanced uremia are recognised to have low body temperatures, reduced stamina and low basal energy expenditure, suggesting a hypometabolic state[124]. Thompson *et al*[125] examined the forearm muscles of patients with ESRD using 31P-magnetic resonance spectroscopy. They noted increased phosphocreatine depletion and increased glycolytic ATP production during exercise, suggesting mitochondrial dysfunction due to either limitation of oxygen supply, reduced mitochondrial content or an intrinsic mitochondrial defect. Exercise-related abnormalities remained despite anemia correction with erythropoietin[125].

Lim *et al*[126] demonstrated a high frequency of mtDNA4977 in the skeletal muscle of chronically uremic patients, and that this correlated with enhanced oxidative damage to DNA, lipids and proteins of mitochondria compared to healthy controls. Liu *et al*[127] found that the incidence and proportion of mtDNA4977 in hair follicles was significantly higher amongst hemodialysis patients compared to age matched controls. Therefore mitochondrial abnormalities, contributing and consequent to high levels of oxidative stress in uremia, are strongly suspected to play a role in the causation of pathological aging in CKD, acting as a nexus for several processes, including defective bioenergetics, telomere attrition, DNA mutations, autophagy, inflammation and cell death. Mitochondrial abnormalities therefore represent a further crossover point between aging and the uremia.

**DISCUSSION**

In this review we have sought to draw the reader’s attention not just to the morphological similarities between advanced aging and uremia, but also to their shared characteristics at a cellular and molecular level (see Table 1). Experimental evidence has been provided to suggest common involvement of established cell death and survival pathways (apoptosis, necrosis, necroptosis and autophagy), and the presence of several of the recognised cellular and molecular features of the aging process in patients with ESRD and in experimental models of uremia. These include mitochondrial dysfunction, damage to genetic material, telomere shortening, impaired proteostasis, cell senescence, stem cell loss, oxidative stress, AGE accumulation, and klotho deficiency. Based on this evidence it could be posited that the physical resemblance between advanced age and uremia is underpinned by shared cellular and molecular “abnormalities”. These observations also reinforce the idea of the “uremic syndrome”, in which dysfunctions in multiple body systems arise due to a pervasive defect at a cellular level.

Information gathered by research into aging pathways and ‘anti-aging therapies’ might inform interventions to avoid, slow the progression of or even reverse some of the pathological changes seen in uremia. Given that these pathways are seen throughout most tissues and cell types it is also possible that a single intervention might treat several pathologies. However, the aging process remains incompletely understood in healthy individuals, and those pathways that are known are complex and heavily interconnected. Disentangling these in the uremic syndrome, in which multiple co-existing and interdependent metabolic abnormalities arise, will be a challenge. Additionally, many of these pathways have known (and possibly unknown) protective mechanisms (against malignant transformation, for example), thus blocking them may have unwanted and deleterious effects. What could be more immediately practicable would be employing some of the therapies known to be effective in improving the health of elderly patients, such as exercise.

The concept of accelerated aging in uremia is an intriguing and complex one that may yield important therapeutic targets and strategies to improve health outcomes in patients with CKD. Much work, however, remains to be done in understanding its cellular and molecular basis before any potential benefits can be realised.

**REFERENCES**

1 **Kooman JP**, Broers NJ, Usvyat L, Thijssen S, van der Sande FM, Cornelis T, Levin NW, Leunissen KM, Kotanko P. Out of control: accelerated aging in uremia. *Nephrol Dial Transplant* 2013; **28**: 48-54 [PMID: 23139404 DOI: 10.1093/ndt/gfs451]

2 **Amann K**, Ritz E. Cardiovascular abnormalities in ageing and in uraemia--only analogy or shared pathomechanisms? *Nephrol Dial Transplant* 1998; **13** Suppl 7: 6-11 [PMID: 9870430]

3 **López-Otín C**, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* 2013; **153**: 1194-1217 [PMID: 23746838 DOI: 10.1016/j.cell.2013.05.039]

4 **Koopman JJ**, Rozing MP, Kramer A, de Jager DJ, Ansell D, De Meester JM, Prütz KG, Finne P, Heaf JG, Palsson R, Kramar R, Jager KJ, Dekker FW, Westendorp RG. Senescence rates in patients with end-stage renal disease: a critical appraisal of the Gompertz model. *Aging Cell* 2011; **10**: 233-238 [PMID: 21108732 DOI: 10.1111/j.1474-9726.2010.00659.x]

5 **Foley RN**, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**: S112-S119 [PMID: 9820470]

6 **van Walraven C**, Manuel DG, Knoll G. Survival trends in ESRD patients compared with the general population in the United States. *Am J Kidney Dis* 2014; **63**: 491-499 [PMID: 24210591 DOI: 10.1053/j.ajkd.2013.09.011]

7 **Kato S**, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3**: 1526-1533 [PMID: 18701615 DOI: 10.2215/CJN.00950208]

8 **Betjes MG**, Meijers RW, Litjens NH. Loss of renal function causes premature aging of the immune system. *Blood Purif* 2013; **36**: 173-178 [PMID: 24496187 DOI: 10.1159/000356084]

9 **Fried LP**, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146-M156 [PMID: 11253156]

10 **Johansen KL**, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. *J Am Soc Nephrol* 2007; **18**: 2960-2967 [PMID: 17942958]

11 **Kurella Tamura M**, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. *Kidney Int* 2011; **79**: 14-22 [PMID: 20861818 DOI: 10.1038/ki.2010.336]

12 **Anand S**, Johansen KL, Kurella Tamura M. Aging and chronic kidney disease: the impact on physical function and cognition. *J Gerontol A Biol Sci Med Sci* 2014; **69**: 315-322 [PMID: 23913934 DOI: 10.1093/gerona/glt109]

13 **Takabatake Y**, Kimura T, Takahashi A, Isaka Y. Autophagy and the kidney: health and disease. *Nephrol Dial Transplant* 2014; **29**: 1639-1647 [PMID: 24520117 DOI: 10.1093/ndt/gft535]

14 **Kerr JF**, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 1972; **26**: 239-257 [PMID: 4561027]

15 **Galluzzi L**, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, Dawson TM, Dawson VL, El-Deiry WS, Fulda S, Gottlieb E, Green DR, Hengartner MO, Kepp O, Knight RA, Kumar S, Lipton SA, Lu X, Madeo F, Malorni W, Mehlen P, Nuñez G, Peter ME, Piacentini M, Rubinsztein DC, Shi Y, Simon HU, Vandenabeele P, White E, Yuan J, Zhivotovsky B, Melino G, Kroemer G. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. *Cell Death Differ* 2012; **19**: 107-120 [PMID: 21760595 DOI: 10.1038/cdd.2011.96]

16 **Kroemer G**, Levine B. Autophagic cell death: the story of a misnomer. *Nat Rev Mol Cell Biol* 2008; **9**: 1004-1010 [PMID: 18971948 DOI: 10.1038/nrm2529]

17 **Shen HM**, Codogno P. Autophagic cell death: Loch Ness monster or endangered species? *Autophagy* 2011; **7**: 457-465 [PMID: 21150268]

18 **Shen HM**, Codogno P. Autophagy is a survival force via suppression of necrotic cell death. *Exp Cell Res* 2012; **318**: 1304-1308 [PMID: 22366289 DOI: 10.1016/j.yexcr.2012.02.006]

19 **Verzola D**, Procopio V, Sofia A, Villaggio B, Tarroni A, Bonanni A, Mannucci I, De Cian F, Gianetta E, Saffioti S, Garibotto G. Apoptosis and myostatin mRNA are upregulated in the skeletal muscle of patients with chronic kidney disease. *Kidney Int* 2011; **79**: 773-782 [PMID: 21228768 DOI: 10.1038/ki.2010.494]

20 **Boivin MA**, Battah SI, Dominic EA, Kalantar-Zadeh K, Ferrando A, Tzamaloukas AH, Dwivedi R, Ma TA, Moseley P, Raj DS. Activation of caspase-3 in the skeletal muscle during haemodialysis. *Eur J Clin Invest* 2010; **40**: 903-910 [PMID: 20636378 DOI: 10.1111/j.1365-2362.2010.02347.x]

21 **Harwood SM**, Allen DA, Chesser AM, New DI, Raftery MJ, Yaqoob MM. Calpain is activated in experimental uremia: is calpain a mediator of uremia-induced myocardial injury? *Kidney Int* 2003; **63**: 866-877 [PMID: 12631067]

22 **Li M**, Wang Z, Ma T, Lu G, Yan R, Zhao L, Deng K, Dai K. Enhanced platelet apoptosis in chronic uremic patients. *Ren Fail* 2014; **36**: 847-853 [PMID: 24655051 DOI: 10.3109/0886022X.2014.899473]

23 **Sobol AB**, Kaminska M, Walczynska M, Walkowiak B. Effect of uremia and hemodialysis on platelet apoptosis. *Clin Appl Thromb Hemost* 2013; **19**: 320-323 [PMID: 22387580 DOI: 10.1177/1076029612437576]

24 **Heidenreich S**, Schmidt M, Bachmann J, Harrach B. Apoptosis of monocytes cultured from long-term hemodialysis patients. *Kidney Int* 1996; **49**: 792-799 [PMID: 8648922]

25 **Majewska E**, Baj Z, Sulowska Z, Rysz J, Luciak M. Effects of uraemia and haemodialysis on neutrophil apoptosis and expression of apoptosis-related proteins. *Nephrol Dial Transplant* 2003; **18**: 2582-2588 [PMID: 14605281]

26 **Soriano S**, Martín-Malo A, Carracedo J, Ramírez R, Rodríguez M, Aljama P. Lymphocyte apoptosis: role of uremia and permeability of dialysis membrane. *Nephron Clin Pract* 2005; **100**: c71-c77 [PMID: 15824510]

27 **Sardenberg C**, Suassuna P, Andreoli MC, Watanabe R, Dalboni MA, Manfredi SR, dos Santos OP, Kallas EG, Draibe SA, Cendoroglo M. Effects of uraemia and dialysis modality on polymorphonuclear cell apoptosis and function. *Nephrol Dial Transplant* 2006; **21**: 160-165 [PMID: 16155068]

28 **Feng B**, Zhang YQ, Mu J, Yuan FH, Ye ZL, Qi W, Guo YH, Zeng W, Luo ZF. Uraemic serum induces dysfunction of vascular endothelial cells: role of ubiquitin-proteasome pathway. *Exp Physiol* 2011; **96**: 801-815 [PMID: 21602294 DOI: 10.1113/expphysiol.2011.058149]

29 **Babelova A**, Jansen F, Sander K, Löhn M, Schäfer L, Fork C, Ruetten H, Plettenburg O, Stark H, Daniel C, Amann K, Pavenstädt H, Jung O, Brandes RP. Activation of Rac-1 and RhoA contributes to podocyte injury in chronic kidney disease. *PLoS One* 2013; **8**: e80328 [PMID: 24244677 DOI: 10: 1371/journal.pone.0080328]

30 **Okamura DM**, Pasichnyk K, Lopez-Guisa JM, Collins S, Hsu DK, Liu FT, Eddy AA. Galectin-3 preserves renal tubules and modulates extracellular matrix remodeling in progressive fibrosis. *Am J Physiol Renal Physiol* 2011; **300**: F245-F253 [PMID: 20962111 DOI: 10.1152/ajprenal.00326.2010]

31 **Grgic I**, Campanholle G, Bijol V, Wang C, Sabbisetti VS, Ichimura T, Humphreys BD, Bonventre JV. Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. *Kidney Int* 2012; **82**: 172-183 [PMID: 22437410 DOI: 10.1038/ki.2012.20]

32 **Gewin L**, Vadivelu S, Neelisetty S, Srichai MB, Paueksakon P, Pozzi A, Harris RC, Zent R. Deleting the TGF-β receptor attenuates acute proximal tubule injury. *J Am Soc Nephrol* 2012; **23**: 2001-2011 [PMID: 23160515 DOI: 10.1681/ASN.2012020139]

33 **Casalena G**, Daehn I, Bottinger E. Transforming growth factor-β, bioenergetics, and mitochondria in renal disease. *Semin Nephrol* 2012; **32**: 295-303 [PMID: 22835461 DOI: 10.1016/j.semnephrol.2012.04.009]

34 **Bhadra R**, Moretto MM, Castillo JC, Petrovas C, Ferrando-Martinez S, Shokal U, Leal M, Koup RA, Eleftherianos I, Khan IA. Intrinsic TGF-β signaling promotes age-dependent CD8+ T cell polyfunctionality attrition. *J Clin Invest* 2014; **124**: 2441-2455 [PMID: 24762437 DOI: 10.1172/JCI70522]

35 **Lexell J**. Human aging, muscle mass, and fiber type composition. *J Gerontol A Biol Sci Med Sci* 1995; **50 Spec No**: 11-16 [PMID: 7493202]

36 **Marzetti E**, Calvani R, Cesari M, Buford TW, Lorenzi M, Behnke BJ, Leeuwenburgh C. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J Biochem Cell Biol* 2013; **45**: 2288-2301 [PMID: 23845738 DOI: 10.1016/j.biocel.2013.06.024]

37 **Lightfoot AP**, McCormick R, Nye GA, McArdle A. Mechanisms of skeletal muscle ageing; avenues for therapeutic intervention. *Curr Opin Pharmacol* 2014; **16**: 116-121 [PMID: 24880707 DOI: 10.1016/j.coph.2014.05.005]

38 **Marzetti E**, Leeuwenburgh C. Skeletal muscle apoptosis, sarcopenia and frailty at old age. *Exp Gerontol* 2006; **41**: 1234-1238 [PMID: 17052879]

39 **Leeuwenburgh C**, Gurley CM, Strotman BA, Dupont-Versteegden EE. Age-related differences in apoptosis with disuse atrophy in soleus muscle. *Am J Physiol Regul Integr Comp Physiol* 2005; **288**: R1288-R1296 [PMID: 15650125]

40 **Park SY**, Kim HY, Lee JH, Yoon KH, Chang MS, Park SK. The age-dependent induction of apoptosis-inducing factor (AIF) in the human semitendinosus skeletal muscle. *Cell Mol Biol Lett* 2010; **15**: 1-12 [PMID: 19685011 DOI: 10.2478/s11658-009-0030-4]

41 **Park SY**, Lee JH, Kim HY, Yoon KH, Park SK, Chang MS. Differential expression of apoptosis-related factors induces the age-related apoptosis of the gracilis muscle in humans. *Int J Mol Med* 2014; **33**: 1110-1116 [PMID: 24584667 DOI: 10.3892/ijmm.2014.1675]

42 **Lim JH**, Kim EN, Kim MY, Chung S, Shin SJ, Kim HW, Yang CW, Kim YS, Chang YS, Park CW, Choi BS. Age-associated molecular changes in the kidney in aged mice. *Oxid Med Cell Longev* 2012; **2012**: 171383 [PMID: 23326623 DOI: 10.1155/2012/171383]

43 **Charriaut-Marlangue C**, Ben-Ari Y. A cautionary note on the use of the TUNEL stain to determine apoptosis. *Neuroreport* 1995; **7**: 61-64 [PMID: 8742417]

44 **Vercammen D**, Brouckaert G, Denecker G, Van de Craen M, Declercq W, Fiers W, Vandenabeele P. Dual signaling of the Fas receptor: initiation of both apoptotic and necrotic cell death pathways. *J Exp Med* 1998; **188**: 919-930 [PMID: 9730893]

45 **Giampietri C**, Starace D, Petrungaro S, Filippini A, Ziparo E. Necroptosis: molecular signalling and translational implications. *Int J Cell Biol* 2014; **2014**: 490275 [PMID: 24587805 DOI: 10.1155/2014/490275]

46 **Hu J**, Du J, Zhang L, Price SR, Klein JD, Wang XH. XIAP reduces muscle proteolysis induced by CKD. *J Am Soc Nephrol* 2010; **21**: 1174-1183 [PMID: 20431038 DOI: 10.1681/ASN.200910101]

47 **He S**, Wang L, Miao L, Wang T, Du F, Zhao L, Wang X. Receptor interacting protein kinase-3 determines cellular necrotic response to TNF-alpha. *Cell* 2009; **137**: 1100-1111 [PMID: 19524512 DOI: 10.1016/j.cell.2009.05.021]

48 **Feoktistova M**, Geserick P, Panayotova-Dimitrova D, Leverkus M. Pick your poison: the Ripoptosome, a cell death platform regulating apoptosis and necroptosis. *Cell Cycle* 2012; **11**: 460-467 [PMID: 22274400 DOI: 10.4161/cc.11.3.19060]

49 **Newton K**, Dugger DL, Wickliffe KE, Kapoor N, de Almagro MC, Vucic D, Komuves L, Ferrando RE, French DM, Webster J, Roose-Girma M, Warming S, Dixit VM. Activity of protein kinase RIPK3 determines whether cells die by necroptosis or apoptosis. *Science* 2014; **343**: 1357-1360 [PMID: 24557836 DOI: 10.1126/science.1249361]

50 **Moujalled DM**, Cook WD, Okamoto T, Murphy J, Lawlor KE, Vince JE, Vaux DL. TNF can activate RIPK3 and cause programmed necrosis in the absence of RIPK1. *Cell Death Dis* 2013; **4**: e465 [PMID: 23328672 DOI: 10.1038/cddis.2012.201]

51 **Yorimitsu T**, Klionsky DJ. Autophagy: molecular machinery for self-eating. *Cell Death Differ* 2005; **12 Suppl 2**: 1542-1552 [PMID: 16247502]

52 **Mizushima N**, Klionsky DJ. Protein turnover via autophagy: implications for metabolism. *Annu Rev Nutr* 2007; **27**: 19-40 [PMID: 17311494]

53 **Kuma A**, Hatano M, Matsui M, Yamamoto A, Nakaya H, Yoshimori T, Ohsumi Y, Tokuhisa T, Mizushima N. The role of autophagy during the early neonatal starvation period. *Nature* 2004; **432**: 1032-1036 [PMID: 15525940]

54 **Yan L**, Vatner DE, Kim SJ, Ge H, Masurekar M, Massover WH, Yang G, Matsui Y, Sadoshima J, Vatner SF. Autophagy in chronically ischemic myocardium. *Proc Natl Acad Sci U S A* 2005; **102**: 13807-13812 [PMID: 16174725]

55 **Nikoletopoulou V**, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. *Biochim Biophys Acta* 2013; **1833**: 3448-3459 [PMID: 23770045 DOI: 10.1016/j.bbamcr.2013.06.001]

56 **Liang J**, Shao SH, Xu ZX, Hennessy B, Ding Z, Larrea M, Kondo S, Dumont DJ, Gutterman JU, Walker CL, Slingerland JM, Mills GB. The energy sensing LKB1-AMPK pathway regulates p27(kip1) phosphorylation mediating the decision to enter autophagy or apoptosis. *Nat Cell Biol* 2007; **9**: 218-224 [PMID: 17237771]

57 **Li H**, Wang P, Sun Q, Ding WX, Yin XM, Sobol RW, Stolz DB, Yu J, Zhang L. Following cytochrome c release, autophagy is inhibited during chemotherapy-induced apoptosis by caspase 8-mediated cleavage of Beclin 1. *Cancer Res* 2011; **71**: 3625-3634 [PMID: 21444671 DOI: 10.1158/0008-5472.CAN-10-4475]

58 **Livesey KM**, Kang R, Vernon P, Buchser W, Loughran P, Watkins SC, Zhang L, Manfredi JJ, Zeh HJ, Li L, Lotze MT, Tang D. p53/HMGB1 complexes regulate autophagy and apoptosis. *Cancer Res* 2012; **72**: 1996-2005 [PMID: 22345153 DOI: 10.1158/0008-5472.CAN-11-2291]

59 **Kim SY**, Song X, Zhang L, Bartlett DL, Lee YJ. Role of Bcl-xL/Beclin-1 in interplay between apoptosis and autophagy in oxaliplatin and bortezomib-induced cell death. *Biochem Pharmacol* 2014; **88**: 178-188 [PMID: 24486574 DOI: 10.1016/j.bcp.2014.01.027]

60 **Jiang Q**, Li F, Shi K, Wu P, An J, Yang Y, Xu C. Involvement of p38 in signal switching from autophagy to apoptosis via the PERK/eIF2α/ATF4 axis in selenite-treated NB4 cells. *Cell Death Dis* 2014; **5**: e1270 [PMID: 24874742 DOI: 10,1038/cddis.2014.200]

61 **Kimura T**, Takabatake Y, Takahashi A, Kaimori JY, Matsui I, Namba T, Kitamura H, Niimura F, Matsusaka T, Soga T, Rakugi H, Isaka Y. Autophagy protects the proximal tubule from degeneration and acute ischemic injury. *J Am Soc Nephrol* 2011; **22**: 902-913 [PMID: 21493778 DOI: 10.1681/ASN.2010070705]

62 **Dai XY**, Zhao MM, Cai Y, Guan QC, Zhao Y, Guan Y, Kong W, Zhu WG, Xu MJ, Wang X. Phosphate-induced autophagy counteracts vascular calcification by reducing matrix vesicle release. *Kidney Int* 2013; **83**: 1042-1051 [PMID: 23364520 DOI: 10.1038/ki.2012.482]

63 **He W**, Wang Q, Srinivasan B, Xu J, Padilla MT, Li Z, Wang X, Liu Y, Gou X, Shen HM, Xing C, Lin Y. A JNK-mediated autophagy pathway that triggers c-IAP degradation and necroptosis for anticancer chemotherapy. *Oncogene* 2014; **33**: 3004-3013 [PMID: 23831571 DOI: 10.1038/onc.2013.256]

64 **Bonapace L**, Bornhauser BC, Schmitz M, Cario G, Ziegler U, Niggli FK, Schäfer BW, Schrappe M, Stanulla M, Bourquin JP. Induction of autophagy-dependent necroptosis is required for childhood acute lymphoblastic leukemia cells to overcome glucocorticoid resistance. *J Clin Invest* 2010; **120**: 1310-1323 [PMID: 20200450 DOI: 10.1172/JCI39987]

65 **Bell BD**, Leverrier S, Weist BM, Newton RH, Arechiga AF, Luhrs KA, Morrissette NS, Walsh CM. FADD and caspase-8 control the outcome of autophagic signaling in proliferating T cells. *Proc Natl Acad Sci U S A* 2008; **105**: 16677-16682 [PMID: 18946037 DOI: 10.1073/pnas.0808597105]

66 **Rubinsztein DC**, Mariño G, Kroemer G. Autophagy and aging. *Cell* 2011; **146**: 682-695 [PMID: 21884931 DOI: 10.1016/j.cell.2011.07.030]

67 **Chen WT**, Hung KC, Wen MS, Hsu PY, Chen TH, Wang HD, Fang JT, Shie SS, Wang CY. Impaired leukocytes autophagy in chronic kidney disease patients. *Cardiorenal Med* 2013; **3**: 254-264 [PMID: 24474954 DOI: 10.1159/000356212]

68 **Siedlecki AM**, Jin X, Muslin AJ. Uremic cardiac hypertrophy is reversed by rapamycin but not by lowering of blood pressure. *Kidney Int* 2009; **75**: 800-808 [PMID: 19165175 DOI: 10.1038/ki.2008.690]

69 **Harrison DE**, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 2009; **460**: 392-395 [PMID: 19587680 DOI: 10.1038/nature08221]

70 **Campisi J**, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 2007; **8**: 729-740 [PMID: 17667954]

71 **Hayflick L**, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res* 1961; **25**: 585-621 [PMID: 13905658]

72 **Harley CB**, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature* 1990; **345**: 458-460 [PMID: 2342578]

73 **Kuilman T**, Michaloglou C, Mooi WJ, Peeper DS. The essence of senescence. *Genes Dev* 2010; **24**: 2463-2479 [PMID: 21078816 DOI: 10.1101/gad.1971610]

74 **Muteliefu G**, Shimizu H, Enomoto A, Nishijima F, Takahashi M, Niwa T. Indoxyl sulfate promotes vascular smooth muscle cell senescence with upregulation of p53, p21, and prelamin A through oxidative stress. *Am J Physiol Cell Physiol* 2012; **303**: C126-C134 [PMID: 22555846 DOI: 10.1152/ajpcell.00329.2011]

75 **Dimri GP**, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc Natl Acad Sci U S A* 1995; **92**: 9363-9367 [PMID: 7568133]

76 **Jimenez R**, Carracedo J, Santamaría R, Soriano S, Madueño JA, Ramírez R, Rodríguez M, Martín-Malo A, Aljama P. Replicative senescence in patients with chronic kidney failure. *Kidney Int Suppl* 2005; **99**: S11-S15 [PMID: 16336562]

77 **Tsirpanlis G**, Chatzipanagiotou S, Boufidou F, Kordinas V, Alevyzaki F, Zoga M, Kyritsis I, Stamatelou K, Triantafyllis G, Nicolaou C. Telomerase activity is decreased in peripheral blood mononuclear cells of hemodialysis patients. *Am J Nephrol* 2006; **26**: 91-96 [PMID: 16543712]

78 **Greider CW**, Blackburn EH. Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. *Cell* 1985; **43**: 405-413 [PMID: 3907856]

79 **Adijiang A**, Higuchi Y, Nishijima F, Shimizu H, Niwa T. Indoxyl sulfate, a uremic toxin, promotes cell senescence in aorta of hypertensive rats. *Biochem Biophys Res Commun* 2010; **399**: 637-641 [PMID: 20691162 DOI: 10.1016/j.bbrc.2010.07.130]

80 **Carracedo J**, Merino A, Briceño C, Soriano S, Buendía P, Calleros L, Rodriguez M, Martín-Malo A, Aljama P, Ramírez R. Carbamylated low-density lipoprotein induces oxidative stress and accelerated senescence in human endothelial progenitor cells. *FASEB J* 2011; **25**: 1314-1322 [PMID: 21228221 DOI: 10.1096/fj.10-173377]

81 **Klinkhammer BM**, Kramann R, Mallau M, Makowska A, van Roeyen CR, Rong S, Buecher EB, Boor P, Kovacova K, Zok S, Denecke B, Stuettgen E, Otten S, Floege J, Kunter U. Mesenchymal stem cells from rats with chronic kidney disease exhibit premature senescence and loss of regenerative potential. *PLoS One* 2014; **9**: e92115 [PMID: 24667162 DOI: 10.1371/journal.pone.0092115]

82 **Kuro-o M**, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997; **390**: 45-51 [PMID: 9363890]

83 **Urakawa I**, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature* 2006; **444**: 770-774 [PMID: 17086194]

84 **Hu MC**, Kuro-o M, Moe OW. Klotho and chronic kidney disease. *Contrib Nephrol* 2013; **180**: 47-63 [PMID: 23652549 DOI: 10.1159/000346778]

85 **Hu MC**, Shi M, Zhang J, Quiñones H, Griffith C, Kuro-o M, Moe OW. Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 124-136 [PMID: 21115613 DOI: 10.1681/ASN.2009121311]

86 **Chang Q**, Hoefs S, van der Kemp AW, Topala CN, Bindels RJ, Hoenderop JG. The beta-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. *Science* 2005; **310**: 490-493 [PMID: 16239475]

87 **Mitani H**, Ishizaka N, Aizawa T, Ohno M, Usui S, Suzuki T, Amaki T, Mori I, Nakamura Y, Sato M, Nangaku M, Hirata Y, Nagai R. In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. *Hypertension* 2002; **39**: 838-843 [PMID: 11967236]

88 **Tsujikawa H**, Kurotaki Y, Fujimori T, Fukuda K, Nabeshima Y. Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. *Mol Endocrinol* 2003; **17**: 2393-2403 [PMID: 14528024]

89 **Silver J**, Naveh-Many T. FGF23 and the parathyroid glands. *Pediatr Nephrol* 2010; **25**: 2241-2245 [PMID: 20526631 DOI: 10.1007/s00467-010-1565-3]

90 **Manya H**, Akasaka-Manya K, Endo T. Klotho protein deficiency and aging. *Geriatr Gerontol Int* 2010; **10 Suppl 1**: S80-S87 [PMID: 20590845 DOI: 10.1111/j.1447-0594.2010.00596.x]

91 **Yamazaki Y**, Imura A, Urakawa I, Shimada T, Murakami J, Aono Y, Hasegawa H, Yamashita T, Nakatani K, Saito Y, Okamoto N, Kurumatani N, Namba N, Kitaoka T, Ozono K, Sakai T, Hataya H, Ichikawa S, Imel EA, Econs MJ, Nabeshima Y. Establishment of sandwich ELISA for soluble alpha-Klotho measurement: Age-dependent change of soluble alpha-Klotho levels in healthy subjects. *Biochem Biophys Res Commun* 2010; **398**: 513-518 [PMID: 20599764]

92 **Koh N**, Fujimori T, Nishiguchi S, Tamori A, Shiomi S, Nakatani T, Sugimura K, Kishimoto T, Kinoshita S, Kuroki T, Nabeshima Y. Severely reduced production of klotho in human chronic renal failure kidney. *Biochem Biophys Res Commun* 2001; **280**: 1015-1020 [PMID: 11162628]

93 **Liu H**, Fergusson MM, Castilho RM, Liu J, Cao L, Chen J, Malide D, Rovira II, Schimel D, Kuo CJ, Gutkind JS, Hwang PM, Finkel T. Augmented Wnt signaling in a mammalian model of accelerated aging. *Science* 2007; **317**: 803-806 [PMID: 17690294]

94 **de Oliveira RM**. Klotho RNAi induces premature senescence of human cells via a p53/p21 dependent pathway. *FEBS Lett* 2006; **580**: 5753-5758 [PMID: 17014852]

95 **Ikushima M**, Rakugi H, Ishikawa K, Maekawa Y, Yamamoto K, Ohta J, Chihara Y, Kida I, Ogihara T. Anti-apoptotic and anti-senescence effects of Klotho on vascular endothelial cells. *Biochem Biophys Res Commun* 2006; **339**: 827-832 [PMID: 16325773]

96 **Maekawa Y**, Ohishi M, Ikushima M, Yamamoto K, Yasuda O, Oguro R, Yamamoto-Hanasaki H, Tatara Y, Takeya Y, Rakugi H. Klotho protein diminishes endothelial apoptosis and senescence via a mitogen-activated kinase pathway. *Geriatr Gerontol Int* 2011; **11**: 510-516 [PMID: 21518171 DOI: 10.1111/j.1447-0594.2011.00699.x]

97 **Liu F**, Wu S, Ren H, Gu J. Klotho suppresses RIG-I-mediated senescence-associated inflammation. *Nat Cell Biol* 2011; **13**: 254-262 [PMID: 21336305 DOI: 10.1038/ncb2167]

98 **Lindberg K**, Amin R, Moe OW, Hu MC, Erben RG, Ostman Wernerson A, Lanske B, Olauson H, Larsson TE. The kidney is the principal organ mediating klotho effects. *J Am Soc Nephrol* 2014; **25**: 2169-2175 [PMID: 24854271 DOI: 10.1681/ASN.2013111209]

99 **Kalim S**, Karumanchi SA, Thadhani RI, Berg AH. Protein carbamylation in kidney disease: pathogenesis and clinical implications. *Am J Kidney Dis* 2014; **64**: 793-803 [PMID: 25037561 DOI: 10.1053/j.ajkd.2014.04.034]

100 **Brownlee M**. Advanced protein glycosylation in diabetes and aging. *Annu Rev Med* 1995; **46**: 223-234 [PMID: 7598459]

101 **Singh R**, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. *Diabetologia* 2001; **44**: 129-146 [PMID: 11270668]

102 **Monnier VM**, Glomb M, Elgawish A, Sell DR. The mechanism of collagen cross-linking in diabetes: a puzzle nearing resolution. *Diabetes* 1996; **45 Suppl 3**: S67-S72 [PMID: 8674897]

103 **Liu J**, Huang K, Cai GY, Chen XM, Yang JR, Lin LR, Yang J, Huo BG, Zhan J, He YN. Receptor for advanced glycation end-products promotes premature senescence of proximal tubular epithelial cells via activation of endoplasmic reticulum stress-dependent p21 signaling. *Cell Signal* 2014; **26**: 110-121 [PMID: 24113348 DOI: 10.1016/j.cellsig.2013.10.002]

104 **Adamopoulos C**, Farmaki E, Spilioti E, Kiaris H, Piperi C, Papavassiliou AG. Advanced glycation end-products induce endoplasmic reticulum stress in human aortic endothelial cells. *Clin Chem Lab Med* 2014; **52**: 151-160 [PMID: 23454718 DOI: 10.1515/cclm-2012-0826]

105 **Weiss MF**, Erhard P, Kader-Attia FA, Wu YC, Deoreo PB, Araki A, Glomb MA, Monnier VM. Mechanisms for the formation of glycoxidation products in end-stage renal disease. *Kidney Int* 2000; **57**: 2571-2585 [PMID: 10844627]

106 **Himmelfarb J**, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 2002; **62**: 1524-1538 [PMID: 12371953]

107 **Taki K**, Takayama F, Tsuruta Y, Niwa T. Oxidative stress, advanced glycation end product, and coronary artery calcification in hemodialysis patients. *Kidney Int* 2006; **70**: 218-224 [PMID: 16723988]

108 **Miyata T**, Wada Y, Cai Z, Iida Y, Horie K, Yasuda Y, Maeda K, Kurokawa K, van Ypersele de Strihou C. Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. *Kidney Int* 1997; **51**: 1170-1181 [PMID: 9083283]

109 **Harman D**. The free radical theory of aging: effect of age on serum copper levels. *J Gerontol* 1965; **20**: 151-153 [PMID: 14284786]

110 **Hekimi S**, Lapointe J, Wen Y. Taking a "good" look at free radicals in the aging process. *Trends Cell Biol* 2011; **21**: 569-576 [PMID: 21824781 DOI: 10.1016/j.tcb.2011.06.008]

111 **Kroemer G**, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization in cell death. *Physiol Rev* 2007; **87**: 99-163 [PMID: 17237344]

112 **Green DR**, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. *Science* 2011; **333**: 1109-1112 [PMID: 21868666 DOI: 10.1126/science.1201940]

113 **Sahin E**, DePinho RA. Axis of ageing: telomeres, p53 and mitochondria. *Nat Rev Mol Cell Biol* 2012; **13**: 397-404 [PMID: 22588366 DOI: 10.1038/nrm3352]

114 **Bernardes de Jesus B**, Vera E, Schneeberger K, Tejera AM, Ayuso E, Bosch F, Blasco MA. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Mol Med* 2012; **4**: 691-704 [PMID: 22585399 DOI: 10.1002/emmm.201200245]

115 **Herskovits AZ**, Guarente L. Sirtuin deacetylases in neurodegenerative diseases of aging. *Cell Res* 2013; **23**: 746-758 [PMID: 23689277 DOI: 10.1038/cr.2013.70]

116 **Rodgers JT**, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature* 2005; **434**: 113-118 [PMID: 15744310]

117 **Lee IH**, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, Tsokos M, Alt FW, Finkel T. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. *Proc Natl Acad Sci U S A* 2008; **105**: 3374-3379 [PMID: 18296641 DOI: 10.1073/pnas.0712145105]

118 **Giralt A**, Villarroya F. SIRT3, a pivotal actor in mitochondrial functions: metabolism, cell death and aging. *Biochem J* 2012; **444**: 1-10 [PMID: 22533670 DOI: 10.1042/BJ20120030]

119 **Qiu X**, Brown K, Hirschey MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab* 2010; **12**: 662-667 [PMID: 21109198 DOI: 10.1016/j.cmet.2010.11.015]

120 **Anderson S**, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJ, Staden R, Young IG. Sequence and organization of the human mitochondrial genome. *Nature* 1981; **290**: 457-465 [PMID: 7219534]

121 **Corral-Debrinski M**, Stepien G, Shoffner JM, Lott MT, Kanter K, Wallace DC. Hypoxemia is associated with mitochondrial DNA damage and gene induction. Implications for cardiac disease. *JAMA* 1991; **266**: 1812-1816 [PMID: 1890710]

122 **Rao M**. Aging and nephrology: the sun sets. *Indian J Nephrol* 2005; **15:** S3-S6

123 **Wang K**, Klionsky DJ. Mitochondria removal by autophagy. *Autophagy* 2011; **7**: 297-300 [PMID: 21252623]

124 **Meyer TW**, Hostetter TH. Uremia. *N Engl J Med* 2007; **357**: 1316-1325 [PMID: 17898101]

125 **Thompson CH**, Kemp GJ, Taylor DJ, Ledingham JG, Radda GK, Rajagopalan B. Effect of chronic uraemia on skeletal muscle metabolism in man. *Nephrol Dial Transplant* 1993; **8**: 218-222 [PMID: 8385287]

126 **Lim PS**, Ma YS, Cheng YM, Chai H, Lee CF, Chen TL, Wei YH. Mitochondrial DNA mutations and oxidative damage in skeletal muscle of patients with chronic uremia. *J Biomed Sci* 2002; **9**: 549-560 [PMID: 12372993]

127 **Liu CS**, Ko LY, Lim PS, Kao SH, Wei YH. Biomarkers of DNA damage in patients with end-stage renal disease: mitochondrial DNA mutation in hair follicles. *Nephrol Dial Transplant* 2001; **16**: 561-565 [PMID: 11239032]

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**Table 1 Events common to aging and uremia covered by this review**

|  |  |
| --- | --- |
| Aging | Uremia |
| TGF-β ↑ | TGF-β ↑ |
| Autophagy ↓ | Autophagy ↓ |
| Apoptosis ↑ (muscle) | Apoptosis ↑ |
| Senescence ↑ | Senescence ↑ |
| Telomere shortening ↑ | Telomere shortening ↑ |
| Stem cell exhaustion ↑ | Stem cell exhaustion ↑ |
| Klotho ↓ | Klotho ↓ |
| AGEs ↑ | AGEs ↑ |
| Mitochondrial dysfunction ↑ | Mitochondrial dysfunction ↑ |