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The Role of Peptidyl Prolyl Isomerases in Aging and Vascular Diseases

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Abstract

Peptidyl prolyl isomerases (PPIases) are proteins belonging to the immunophilin family and are characterised by their cis-trans isomerization activity at the X-Pro peptide bond, in addition to their tetratricopeptide repeat (TPR) domain, important for interaction with the molecular chaperone, Hsp90. Due to this unique structure these proteins are able to facilitate protein-protein interactions which can impact significantly on a range of cellular processes such as cell signalling, differentiation, cell cycle progression, metabolic activity and apoptosis. Malfunction and/or dysregulation of most members of this class of proteins promotes cellular damage and tissue/organ failure, predisposing to ageing and age-related diseases. Many individual genes within the PPIase family are associated with several age-related diseases including cardiovascular diseases (CVDs), atherosclerosis, type II diabetes (T2D), chronic kidney disease (CKD), neurodegeneration, cancer and age-related macular degeneration (AMD), in addition to the ageing process itself. This review will focus on the different roles of PPIases, and their therapeutic/biomarker potential in these age-related vascular diseases.

Keywords: PPIases, FKBP, CypA, Pin1, aging, age-related diseases, vascular

Introduction

With an increase in life expectancy, the biggest challenge facing healthcare organisations is the management of age-related diseases. Age is the most strongly associated risk factor for diseases such as CVDs, cancer, T2D, CKD, neurodegenerative diseases, AMD and atherosclerosis¹. Therefore finding a way of slowing down aging and delaying or preventing these age-related

diseases will lead to longer life expectancy, healthy aging, and a better quality of life, thus reducing the financial burden on healthcare systems.

Twin studies have shown that for cohorts born about 100 years ago, approximately 25% of the variation in population lifespan is determined by genetic differences and that the genetic influence on lifespan and age-related diseases in particular, becomes relevant in those people who survive to 60 years². There have been major successes in the identification of new genetic variants involved in important age-related disorders including: cancer (in particular, prostate, breast and colon³⁻⁵; CVDs^{6,7} and CKD⁸. However, many of these genetic variants, individually or combined, explain only a small component of the heritability of each disease. This modest contribution does not match with the high recurrence risks of age-related disorders in families. This apparent paradox may in part be explained by the contribution of low frequency variants, unrecognized single nucleotide polymorphism (SNP) epistasis, gene-environment interactions and epigenetic and gene expression changes. Epigenetic data is particularly valuable to help interpret genome wide association studies (GWAS) by adding biological/mechanistic information^{9,10}. One of the major challenges over the next few decades will be to unravel the interactions between genetic variants and environmental factors. GWAS have shown that SNPs linked to multiple diseases are generally clustered on chromosome 6, in particular the Major Histocompatibility (MHC) locus within 6p21, in addition to the INK4/ARF (CDKN2a/b) tumour suppressor locus on chromosome 9p21.3. These SNPs accounted for almost a third of all the diseases analysed by GWAS¹¹.

Aberrantly activated pathways in aging identified by association studies using long-lived cohorts include the insulin/insulin growth factor-1 (IGF-1), antioxidant, inflammatory, sirtuin, lipid metabolism, stress resistance and the mammalian target of rapamycin (mTOR)

pathways¹²⁻¹⁸. The main targets of the insulin and IGF-1 pathway are the FOXO transcription factors which have important roles in stress resistance, immunity and metabolism^{19,20}. The sirtuin and mTOR pathways are nutrient-sensing pathways and these pathways are linked to longevity (high sirtuin and low mTOR levels) because of their ability to mediate the effects of nutrients and insulin. Since the mTOR pathway is a strongly implicated pathway, it represents a viable target for prevention of aging and age-related disease. Peptidyl prolyl isomerases (PPIases) also known as immunophilins, are a family of proteins that bind to rapamycin-mTOR complexes and regulate the mTOR signaling pathway. These proteins therefore play a significant role in aging and age-related diseases²¹. Therefore, the focus of this review will be on the role of PPIase in aging and age-related diseases: CVDs, T2D, CKD, ND, AMD and cancer.

PPIases

The PPIase family are important determinants of ageing and disease. Many individual genes within the PPIase family are associated with several age-related diseases, in addition to the ageing process itself. Peptidyl prolyl isomerases (PPIases) are proteins belonging to the immunophilin family and are characterised by their cis-trans isomerization activity at the X-Pro peptide bond. The term immunophilin is derived from the ability of these proteins to bind immunosuppressive drugs; cyclophilins (18 members, 17 genes) bind to cyclosporine A and FKBP (FK506 binding proteins; 17 members, 17 genes) bind to the macrolide, FK506. A third subfamily, parvulins (3 members, 2 genes), contain the PPIase domain but do not bind immunosuppressive drugs²². Immunosuppression is generally associated with the smaller PPIase-complexes and the larger PPIases lack this effect but they contain the tetratricopeptide repeat (TPR) domain facilitating protein-protein interactions, significantly impacting many essential cellular processes. Therefore, aberrant function of these proteins can lead to tissue damage and predisposition to aging and age-related disease^{23,24}.

Aging

Aging, in terms of endothelial system changes, encompasses molecular and functional modifications such as shortening of telomeres, structurally and functionally altered endothelial cells, increased levels of vasoconstrictive, pro-inflammatory, proliferative and pro-coagulatory substances, reduced nitric oxide (NO) bioactivity and apoptosis²⁵. These processes lead to an increase in blood pressure, a reduction in the glomerular filtration rate, atherosclerosis and therefore to age-related diseases.

More recently, cellular senescence and changes in immune system surveillance have been identified as being the most significant processes in aging due to their ability to activate pro-inflammatory pathways^{26–28}. Other aberrant aging processes include protein aggregation, DNA damage, mitochondrial damage and accumulation of reactive oxygen species (ROS; Figure 1). More recently, research has focused on the role of aging stem cells on age-related diseases and the aging process itself. Due to their long lifespan, stem cells are more prone to cellular damage as they accumulate ROS, damaged proteins, DNA damage, epigenetic alterations and mitochondrial dysfunction²⁹. All of these aberrant changes can lead to stem cell apoptosis, senescence, dysfunction and thus the inability of stem cells to orchestrate tissue regeneration and proliferation.

The role of PPIases in aging

The role of many individual PPIases in ageing has been studied. PPIases play a significant role by binding to and regulating the mTOR signalling pathway which has very well characterised roles in ageing and age-related diseases²¹. Furthermore, other PPIases such as CypA expression increases with ageing^{30–32} and suppression of CypB induces cellular senescence³³ and its

expression decreases in ageing rats³⁴. Likewise, CypC^{35,36}; CypD³⁷⁻³⁹; CypJ⁴⁰ have all demonstrated significant roles in animal models of ageing. FKBP, a divergent member of the FKBP group of immunophilins, resides on the gene loci, 6p21.3 which is within a significant peak of age-related disease association¹¹. Furthermore, it controls the levels of Sirt1 (unpublished data from our lab), a direct regulator of aging⁴¹. Importantly, Pin1 has the strongest link to ageing and is indeed a critical regulator of aging; Pin1^{-/-} mice develop normally but show pronounced and premature aging, with reduced body size and bone density as well as atrophy of the skin, testis and breast⁴². Pin1 appears to control ageing by telomere shortening, via TRF1 phosphorylation and stability⁴³, and also regulates senescence, via the p53-BTG2 pathway⁴⁴.

Cardiovascular diseases

CVDs are the most common of all age-related diseases and are the leading cause of death in people over the age of sixty five⁴⁵. Because the aging process leads to an overproduction of pro-inflammatory, pro-coagulatory, vasoconstrictive and other related factors, it can lead to brittle heart walls, leaky/thickened heart valves and deterioration in the heart muscle, leading to poorer ability to pump blood efficiently around the body⁴⁶. Therefore, these changes together with the age-related changes in the endothelial system mentioned above, can lead to atherosclerosis, angina, atrial fibrillation and orthotropic hypertension, potentially causing myocardial infarction and stroke⁴⁷. The key signalling pathways associated with CVDs include the insulin and IGF-1, sirtuin and mTOR pathways. The IGF-1 pathway appears to have a protective mechanism against atherosclerosis in humans whereas in mice it led to an increase in life span^{48,49}. The role of the sirtuin pathway in CVD is unclear due to a lack of consistency in the published data to suggest a strong role for this pathway in the development of CVDs;

further research is therefore required⁵⁰. On the other hand, the inhibition of the mTOR pathway, has demonstrated a role in longevity⁵¹; rapamycin can alleviate cardiac hypertrophy, T2D, adipogenesis and lipogenesis as such has a vital role in aging and CVDs^{47,52}. Furthermore, the AMPK (AMP-protein activated kinase) signalling pathway, which negatively regulates mTOR, is also involved in CVDs; aberrant expression of AMPK in simple organisms, mice and humans has been implicated CVDs and aging^{53–55}.

The role of PPIases in CVDs

FKBP12, a cytoplasmic FKBP, has a well-established interaction with the ryanodine receptor, RyRs, resulting in stabilisation of this channel. FKBP12 knockdown results in the opening of the RyRs channel and augments calcium release into a wide range of tissues^{56,57}. Therefore, FKBP12 and FKBP12.6 have an important role in cardiac regulation and deficiency of these proteins contributes to the pathogenesis of hypertension. In murine models, FKBP12 knockout (KO) resulted in cardiac defects and altered ryanodine receptor function^{58–61}. Therefore the treatment with FK506 and rapamycin may contribute to vascular dysfunction and hypertension by induced intracellular leakage of calcium ions in endothelial cells^{56,62}. A novel antiarrhythmic compound, K201 (JTV– 519), which binds to FKBP12.6, thus stabilising RyRs channels and decreasing spontaneous calcium release, is currently in clinical trials⁶³.

The most abundant member of the cyclophilin family, CypA, is excreted exogenously in response to inflammatory stimuli and able to increase ROS formation in endothelial cells, macrophages and vascular smooth muscle cells^{64–67}. Therefore, CypA is a critical regulator of CVDs. In terms of vascular remodeling, CypA KO mice had significantly less thickened arteries when compared to the wild type (WT) mice and therefore are less likely to developed

cardiac/vascular hypertrophy or myocardial ischaemia which can lead to myocardial injury⁶⁸⁻⁷⁰. CypA's involvement in ROS generation and cardiac fibroblast proliferation and migration, renders it responsible for the development of cardiac hypertrophy, the basis of most of the CVDs^{70,71}. Interestingly serum levels of CypA were significantly higher in patients with acute coronary syndrome (ACS) when compared to healthy patients or patients with stable angina and the levels also correlated with the severity of ACS, potentially suggesting a role for CypA as a biomarker to predict the severity of ACS⁷². Furthermore, CypA has a well-established role in atherosclerosis and the mechanisms involve an increase in the uptake of low-density lipoproteins by the vessel wall due to CypA-mediated overexpression of the scavenger receptors, pro-inflammatory and endothelial cell activation of vascular cell adhesion molecule-1 (VCAM-1) and a decrease of the endothelial nitric oxide synthase³². Another cyclophilin with a role in CVDs is CypD. Interestingly, it has a cytoprotective role during ischaemia-reperfusion injury as a regulator of the mitochondrial permeability transition pore (mPTP) complex formation^{73,74}.

Finally, Pin1, the most extensively researched member of the parvulins subgroup (Pin1-3), has a significant role in cardiac hypertrophy. The loss of Pin1 attenuates cardiac hypertrophic responses following severe vasoconstriction by binding to Akt, mitogen activated protein kinase (MEK) and Raf-1; all essential components of the cardiac hypertrophy⁷⁵.

Type II diabetes

T2D is an age-associated disease, more specifically related to accelerated aging. Most T2D patients are between the age of 65 and 74⁷⁶. T2D is more prevalent in men within this age group and its incidence decreases above 75 years of age⁷⁷. The pathophysiology of T2D is very

closely linked to the dysfunction of pancreatic islet β -cells in addition to insulin resistance⁷⁸. The pancreatic β -cells appear to lose their proliferative, secretory and regenerative function as part of aging, mainly due to cellular senescence⁷⁹. Furthermore, the proliferative and apoptotic ability of the pancreatic β -cells seem to be the most apparent change in aging, obese and diabetic patients. These cells are also able to adjust their proliferative activity in metabolic distress e.g. in metabolic syndrome, by increasing their self-renewal capacity to manage the increasing demand for glucose utilisation⁷⁹. Interestingly, the pancreatic β -cells display similar characteristics to stem cells such as low proliferative profile and a very long lifespan⁸⁰. The proliferative and regenerative capacity of β -cells might be diminished with age as a result of accumulation of DNA damage during their long lifespan or it could be that these cells undergo senescence or apoptosis as a result of age-mediated shortening of the telomeres and/or activation of p53 and/or p16^{INK4A}^{81,82}.

Aberrant molecular mechanisms involved in the induction of cellular senescence of the pancreatic β -cells include telomere shortening, cycle-dependent kinase inhibition by p53 and p16^{INK4A}, which are also tumour suppressor genes⁸³. Other pathways involved in the dysfunction of the pancreatic β -cells include the mTOR, sirtuin and IGF-1 pathways, also strongly associated with aging and other age-related diseases⁸⁴. Furthermore, the negative regulator of the mTOR pathway, AMPK, has also been significantly implicated in the metabolic disorders and T2D; aberrant expression of AMPK in both mice and humans leads to insulin resistance⁵⁴.

The role of PPIases in T2D

The role of PPIases in T2D is still in its infancy however some interesting data has been recently reported to suggest important role for this group of proteins in T2D. For example, FKBP51 SNPs were found to be associated with T2D phenotypes in large population studies⁸⁵. Also, the change in FKBP51 gene expression was demonstrated in response to stress and diet therefore indicating a correlation between FKBP51 levels and higher food intake. Similarly, in mice, FKBP51 KO demonstrated a leaner phenotype when compared to the WT mice⁸⁶. Furthermore, in conjunction with insulin resistance markers, FKBP51, as a steroid hormone responsive and regulatory gene, demonstrated an increase in the expression, following dexamethasone exposure⁸⁵.

Moreover, CypA has a role in T2D and vascular complications of T2D due to its pro-inflammatory role; patients with T2D were reported to have lower levels of CypA in high glucose-primed monocytes but high plasma levels of CypA when compared to healthy volunteers therefore suggesting a role for CypA as a biomarker of inflammation in T2D patients⁸⁷. Moreover the role of the PPIase, FKBP51, in the regulation of vascular/angiogenic functions implicates their potential in T2D-mediated vascular abnormalities (Yakkundi et al, unpublished data).

Chronic Kidney Disease

CKD is a leading cause of morbidity and mortality. Epidemiological studies demonstrated around 13% prevalence worldwide^{88,89}. CKD arises from complete progressive destruction of nephrons resulting in the intact nephrons having to manage an increased load^{8,90}. Despite research efforts, the pathophysiology of CKD is still not fully understood, although vascular,

glomerular and tubular events are implicated in the disease^{91,92}. Furthermore, podocytes or visceral epithelial cells within the Bowman's capsule have a role in preventing protein escape into the urine and therefore the loss of podocytes has been associated with the development of diabetic neuropathy^{93,94}. Aberrant mTOR activation is associated with this process and its inhibition by drugs such as rapamycin may be of a potential clinical benefit^{93,95}. Similarly, the mTOR pathway is involved in aldosterone mediated signalling through the mineralocorticoid receptor within renal tubular epithelial cells of distal nephrons; important for the regulation of fluid homeostasis^{96,97}. The activation of the mineralocorticoid receptor and its target genes including some of the PPIases, has been linked to tissue inflammation and fibrosis leading to CKD⁹⁸⁻¹⁰⁰.

The role of PPIases in CKD

In relation to CKD, FKBP12 exhibits an inhibitory activity on calcium oxalate crystal deposition and may prevent nephrolithiasis¹⁰¹. Nephrolithiasis is often perceived as a relatively minor acute illness, but increasing evidence suggests that it can lead to CKD¹⁰²⁻¹⁰⁴. Furthermore, the pathogenesis of the condition shares overlapping features of many diseases of ageing such as hypertension, CVD and diabetes mellitus^{103,105,106}. Recently, using a GWAS population analysis approach, FKBP51 has shown significant differences in DNA methylation in CKD patients¹⁰⁷. Aldosterone plays a significant role in the development of CKD and evidence suggests that FKBP51 protein and mRNA expression are induced by aldosterone in the kidney and intestinal tissues¹⁰⁸⁻¹¹⁰. On the other hand, CypA has a role in renal acidosis¹¹¹, diabetic nephropathy¹¹² and renal cell carcinoma¹¹³. Furthermore, Pin1 inhibition affects CKD associated with secondary parathyroidism¹¹⁴.

Neurodegeneration

Neurodegeneration is the umbrella term for the progressive failure of neuronal networks leading to neuron death; many of these diseases share similarities at the sub-cellular level^{115,116}. Ageing is the main risk factor for development of these diseases and the accumulation of atypical proteins, abnormal tangles and network dysfunction are classic hallmarks of these diseases¹¹⁷.

Protein aggregation is a well-known feature of these diseases; however, the role of this process is not fully understood. Post-mortem examination of deceased brains have revealed that amyloid plaques in Alzheimer's disease and Lewy bodies in Parkinson's disease can be present even in asymptomatic patients and the extent of plaques present does not correlate to the severity of the disease at the time of death¹¹⁸.

Sustained activation of neuronal PI3K/Akt/mTOR signalling has been noted in early Alzheimer's disease¹¹⁹. In the temporal lobes of Alzheimer's patients, Akt activation leads to mTOR and tau phosphorylation and a decrease in cyclin-dependent kinase inhibitor 1¹²⁰. Furthermore, the aberrant activation of the Akt pathway has been linked to disrupted clearance of A β and tau resulting in synaptic loss and cognitive decline¹¹⁹. Nevertheless, the cause of Alzheimer's disease is still largely unknown however the most prevalent genetic risk factor is the presence of ϵ 4 allele of the apolipoprotein E (APOE) and it is expressed in half of sporadic Alzheimer's disease cases^{121,122}.

On the other hand, Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's diseases. It is a degenerative disorder resulting from the death of the

dopamine producing cells in the substantia nigra (SN)^{123–125}. Age-related mitochondrial dysfunction and alterations in protein degradation are more detrimental to the neurons in the SN than in any other regions of the brain¹²⁶. The classic hallmark of this disease is the presence of the protein alpha synuclein which binds to ubiquitin in damaged cells forming eosinophilic cytoplasmic inclusions called Lewy bodies^{124,125,127}. In Parkinson's disease, the PI3K/Akt/mTOR pathway is dysregulated in a different manner than in Alzheimer's disease. The dopaminergic neurons from Parkinson's patients display downregulation of phosphorylated Akt and suppressed mTOR signalling resulting in neuronal death¹²⁸. Furthermore, rapamycin, the inhibitor of mTOR, has a neuroprotective effect by protecting phosphorylated Akt at a critical site for cell survival¹²⁹.

The role of PPIases in neurodegeneration

Calcium dysregulation contributes to unhealthy brain aging by reducing neural excitability and impairing memory. Disruption of FKBP12 in the hippocampal neurons destabilised calcium and *in vivo* FKBP12 knockdown is associated with an upregulation of RyR2 and mTOR protein expression¹³⁰. FKBP12 has been shown to bind to the intracellular domain of the amyloid precursor pathway and shift APP processing to the amyloidogenic pathway^{131,132}. Moreover, the FKBP12 gene expression is downregulated in the hippocampus of aging rats and in early stage Alzheimer's patients¹³³. When FK506 is used as an immunosuppressant agent, it appears to have neuroprotective effects¹³⁴.

FKBP38 is a well-known inhibitor of apoptosis through a reduction in mitochondrial Bcl-2^{135,136}. Hsp90 can inhibit the apoptotic function of FKBP38 by interfering with the FKBP38/calmodulin/calcium complex which regulates the anti-apoptotic protein, Bcl-2¹³⁷.

This property of FKBP38 protein has been exploited for the treatment of neurodegenerative diseases^{136,138}.

FKBP51's PPIase activity has a role in microtubule stabilisation through Hsp90-mediated dephosphorylation of tau^{139,140}. On the other hand, FKBP52 is ubiquitously expressed at high levels and has been associated with microtubule destabilisation and tubulin depolymerisation¹⁴⁰⁻¹⁴². FKBP51/FKBP52 bound to heat shock proteins may have a role in neurodegeneration by modulating protein folding and aggregation²³. FKBP51 siRNA knockdown reduced tau levels in HeLa cells and FKBP51 overexpression increased levels of tau¹³⁹. In addition, knockdown of Hsp90 also reduced levels¹⁴³. In contrast, FKBP52 overexpression downregulated *tau* protein levels and knockdown resulted in increased *tau* binding to microtubules, resulting in longer projections^{131,142}. Cao and Konsolaki proposed that the opposing effects of FKBP51 and FKBP52 could be due to the differences in PPIase activity as *tau* contains a high percentage of proline residues¹³¹. Furthermore, FKBP52 is upregulated after injury in regenerating neurons and Alzheimer's patients have a lower expression of FKBP52 in the temporal lobe and hippocampus¹³¹. FKBP52 is involved in the regulation of intracellular copper and this may cause FKBP52 to have an effect on A β levels¹⁴⁴⁻¹⁴⁶. Furthermore, Conejero-Goldberg and colleagues demonstrated that FKBP52 was one of the key genes differentially expressed in the brain tissue, where it appeared to act in a protective role, in young individuals at high risk of Alzheimer's disease preselected by the APO4 signature¹⁴⁷.

The role of CypA in Alzheimer's disease has also been reported, possibly due to its ability to activate pro-inflammatory pathways, NF- κ B and MMP-9; these pathways in brain capillary pericytes regulate the release of neurotoxins. This whole process is initiated by APO4 within astrocytes¹⁴⁸. CypD's involvement in the mPTP complex has also found application in

Alzheimer's disease due to recent reports which suggest that A β proteins influence mPTP formation when in a complex with CypD¹⁴⁹. Conversely, the loss of Pin1 expression is correlated with Alzheimer's disease and neurodegeneration due to Pin1's important role in the stabilisation and regulation of tau and A β proteins⁴². Tau protein hyperphosphorylates in the absence of Pin1 leading to its dysfunction and inability to regulate microtubule stabilisation in the neurons¹⁵⁰.

Age-related macular degeneration

Age-related macular degeneration (AMD) is a leading cause of blindness worldwide and old age is the major risk factor with an incidence of 10% in individuals over 80 years of age^{151,152}. It results from degeneration of the macular region of the retina, a central part of the retina and AMD susceptibility is increased by age, environmental (e.g. smoking) and genetic factors^{152,153}. Many different genetic factors have been implicated in AMD including SNPs within some of the proteins involved in the mTOR pathway¹⁵⁴.

The role of PPIases in AMD

In AMD GWAS the presence of SNPs on chromosome p6.21 in the FKBPL region was demonstrated therefore suggesting a potential role for FKBPL as an AMD susceptible gene¹⁵⁵. This study was carried out using two cohorts of advanced AMD patients against matched controls to validate the findings and it also indicated Notch4 as a potential AMD susceptible gene. Our own lab has generated data to suggest that in addition to the well-established FKBPL's regulatory role of the CD44 pathway, it is also involved in the regulation of the Notch pathway (unpublished data).

Cancer

Cancer is defined as the development of ‘abnormal cells’ due to genetic and epigenetic changes in oncogenes and tumour suppressors¹⁵⁶. These genetic changes can be inherited, acquired by various DNA damaging agents or certain types of viruses. There are a few theories of carcinogenesis nevertheless it is considered a multistep process involving genetic instabilities which drive normal cells to malignant, cancer cells. More recently, a subgroup of cancer cells, termed cancer stem cells (CSCs) or tumour initiating cells, have been characterised as a group of cells carrying the oncogenic and tumour suppressor mutated genes responsible for tumour initiation and progression¹⁵⁷.

Numerous cellular and intracellular pathways regulating tumourigenesis have been implicated in the development of cancer. A pathway readily activated as a result of a loss of the main tumour suppressor genes, p53 or PTEN, is PI3K-Akt survival pathway¹⁵⁸. This pathway regulates the mTOR pathway and once the mTOR pathway is activated, negative feedback results in PI3K inhibition. Therefore when the mTOR pathway is inhibited by rapamycin, for example, the mutated or lost negative feedback loops, commonly present within cancer cells, activate the PI3K-Akt pathway instead of inhibiting it, thereby preventing the anti-proliferative effect of the mTOR pathway inhibition^{159,160}.

The role of PPIases in cancer

The roles of PPIases in cancer have been studied extensively. Some members appear to have oncogenic activity whilst others behave as tumour suppressors. FKBP12 is overexpressed in benign and malignant endothelial-lined vasculature and as a natural ligand of TGF- β receptor I is subsequently involved in regulating cancer invasion¹⁶¹. Knockdown of FKBP12 results in the cell cycle arrest at the G1 phase by downregulation of TGF- β signalling¹⁶². Furthermore, FKBP12 activates TGF- β receptor I kinase thus triggering apoptosis by a mitochondrial

dependent pathway¹⁶³. In addition, it is a regulator of H-Ras trafficking by promoting depalmitoylation through its PPIase activity¹⁶⁴. Disruption of the interaction between FKBP12 and calcineurin signalling leads to potent anti-angiogenic effects and tumour growth inhibition in breast cancer¹⁶⁵.

FKBP38 is capable of potentiating the biological function of Bcl-2 protein leading to tumourigenesis and chemoresistance^{136,166}. Furthermore, Bcl-2 overexpression has been associated with the cancer stem cell phenotype and it may contribute to chemoresistance within these cells¹⁶⁷.

FKBP51 expression is hormone related and its overexpression has been associated with leukaemia, breast, prostate and brain tumours^{168,169}. FKBP51 is a negative regulator of the Akt pathway and regulates cell response to chemotherapy¹⁷⁰. Furthermore, FKBP51 regulates the NF- κ B pathway which is implicated in apoptosis and radioresistance in melanoma cells^{171,172}. More recently, the role of FKBP51 in stemness and metastasis in melanoma was demonstrated by Romano et al (2013), where FKBP51 was overexpressed and associated with tumour aggressiveness and treatment resistance by stimulation of the EMT process, migration and invasion via the TGF- β pathway¹⁷³. Furthermore, androgens upregulate FKBP51 by initiating direct binding between FKBP51 and the androgen receptor (AR)¹⁷⁴. In murine xenograft models it was demonstrated that FKBP51 is a direct regulator of cell growth and may have a role in the highly invasive androgen-independent type of prostate cancer^{174,175}. The FKBP51/AR interaction is mediated by Hsp90, and Hsp90 inhibitors such as geldanamycin are currently in clinical trials in a variety of cancers^{176,177}. In pancreatic cancer, FKBP51 acts as a scaffolding protein to the phosphatase PHLPP resulting in upregulation of the pro-survival Akt pathway and reducing sensitivity to the chemotherapy¹⁷⁰. Conversely, in colorectal

adenocarcinoma, FKBP51 suppresses proliferation through its action on the glucocorticoid receptor¹⁷⁸.

Less is known about the role of FKBP52 in cancer, although its inhibition has been shown to block androgen receptor dependent gene expression and prostate cancer cell proliferation¹⁷⁹. Moreover, FKBP52 is highly expressed in hormone-positive cancers such as oestrogen receptor positive (ER+) breast cancer; its expression in pre-invasive breast cancer was also much higher than the surrounding normal breast tissue speculating its role in breast cancer initiation^{180,181}. FKBP52 is not a functional regulator of the oestrogen receptor but interestingly, it is upregulated in breast tumours and FKBP52 gene methylation only occurs in ER negative breast cancer cells¹⁸². Furthermore, FKBP52 auto-antibodies may be a useful biomarker for early diagnosis and monitoring of breast cancer¹⁸³.

FKBP65 is highly expressed in early benign lesions in the colon, compared to normal mucosa¹⁸⁴. This suggests that FKBP65 may be involved in colorectal carcinogenesis and could be a novel colorectal biomarker¹⁸³. FKBP65 is strongly expressed in normal and benign ovarian epithelium but a low expression in high grade serous carcinoma (HGSC) is probably due to frequent loss of chromosome 17 in HGSC^{185,186}. This indicates a tumour suppressor function for FKBP65 in ovarian carcinomas.

FKBPL has a well-established role in cancer and whilst most FKBP's are positive regulators of cancer growth, FKBPL, as a divergent member of this family, is not. FKBPL acts as a co-chaperone protein in a complex with Hsp90 where it has a regulatory role in steroid receptor signalling (ER)¹⁸⁷; (AR)¹⁸⁸; (GR)¹⁸⁹. Due to this negative regulatory effect of the steroid receptors, overexpression of FKBPL demonstrated inhibition of cancer cell growth in ER+

breast cancers¹⁸⁷; in lymphoma this inhibitory effect was associated with a FKBPL, Hsp90 and p21 complex¹⁹⁰. Furthermore, in ER+ breast cancer, high FKBPL levels improved the response to endocrine therapy such as tamoxifen and fulvestrant and sensitised cells to oestrogen deprivation and was also prognostic for survival¹⁸⁷. Other relevant roles of endogenous FKBPL in a complex with Hsp90, p21 and GTSE-1 (G2 and S phase expressed protein 1) include, chemo- and radiosensitivity via regulation of the cell cycle protein, p21^{CIP1/WAF1}, and a reduction in the DNA repair^{191,192}. All of these FKBPL-related roles are associated with intracellular FKBPL however more recently, an extracellular role for FKBPL was identified. This extracellular role was associated with a potent anti-angiogenic and anti-CSC function which is initiated following binding of FKBPL to the CD44 cell surface receptor¹⁹³⁻¹⁹⁵. The region responsible for this interaction is the N-terminal region of FKBPL, which is unique and not homologous to other FKBP. Based on this anti-angiogenic domain, a clinical candidate 23-amino acid therapeutic peptide, ALM201, was designed in collaboration with Almac Discovery which will enter clinical trials this year¹⁹⁶. Therefore, FKBPL as a divergent member of the FKBP appears to be involved in similar biological processes in cancer to other FKBP whilst exerting an opposite function as an anti-cancer or tumour suppressor protein.

In cancer CypA is significantly upregulated and as such is involved in malignant transformation, tumour growth, invasion, metastasis and the inhibition of apoptosis¹⁹⁷⁻²⁰⁰. This is not surprising considering CypA has a role in the stimulation of endothelial cell migration which is important for tumour growth and invasion⁶⁹. Furthermore, CypA is transcriptionally regulated by p53 and hypoxia inducible factor-1 α (HIF-1 α) both factors commonly mutated in cancer²⁰¹. CypA seems also responsible for paclitaxel-induced resistance in endometrial cancer and overexpression of CypA can reduce cisplatin and hypoxia-induced apoptosis^{202,203}. **On the other hand, CypA has also an important role in the cytokinesis where it relocates from its**

original position, in the centrosome, to the midbody; the loss of CypD leads to defective cytokinesis which can increase genomic instability associated with cancer²⁰⁴. Other members of the Cyp family group CypB, CypC and CypD in addition to CypA also appear to be upregulated at the transcriptional levels in various cancers²⁰¹. CypB and CypC are associated with the ER and as such form various complexes with other oestrogen-related chaperones and CypB, in particular, protects cells from oestrogen receptor stress-induced death^{205,206}. However, overexpression of CypB has been linked to tumour progression because it regulated various hormone receptors and their downstream targets²⁰⁷. Also, CypB could be a useful target for delivery of anti-cancer vaccines due to its two antigenic epitopes identifiable by the cytotoxic T-lymphocytes²⁰⁸. Moreover, Cyp40 mRNA levels were reported to be high in response to stress in breast and prostate cancer cell lines when compared to normal breast and prostate cell lines²⁰⁹. CypD, as mentioned above, is involved in mPTP complex formation and as such has a role in the resistance to mPTP-induced cancer cell death. This is mediated by other co-chaperone proteins such as Hsp90, TRAP and Hsp60 highly expressed in cancer cell mitochondria and their ability to inhibit CypD therefore disabling mPTP formation and its apoptotic effects²¹⁰. Also, mitochondrial CypD knockdown is associated with STAT3 activation which leads to an increase in cell proliferation, by accelerating entry into S-phase, and migration, via the chemokine network, CXCL12-CXCR4²¹¹. Both of these phenotypes are closely linked to cancer progression and metastasis. Furthermore, CypD^{-/-} mice exhibit similar phenotype to Pin1^{-/-} mice in terms of abnormalities observed in retina and breast development which could potentially lead to malignant transformations in these organs^{212,213}. Also, transcriptional and posttranslational regulation of CypD by Pin1 was demonstrated in the more recent study therefore explaining the phenotypical similarities observed in CypD^{-/-} and Pin1^{-/-} mice²¹³.

Pin1 has been researched extensively for its oncogenic role in cancer²¹⁴. Pin1 is also important for tumourigenesis and for the regulation of CSCs via the Notch pathway²¹⁵. In fact, deletion of Pin1 in mice prevented oncogenic activation of Neu and Ha-Ras which abrogated breast cancer²¹⁶. In p53-KO mice Pin1 deletion was able to completely abrogate tumour development but had adverse effects including thymic hyperplasia mediated via the Notch pathways²¹⁷. Nevertheless, Pin1 does not affect the p53 tumour suppressor activity²¹⁸. Other cancer-associated processes that Pin1 affects include regulation of cell cycle, DNA damage, cell signaling, transcription and splicing²¹⁹. **In terms of cell-cycle regulation, Pin1 also has a role in cytokinesis by binding to the crucial centrosome protein, Cep55, which further explains its role in tumourigenesis²²⁰**

PPIases as targets to prevent ageing or to treat age-related diseases

An advantage of characterising this gene family is that they are targetable and various drugs targeting these proteins have been reported, including FK506, sirolimus/rapamycin, cyclosporine, and tacrolimus²². Ligands of these proteins, although first approved as immunosuppressive agents, for the prevention of allograft rejection, are effective against age-related diseases. Several FKBP-binding macrocyclic drugs, everolimus, zotarolimus and temsirolimus are in phase III trials as targets for cell proliferation, immunosuppression and anti-cancer effects²³. Recent evidence has also identified rapamycin/sirolimus as being the first drug to extend lifespan in a range of species from yeast to mammals^{221,222}, highlighting the potential for drug targeting within this gene family to alleviate the ageing process. Importantly, recent studies have also shown that FK506-binding proteins can modulate Akt-mTOR signalling in the absence of rapamycin²¹.

One of the problems associated with PPIase inhibitors however, is their off-target effects, particularly and not surprisingly, immunosuppression. However, more recently there has been a concerted effort to generate compounds that lack immunosuppressive activity, with various levels of success. Examples of such compounds include non-immunosuppressive analogues of cyclosporine A which may have applications in multiple therapeutic areas e.g. Alisporivir (Debio 025) and NIM811^{223,224}. Similarly, the development of cell impermeable, non-immunosuppressive analogues of cyclosporine A has permitted the inhibition of extracellular CypA in mouse models of inflammation²²⁵. Such drugs have huge potential in the treatment of ageing disease in which CypA is involved.

The novel FKBPL-based therapeutic, ALM201, unlike other PPIases, appears to be protective of age-related diseases^{147,154,187,193,194,196}; ALM201 is a peptide mimetic of FKBPL and could essentially correct a deficiency in FKBPL in a number of diseases. It has already completed preclinical evaluation for imminent phase I/II clinical trials in cancer patients¹⁹⁶; our unpublished data also suggests that it has activity against a number of other inflammatory conditions.

Conclusion

In conclusion, there are many different significant roles of PPIases in age-related processes and diseases as indicated above (Table 1; Figure 2). Even though these proteins belong to the same family group, their roles are quite diverse and in some instances opposite. Therefore, it is of a paramount importance to elucidate the mechanisms involved in the interactive regulation of this gene family. This may allow the development of a genetic signature which could stratify patients with higher predisposition to unhealthy aging therefore enabling early treatment to

delay or prevent these age-related vascular diseases and their complications. Members of this family of proteins are therefore excellent targets for interventions as well as biomarkers of aging and age-related diseases. Because many of the PPIase family members are secreted^{226,227}, monitoring them within ageing populations will be minimally invasive and therefore practical for routine clinical use or home test.

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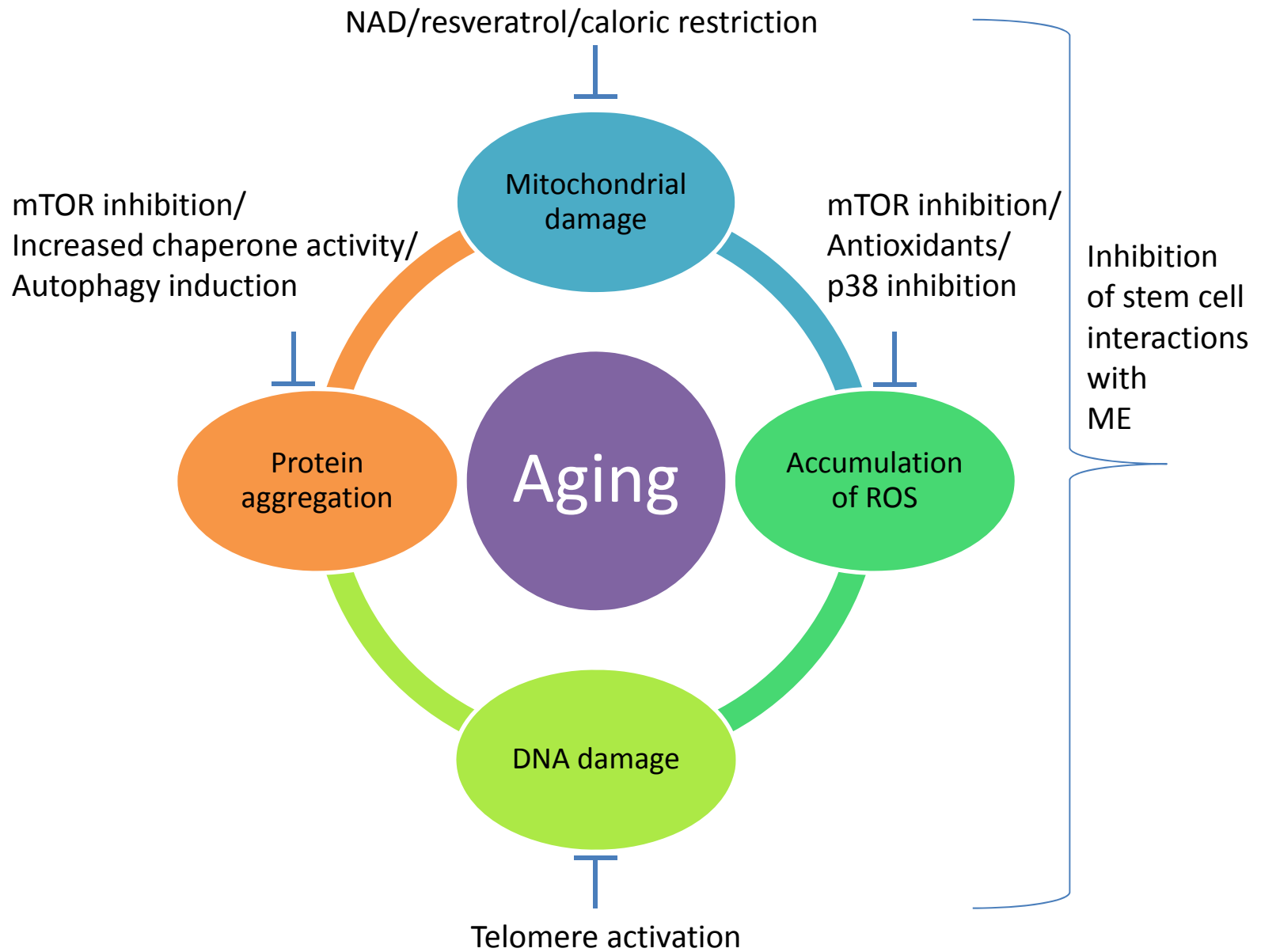


Figure 1. Different mechanisms involved in aging and the associated targeting strategies. *ME* – *microenvironment*; *NAD* - *nicotinamide adenine dinucleotide (the sirtuin pathway activator)*.

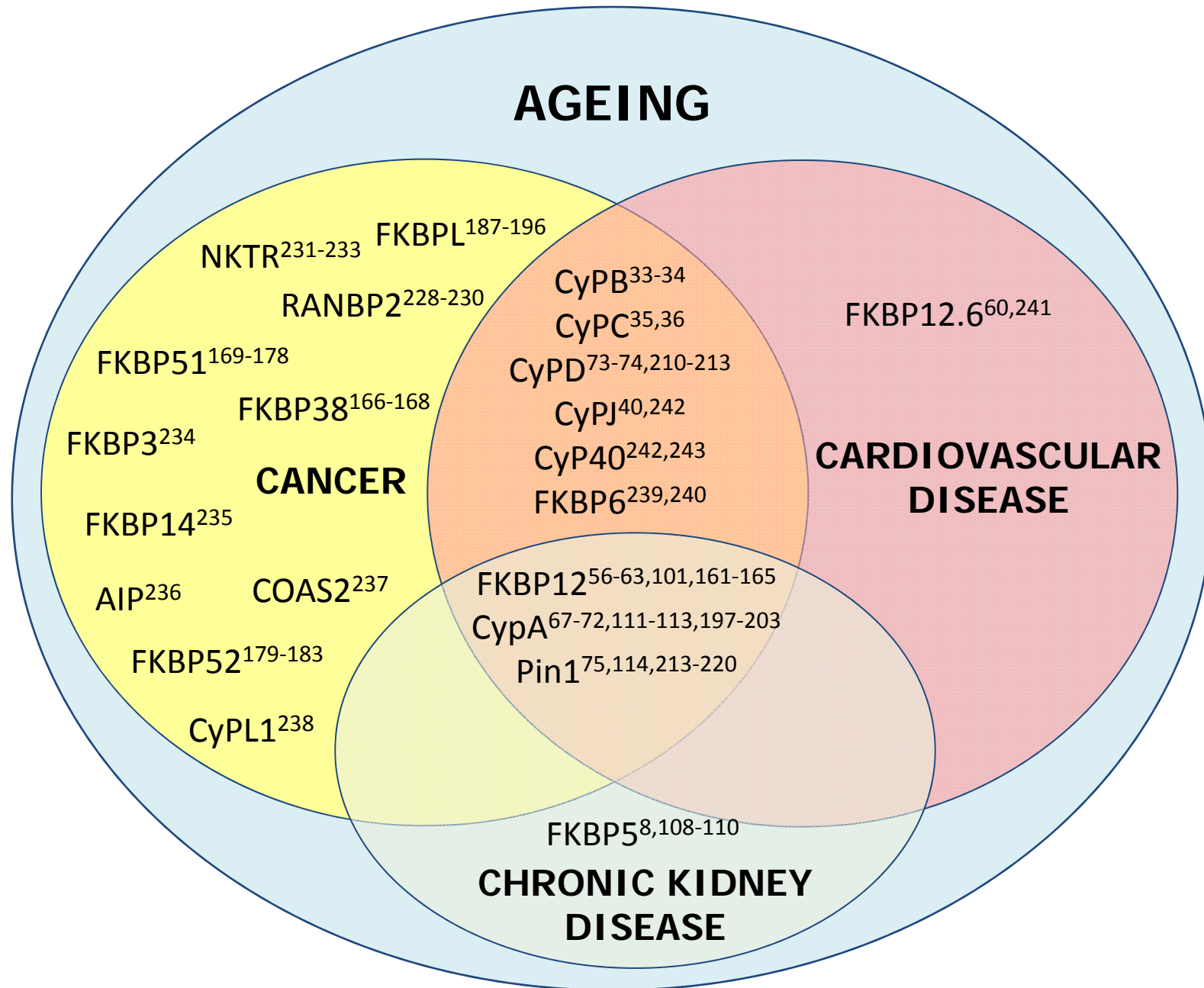


Figure 2. PPIases in aging and age-related diseases (cancer, cardiovascular disease and chronic kidney disease).

Age-Related Diseases	PPIase	Mechanisms	References
Cardiovascular diseases	FKBP12 Cyclophilin A Cyclophilin D Pin1	Calcium augmentation; RyRs channel regulation; hypertension Pro-inflammatory; generation of ROS; atherosclerosis, ACS biomarker Stabilisation of the mPTP complex; Binds to Akt, MEK and Raf-1	56-63 67-72 73,74 75
Type II diabetes	FKBP51 Cyclophilin A	Associated with T2D phenotype; gene expression changes in response to stress and diet Biomarker of inflammation in T2D and vascular complications	85,86 70,87
Chronic Kidney Disease	FKBP12 FKBP51 Cyclophilin A Pin1	Calcium oxalate crystal deposition DNA methylation; expression induced by aldosterone Association with renal acidosis, diabetic nephropathy, renal cell carcinoma Downregulation in secondary parathyroidism, complication of CKD	101 108-110 111-113 114
Neurodegeneration	FKBP12 FKBP38 FKBP51 FKBP52 FKBPL Cyclophilin A Cyclophilin D Pin1	Augmentation of calcium and APP processing; downregulation in Alzheimer's disease Inhibition of mitochondrial Bcl-2 in the brain Microtubule stabilisation through Hsp90 dephosphorylation of tau Microtubule destabilisation and tubulin depolymerisation Protective role in Alzheimer's disease Regulation of inflammatory pathways, NF- κ B and MMP-9; release of neurotoxins Stabilisation of mPTP complex; regulation of A β protein activity within mPTP complex Stabilisation and regulation of tau and A β	130-134 135-138 139-141 132,141-146 147 148 149 42,150
Age-related macular degeneration	FKBPL	AMD susceptibility gene	154,155
Cancer	FKBP12 FKBP38	Apoptosis via TGF- β mitochondrial pathway Chemoresistance via Bcl-2	161-165 166-168

FKBP51	Regulation of Akt, NF- κ B pathways and AR; chemoresistance, apoptosis, stemness	169-178
FKBP52	AR-dependent gene expression in prostate cancer; novel breast cancer biomarker; DNA methylation in ER- breast cancer	179-183
FKBP65	Malignant transformation in colorectal cancer; downregulation in ovarian carcinoma	184-186
FKBPL	Anti-angiogenic and anti-cancer stem cell properties via CD44 dependent mechanism; steroid receptor and cell cycle regulation	187-196
Cyclophilin A	Regulated by p53 and HIF-1 α ; stimulation of endothelial cell migration; apoptosis, invasion, metastases chemoresistance	113,197-204
Cyclophilin B	Regulates ER complexes; protection against ER stress induced death, tumour progression in breast cancer	205-208
Cyclophilin 40	mRNA levels regulated in response to stress in breast and prostate cancer	209
Cyclophilin D	mPTP complex formation; apoptosis resistance	210-213
Pin1	Oncogenic potential; regulation of CSCs through the Notch pathway	213-220

Table 1: Summary of the roles of PPIases in the age-related diseases. *ROS* – reactive oxygen species; *ACS* – acute coronary syndrome; *MEK* – mitogen activated protein kinase; *mPTP* – mitochondrial permeability transition pore; *APP* – amyloid precursor protein; *T2D* – type II diabetes; *RyRs* – ryanodine receptors; *AR* – androgen receptor; *HIF-1 α* – hypoxia inducible factor 1 α ; *ER* – oestrogen receptor; *CSCs* – cancer stem cells