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REVIEW

Peptidyl-prolyl isomerases: a full cast of critical actors in cardiovascular diseases

Gianluca Lorenzo Perrucci[1], Aoife Gowran[2], Marco Zanobini[1,3], Maurizio Colognesi Capogrossi[4], Giulio Pompilio[1,2,3], and Patrizia Nigro[2]*

[1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [2]Laboratory of Vascular Biology and Regenerative Medicine, Centro Cardiologico Monzino-IRCCS, Via Parea 4, Milan 20138, Italy; [3]Department of Cardiovascular Surgery, Centro Cardiologico Monzino-IRCCS, Milan 20138, Italy; and [4]Laboratory of Vascular Pathology, Istituto Dermopatico dell'Immacolata-IRCCS, Rome 00167, Italy

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Abstract Peptidyl-prolyl *cis-trans*-isomerases are a highly conserved family of immunophilins. The three peptidyl-prolyl *cis-trans*-isomerase subfamilies are cyclophilins, FK-506-binding proteins, and parvulins. Peptidyl-prolyl *cis-trans*-isomerases are expressed in multiple human tissues and regulate different cellular functions, e.g. calcium handling, protein folding, and gene expression. Moreover, these subfamilies have been shown to be consistently involved in several cardiac and vascular diseases including heart failure, arrhythmias, vascular stenosis, endothelial dysfunction, atherosclerosis, and hypertension. This review provides a concise description of the peptidyl-prolyl *cis-trans*-isomerases and presents an incisive selection of studies focused on their relationship with cardiovascular diseases.

Keywords Cyclophilins • FKBPs • Parvulins • Cardiovascular disease

1. Introduction

Cardiovascular diseases (CVDs) are a broad spectrum of pathologies. Presently, CVDs cause over 4 million deaths per year and remain the leading cause of approximately half of all deaths in Europe.[1] In the last 10 years, scientific research has highlighted the relevance of a specific protein family, the peptidyl-prolyl *cis-trans*-isomerases (PPIases), in a variety of CVDs.

PPIases are immunophilins, which catalyze the isomerization of peptide bonds from *trans* to *cis* conformation to accelerate protein folding.[2,3] They have specific catalytic isomerase activity at the level of X-Pro peptide bond (X represents any amino acid, a.a.). PPIases comprise several protein subfamilies, which are well conserved in all organisms.[4] Several of these were discovered because of their high specific affinity for immunosuppressant drugs, such as cyclosporin A (CSA), tacrolimus (FK-506), and sirolimus (rapamycin), which are inhibitors of PPIase enzymatic function.[5–7] Depending on drug-binding abilities, PPIases showing affinity with CSA have been classified as cyclophilins (Cyps),[2,8] while molecules sensitive to tacrolimus and sirolimus have been named FK-506-binding proteins (FKBPs).[9–11] Ultimately, the number of proteins encompassed by the PPIase family is growing and many have no affinity to immunosuppressive drugs, such as the peptidyl-prolyl *cis-trans*-isomerase NIMA-interacting 1 (Pin1), a member of the parvulin (Pars) family of PPIases. Besides not having affinity with immunosuppressive drugs, Pars do not show a high degree of sequence homology with other subfamilies of PPIases, apart from their catalytic domain.[12] All three PPIase subfamilies play a central role in the regulation of several physiological functions and a wide spectrum of diseases with different pathological mechanisms. This review highlights the main features of PPIases and clarifies their role in CVDs.

2. Cyclophilins

Cyps are a highly conserved protein subfamily that includes 18 isoenzymes encoded by 17 genes. Although the function of most cyclophilin isoforms is unknown, six are implicated in CVDs (summarized in *Table 1*).

2.1 Cyclophilin A

CypA was the first PPIase to be discovered.[13] It is the most abundant Cyp expressed in all tissues and localizes to the cytosol, nucleus, and extracellular space.[14–16] Many biological activities have been reported for CypA which converge on CypA acting as a key protein involved in protein folding, trafficking, and assembly, immune modulation, and cell signalling.[17] CypA was identified as the primary cytosolic-binding protein of the immunosuppressive drug CSA.[18,19] In mammals, the CSA-CypA complex binds to and inhibits calcineurin, a calcium-calmodulin-activated serine/threonine-specific phosphatase.[20] Calcineurin inhibition blocks nuclear

* Corresponding author. Tel: +39 02 58002028; fax: +39 02 58002342, Email: patrizia.nigro@ccfm.it

Table I PPIases involved in CVDs

PPIase subfamilies	Protein/alternative name	Gene	MW (KDa)	Cell localization	Tissue distribution	CVD involvement	References
Cyps	CypA/Cyp18	PPIA	18.012	Cytoplasm, nucleus, extracellular space	Ubiquitous	Vascular remodelling, AAA, cardiac hypertrophy, atherosclerosis, I/R injury, hypertension, arterial thrombosis, CAD, essential hypertension, diabetes	16,26,27,37–39,40–45
	CypB/Cyp23/SCYLP	PPIB	23.742	ER, nucleus, extracellular space	Ubiquitous	Hypertension, HF	66,67
	CypC/Cyp22a	PPIC	22.763	ER, Golgi apparatus, extracellular space	Kidney	Middle cerebral artery ischaemia	77
	CypD/Cyp22/CypF/Cyp3	PPIF	22.040	Mitochondria	Ubiquitous	I/R injury, HF, arterial thrombosis, cardiac hypertrophy, atherosclerosis, diabetes	80,82,84,96,97,102,104, 105,107,108
	CypJ/Cyp18.1	PPIL3	18.155	Nucleus, cytoplasm	Ubiquitous	Congenital heart defects	123
	Cyp40	PPID	40.764	Nucleus, cytoplasm	Ubiquitous		
FKBPs	FKBP12/FKBP1A	FKBP1A	11.951	Cytoplasm, SR	Skeletal muscle, heart, brain	Cardiac development, hypertension, arrhythmia	133–136
	FKBP12.6/FKBP1B	FKBP1B	11.782	Cytoplasm, SR	Skeletal muscle, heart, brain	HF, AF, CPVT, ARVC, arrhythmias in DMD, hypertrophy, diabetic cardiomyopathy	142,144,147,149–152, 154,157,159
	FKBP6/FKBP36	FKBP6	37.214	Nucleus	Skeletal muscle, heart, brain	SVAS in William's syndrome	164
Pars	Pin1	PIN1	18.200	Nucleus, cytoplasm	Ubiquitous	Cardiac hypertrophy, restenosis, hypertension, diabetes	173–176

factor of activated T cells (NFAT) translocation from the cytosol to the nucleus, thus preventing the transcription of genes encoding cytokines, e.g. IL-2. We and others have provided evidence that CypA is secreted in response to inflammatory stimuli such as reactive oxygen species (ROS), hypoxia, and infection.[21–24] Secreted CypA, partially through CD147, acts as a paracrine and autocrine factor that mediates cell-to-cell communication.[25] In fact, extracellular CypA induces endothelial cell (EC) dysfunction,[21,26] vascular smooth muscle cell (VSMC), and fibroblast proliferation, and promotes cardiomyocyte hypertrophy[16,27] (*Figure 1*). Furthermore, extracellular CypA is a potent chemoattractant for inflammatory cells.[23,28] CypA has been implicated in the following pathologies: viral infections,[29] neurodegeneration,[30] cancer,[31] rheumatoid arthritis,[32] sepsis,[33] asthma,[34] periodontitis,[35] and ageing.[36]

Recently, we have demonstrated the involvement of both intracellular and extracellular CypA in several CVDs. Using a complete carotid ligation model in wild-type (WT), CypA knockout ($CypA^{-/-}$), and CypA overexpressing mice (specifically in VSMCs), we understood that CypA is critically involved in 'vascular remodelling' (neointima formation as well as medial and adventitial thickening).[16] Additionally, we demonstrated that deletion of CypA in $ApoE^{-/-}$ mice prevents the formation of abdominal aortic aneurysm (AAA)[37] and cardiac hypertrophy[27] in response to angiotensin II infusion and the development of atherosclerosis in mice fed a high-fat diet.[26] Mechanistic studies revealed that deletion of CypA in all models reduced inflammation, oxidative stress, and extracellular matrix degradation.[38] Seizer *et al.*[39] reported that CypA is involved in myocardial 'ischaemia and reperfusion (I/R) injury' by the regulation of macrophage and neutrophil recruitment into the damaged tissue. CypA was also implicated in 'arterial thrombosis' by a mechanism involving the regulation of Ca^{2+} in platelets.[40] The involvement of CypA in the pathogenesis of hypertension has been suggested by the finding that CypA regulates the activity of the atrial natriuretic factor and its receptor, the membrane-bound guanylate cyclase-A, which regulates blood pressure.[41] Consistently, our studies demonstrated that CypA modulates endothelial nitric oxide synthase (eNOS) expression, a critical protein for nitric oxide (NO) generation and blood pressure regulation.[26] A clear involvement of CypA in pulmonary hypertension (PH) was found by a mechanism of ERK1/2 activation and secretion of cytokines/chemokines and growth factors, e.g. PDGF-BB.[42] Interestingly, high plasma levels of CypA, which predicted poor prognosis, were found in PH patients. Additionally, CypA has been proposed as a valuable biomarker for coronary artery disease (CAD),[43,44] essential hypertension,[45] and type-2 diabetes.[46] Hence, the development of drugs blocking its deleterious effects may offer a successful novel approach for the treatment of cardiovascular pathologies.

2.2 Cyclophilin B

CypB is an abundant protein expressed in all tissues, at levels lower than CypA,[47] and shares 65% sequence homology with CypA. It localizes within the endoplasmic reticulum (ER), nucleus, and extracellular space. The major functions of CypB were found to be related to the control of ER redox homeostasis,[48] collagen folding,[49] ribosome biogenesis,[50] Ca^{2+} homeostasis,[51] and prolactin signalling.[52] Both anti- and pro-inflammatory effects were reported for CypB. For instance, CypB was demonstrated as an essential protectant against ROS[53] and pro-inflammatory stimuli.[54,55] Conversely, extracellular CypB, like CypA, was found to induce the chemotaxis of inflammatory cells into damaged tissues.[23,28,56,57] In particular, CypB induced integrin-mediated cell adhesion by its interaction with CD147, CD98, and beta-1

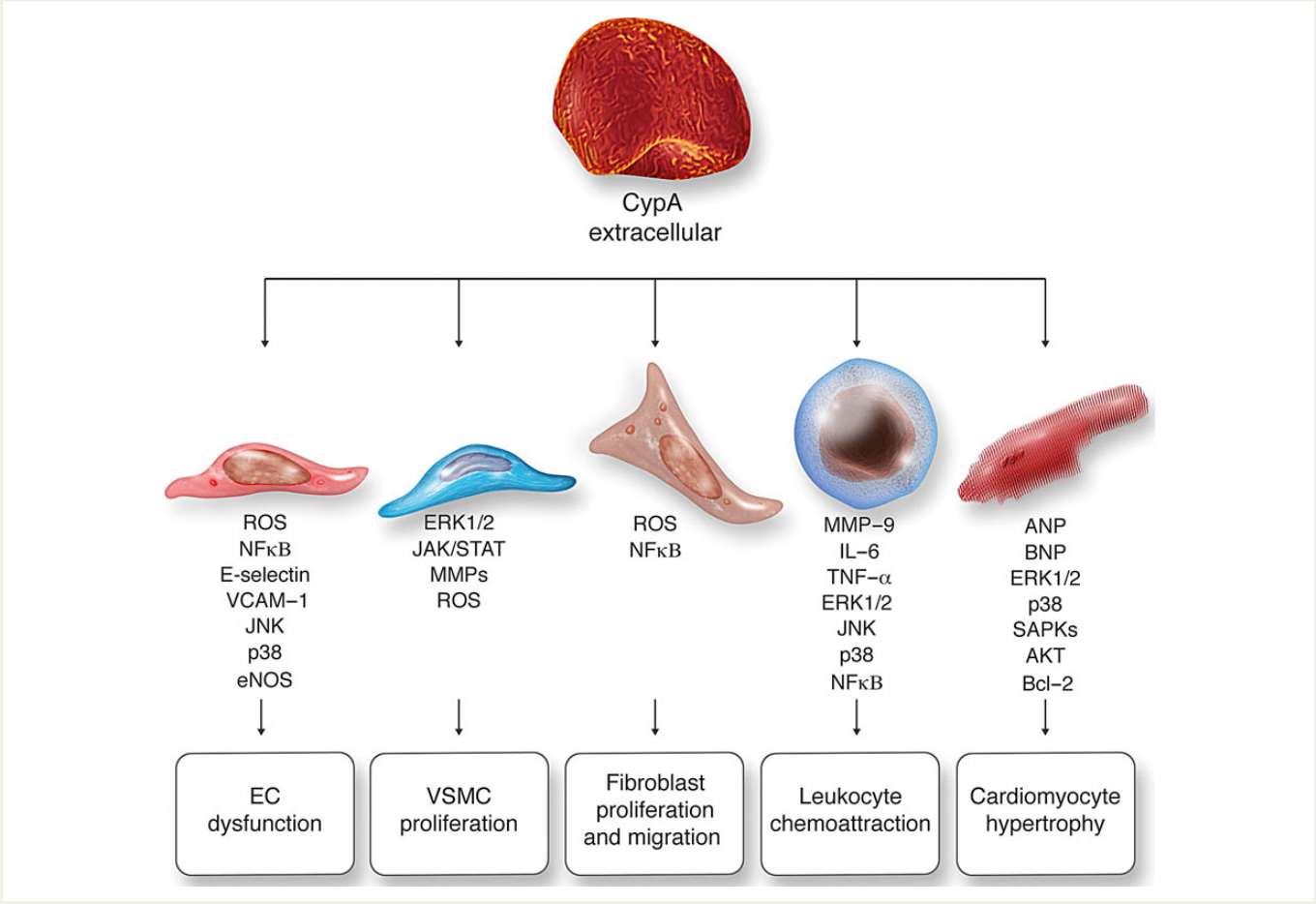

Figure 1 Cellular effects of CypA. CypA modulates different cardiovascular cell functions. Particularly, CypA, by activating the signalling proteins depicted in the figure, provokes endothelial dysfunction, increases proliferation of vascular smooth muscle cells and fibroblasts, acts as chemoattractant mediator for monocytes and other inflammatory cells, and stimulates cardiomyocyte hypertrophy.

integrins,[58] which was dependent on protein kinase (PK) C-delta activation and was critical for ERK1/2-mediated signalling. CypB has been associated with osteogenesis imperfecta,[49,59] cancer,[55,60,61] CMV infection,[62,63] HIV,[64] neurodegeneration,[65] asthma,[34] and ageing.[66]

A study by Kainer and Doris[67] suggested the importance of CypB in hypertension as they showed increased CypB levels in the renal proximal tubules of spontaneous hypertensive rats (SHR). These data indicate that CypB may participate in the abnormal functioning of renal transport-epithelium in SHR. Moreover, the beneficial effect of shock wave therapy (SWT) in 'ischaemic heart failure' (HF) was proposed to be mediated by CypB in parallel with Toll-like receptor 3 activation in ECs.[68] These molecular events are the basis for the pro-inflammatory response characteristic of the early response to SWT. The involvement of CypB in cardiovascular pathologies was also suggested by Berk and collaborators whom identified CypB in conditioned medium from VSMCs treated with a ROS generator (LY83583).[56] This secreted CypB mediated ROS-induced activation of ERK1/2 and regulated the effects of ROS on vascular function.

2.3 Cyclophilin C

CypC differs from CypA and CypB as it displays a restricted tissue distribution, with the most abundant expression observed in the kidney.[69] CypC localizes in the ER, Golgi, and extracellular space,[70,71] is inhibited by CSA,[72] regulates ER redox homeostasis,[48] and degrades DNA *in vitro*.[73] Interestingly, CypC associates with a secreted glycoprotein, CypC-associated protein (CypCAP)[74] which modulates macrophage activation (via NFAT),[75] endotoxin signalling,[76] and metalloproteinase-13 expression.[77]

Interestingly, Shimizu *et al.*,[78] by modelling middle cerebral artery occlusion (MCAO) ischaemia in rat, reported increased expression of CypC and CyCAP predominantly in microglia of the ischaemic core 7 days after MCAO. Although the cellular role of the proteins remains somewhat unclear, the authors suggested that CypC and CyCAP might participate in neuroprotection by modulating neuroinflammation.

2.4 Cyclophilin D

CypD is expressed in all human cell types, however at lower levels compared with CypA.[79] In light of its mitochondrial targeting,[80] CypD is known to play a pivotal role in regulating mitochondrial permeability transition pore (mPTP) opening and mitochondrial Ca^{2+} homeostasis control, ensuring optimal metabolic function[81,82] and appropriate cell death activation[83–86] (*Figure 2*). The hypothesis that CypD contributes to mPTP opening has been corroborated by genetic studies demonstrating that CypD deficiency reduces the propensity of the mPTP to open[83–85,87] while overexpression increases opening.[88,89] Recent investigations revealed that CypD is involved in muscular dystrophy,[90,91]

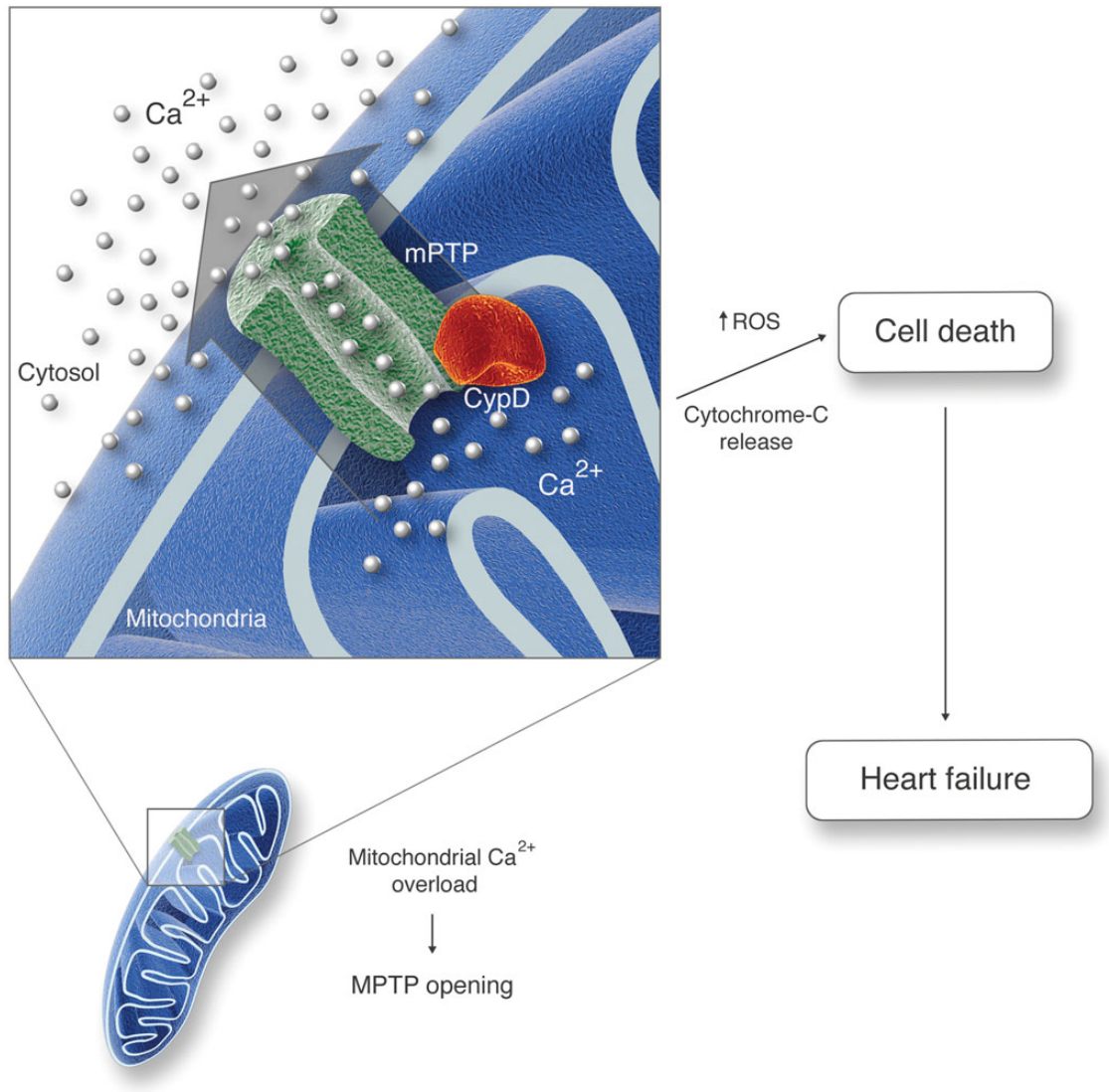

Figure 2 Intracellular role of CypD in heart failure. Mitochondrial calcium (Ca^{2+}, blue dots) concentration overload is the stimulus required for CypD-mPTP coupling. This provokes mPTP opening, Ca^{2+} release into the cytoplasm, and subsequent mitochondrial-mediated process leading to cardiac cell death.

Alzheimer's disease,[92,93] Parkinson's disease,[94] multiple sclerosis,[95] and ageing.[96]

Numerous studies utilizing $CypD^{-/-}$ mice determined that CypD knockout provides protection in several I/R models, including injury to the heart,[83,85,97,98] brain,[84] and kidney.[99,100] However, some factors, such as duration of ischaemia[101] or age,[102] were shown to shift CypD from a pro-survival protein to a cell death mediator. A cardioprotective effect of CypD knockdown was also shown using a CypD-siRNA-based approach followed by two-photon imaging in perfused rat hearts subjected to I/R injury.[103] Furthermore, mitochondrial-targeted CSA consistently improved cytoprotection in isolated rat cardiomyocytes subjected to transient glucose and oxygen deprivation, a pseudo-I/R model.[104] Interesting results were also found in a HF model where mice lacking CypD showed decreased infarct size and adverse left ventricular (LV) remodelling in addition to improved heart function after myocardial infarction (MI).[105] Moreover, loss of CypD blocked Ca^{2+}-influx-induced necrosis of cardiomyocytes, isoproterenol-induced premature cell death, and HF.[106] Surprisingly, decreased cytoprotection was observed in $CypD^{-/-}$ mice subjected to ischaemic preconditioning.[107] Similar negative effects were observed in a model of pressure overload-induced HF.[81] In fact, these mice exhibited substantially greater cardiac hypertrophy, fibrosis and reduced myocardial function compared with WT mice. Even more remarkably, physiological exercise (swimming) in $CypD^{-/-}$ mice worsened cardiac hypertrophy in comparison to control mice. Mechanistically, the maladaptive cardiac phenotype of $CypD^{-/-}$ mice was associated with an alteration in mPTP-mediated Ca^{2+}-efflux, resulting in elevated levels of mitochondrial matrix Ca^{2+} and enhanced activation of Ca^{2+}-dependent dehydrogenases. This alteration, in turn, led to increased glucose oxidation relative to fatty acid, thereby limiting the metabolic flexibility of the heart that is critically involved in compensation during stress. The involvement of CypD in metabolic pathways was confirmed recently by Menazza *et al.*[82] who used proteomic and metabolomic analysis to show that $CypD^{-/-}$ hearts have altered levels of proteins involved in

the Krebs cycle, branch chain a.a. degradation, and pyruvate metabolism. CypD was also implicated in platelet activation and arterial thrombosis.[108] In fact, in an embolic-stroke model, thrombosis was found to be markedly accelerated in CypD-deficient mice. Other studies associated CypD with atherosclerosis and diabetes. Genetic ablation of CypD in adult mice maintained on a high-fat diet, normalized glucose and insulin responses to acute glucose challenge, and prevented diabetes in Pdx1-deficient mice.[109] Thus, CypD is engaged in many cardiovascular pathologies, likely due to its critical role in the regulation of the mPTP which underpins metabolism and cell death.

2.5 Cyclophilin J and cyclophilin 40

CypJ is a novel member of the Cyp family which shares 50% of its sequence identity with CypA. The biological functions of CypJ are still unclear. Studies demonstrated that CypJ is involved in cancer biology, e.g. CypJ overexpression up-regulates drug resistance-related genes and may play a role in the clinical resistance to chemotherapy.[110] It was reported that CypJ gene expression may be correlated with the development of human glioma and might control the conformation of apoptin, a pro-apoptotic protein in tumour cells.[111]

Cyp40 is a large ubiquitously expressed protein with an immunophilin-like domain together with a conserved tetratricopeptide repeat (TPR) domain which is involved in protein interaction.[112] Cyp40 localizes predominantly to the nuclei. However, evidence of diffuse staining within the cytoplasm has been reported.[113] Cyp40 contributes to protein folding, ligand binding, and glucocorticoid-, estrogen-, progesterone-, and aryl-receptor signalling.[114–117] Interestingly, Cyp40 regulates the ATPase activity of heat shock protein 90 (Hsp90) favouring assembly into chaperone protein-folding machinery.[118] Additionally, Cyp40 is required for the activity of microRNAs in *Arabidopsis thaliana* and may chaperone Argonaute1 (AGO1) or a protein that is critical for AGO1 function (R.S. Poethig, personal communication).[119] Intriguingly, either the up-regulation of Cyp40 gene expression or loss of function might have pro-tumorigenic effects.[120–122] Moreover, Cyp40 was altered in prenatal alcohol-exposed mice suggesting its involvement in learning deficits.[123]

CypJ and Cyp40 were found to be implicated in the congenital heart defects observed in helicase-like transcription factor (Hltf) *null* mice[124] which die a few hours after birth because of reduced cardiac output. A genome-wide transcriptome profiling of Hltf *null post-partum* hearts revealed that CypJ and Cyp40 were down-regulated 2.57- and 2.71-fold, respectively. Although more studies are necessary, these results link CypJ and Cyp40 activity to heart development and cardiac functions.

3. FK-506-binding proteins

The FKBP subfamily includes >20 members which are named on the basis of their molecular weight. A number of FKBP genes have been cloned, but few cases suggest a specific cellular function.[6] FKBPs associated with CVDs are summarized in *Table 1*.

3.1 FKBP12

FKBP12 is one of the smallest and most extensively studied FKBP identified to date.[125] FKBP12 displays an overall cytoplasmic and sarcoplasmic reticulum (SR) expression profile and is strongly involved in protein–protein interactions.[126] FKBP12 binds both isoforms of ryanodin receptors (RyR1 and RyR2), with higher selectivity for RyR1 which is mainly expressed in skeletal muscle. FKBP12-RyR1 binding induces allosteric mechanisms to stabilize the closed-channel state.[127–129] Rapamycin and FK-506 inhibit FKBP12-RyRs binding. Further, FKBP12 also interacts with inositol trisphosphate receptors via PKA phosphorylation. Furthermore, FKBP12 interacts and inhibits calcineurin and mTOR[126,130–133] which limit T-cell translocation toward inflammatory loci by inhibiting cytokine production, e.g. IL-2.[130]

FKBP12$^{-/-}$ mice die *in utero*, due to cardiac abnormalities including: severe dilated cardiomyopathy, hypertrabeculation, ventricular non-compaction, and ventricular septal defects, suggesting an essential physiological function of FKBP12 in cardiac development.[134,135] However, further experiments highlighted the important role for FKBP12 in the regulation of ionic currents such as Na^+, voltage-dependent K^+, transient outward K^+, sustained K^+, L-type and transient Ca^{2+} currents.[136] In light of this regulation, FKBP12 was found to be a critical regulator of heart rhythm. In fact, Maruyama *et al.* has illustrated the role of FKBP12 in cardiac arrhythmia using two different approaches: mice overexpressing FKBP12 and a conditional FKBP12 knockout model (cardiomyocyte restriction under the control of alpha-myosin heavy chain). In both models a significantly enlarged heart, related to the dysregulation of the voltage-gated sodium current I(Na), was observed.[136] In 2011, Chiasson *et al.* showed that FKBP12 deficiency leads to the development of hypertension.[137] Consistently, immunosuppressive drugs inhibiting FKBP12 (and also FKBP12.6) were able to cause arterial hypertension, reducing vasodilation and also acting on vasoconstriction.[138]

3.2 FKBP12.6

FKBP12.6 shares 85% sequence homology with FKBP12[126,139] and also contains a single FK-506-binding domain. FKBP12.6 plays an important role in RyR2 stabilization[140,141] and colocalizes with RyR2 in the heart[142] and vascular tissues, where it is the predominant isoform.[143] FKBP12.6-immunosuppressant drug complexes inhibit calcineurin[130,131] and bind mTOR,[132,133] inducing the previously mentioned inhibitory effects on cytokine production and cytotoxic T-cell proliferation.[130,132,133]

The main mechanism explaining the involvement of FKBP12.6 in several CVDs is its role in the regulation of intracellular Ca^{2+} handling. During HF aetiology, PKA hyperphosphorylates RyR2, this in turn leads to detachment of FKBP12.6 from RyR2, negative feedback for FKBP12.6 expression, and defective Ca^{2+} channel function (*Figure 3*).[141,144–148] Indeed, Hu *et al.* demonstrated reduced expression of FKBP12.6, RyR2, and SERCA2a in a rat model of HF, showing the contribution of Ca^{2+} leakage and reduced Ca^{2+} uptake to the development of HF.[144] Furthermore, FKBP12.6 plays an important role in several arrhythmogenic diseases, such as atrial fibrillation (AF),[149–151] cathecolaminergic polymorphic ventricular tachycardia (CPVT),[152] and arrhythmogenic right ventricular cardiomyopathy (ARVC).[153,154] Hyperphosphorylated RyR2 were isolated from the atria of canines affected by AF.[149,150] Atrial cardiomyocytes isolated from FKBP12.6-deficient mice showed enhanced SR Ca^{2+} leakage, in addition to an increased propensity for developing AF.[151] PKA-induced RyR2 hyperphosphorylation was also highlighted in cardiac RyR2 of diabetic rats where FKBP12.6 levels were depleted.[155] Moreover, Ca^{2+} sparks showed a time-dependent decay together with progression of diabetic cardiomyopathy potentially due to the alteration of FKBP12.6 levels.[156] Lehnart *et al.*[157] have shown SR Ca^{2+} leakage during diastole in FKBP12.6$^{-/-}$ mice, implicating FKBP12.6 deficiency in triggering cardiac arrhythmias. In 2008, a conditional cardiac-specific overexpression of FKBP12.6 demonstrated that increased FKBP12.6-RyR2 binding prevents stress-evoked ventricular tachycardia in normal hearts

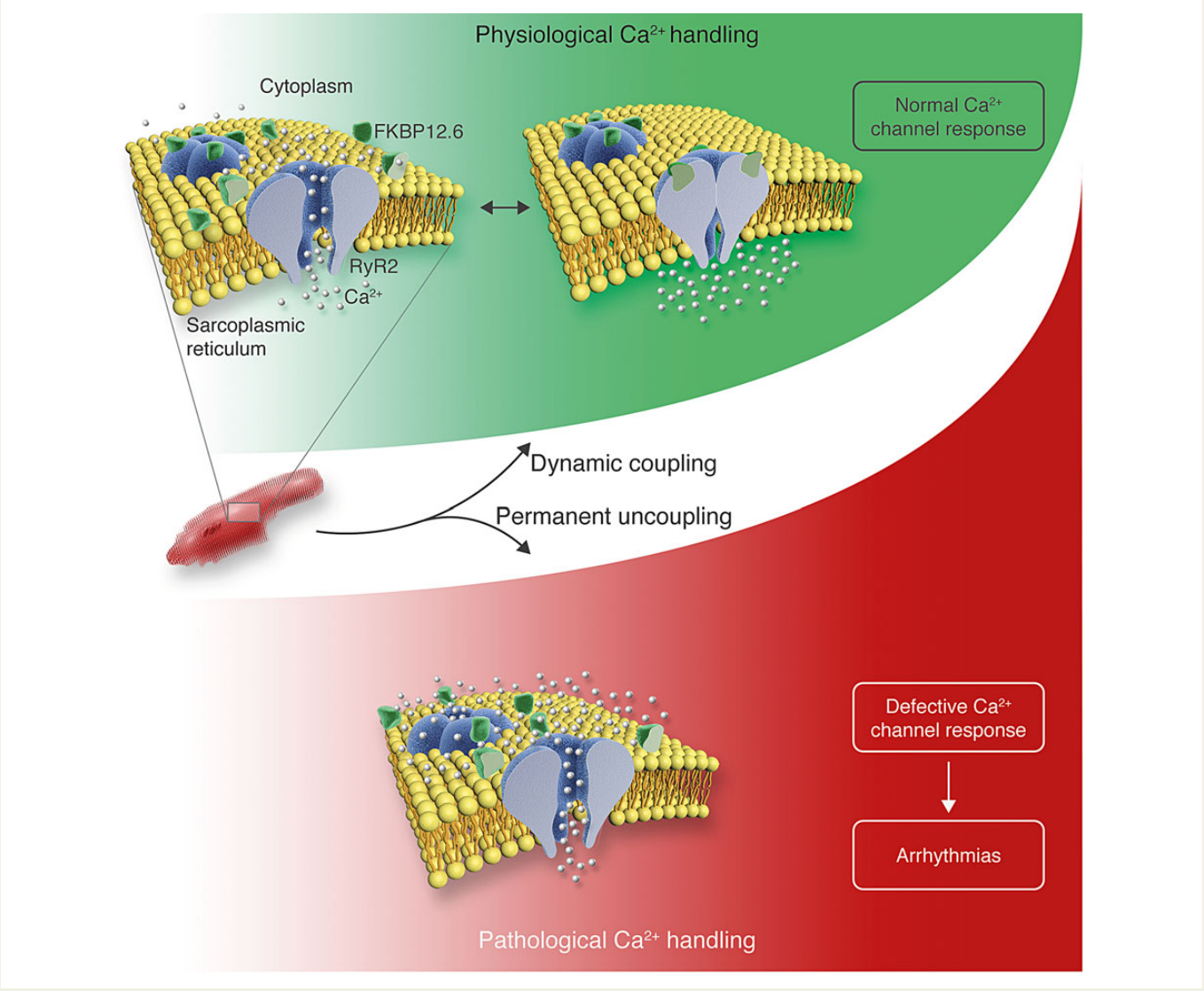

Figure 3 The role of FKBP12.6 in calcium-ion homeostasis. FKBP12.6 plays an essential role in the stabilization of the tetrameric RyR2 located in the membrane of the sarcoplasmic reticulum. In physiological conditions, four FKBP12.6 molecules are bound to RyR2 (one per subunit), thus instigating the channel closed state. In pathological conditions, FKBP12.6 uncouples from RyR2 subunits (concomitant with FKBP12.6 down-regulation), inducing the channel open state, thus provoking Ca^{2+} leakage and subsequent cytoplasmic overload.

potentially by reducing diastolic SR Ca^{2+} leakage.[146,152,158] Thus, the FKBP12.6-RyR2 complex is an evident target for future pharmacological treatments of ventricular tachycardia.[146] Indeed, decreased FKBP12.6 expression has been linked to the increased probability of RyR2 in the open-channel state in naturally occurring canine models of ARVC. However, sequence analysis of the canine FKBP12.6 promoter regions did not identify any mutations,[153,154] indicating that FKBP12.6 is not an ARVC-associated gene, despite PPIase involvement in the pathological process. Fauconnier *et al.* demonstrated that FKBP12.6 expression was down-regulated, resulting in Ca^{2+} leakage in the *'mdx'* mouse model. These results suggest that FKBP12.6 is implicated in the arrhythmogenic events related to muscular dystrophy.[159] Liu *et al.*[160] generated a FKBP12.6$^{-/-}$ mouse model with a conditional expression of FKBP12.6 in heart tissue which exhibited the rescue of the cardiac hypertrophic phenotype through reduced abnormal calcium release. More controversial results stem from the cardiac effects of FKBP12.6 overexpression. Some authors have provided results showing that FKBP12.6 overexpression leads to hypertrophy and hyperplasticity, with increased activation of p38 MAPK and ERK1/2 and levels of apoptotic factors.[161] Conversely, other studies have shown a protective effect of FKBP12.6 overexpression on LV hypertrophy progression in hypertensive mice.[158]

3.3 FKBP6

FKBP6, the most recently discovered member of the FKBP subfamily of immunophilins, has a three-unit TPR motif at its C-terminal which is essential for mediating protein–protein interactions and the assembly of protein complexes.[162,163] FKBP6 has a nuclear intracellular localization with an expression level similar to that of other FKBPs; higher levels in heart and skeletal muscle, and lower levels in the brain.[112]

In 2004, a segment of murine chromosome 12, which includes the *FKBP6* gene, was shown to correspond to a region which is deleted in Williams–Beuren Syndrome (WBS), a disease characterized by congenital cardiovascular anomalies.[164] Hemizygosity of the deleted genes

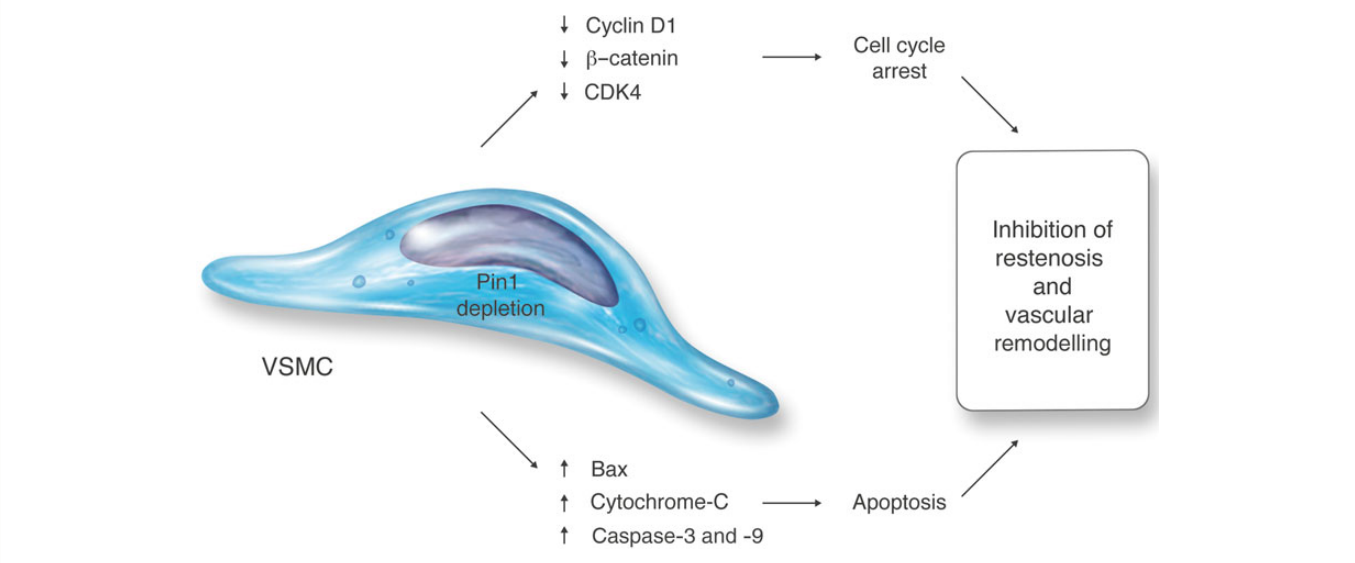

Figure 4 Cellular effects of Pin1 on vascular remodelling. Pin1 deficiency in vascular smooth muscle cells determines both cell cycle arrest and enhancement of apoptosis. These effects are mediated by down-regulation of cyclin D1, beta-catenin, CDK4, increased Bax, released cytochrome-C, and activation of caspase-3 and -9.

in WBS, and possibly also the FKBP6 gene, is responsible for supravalvular aortic stenosis (SVAS), which involves ascending aortic branch narrowing, as well as connective tissue manifestations.[165] In fact, a SVAS phenotype with concomitant deficits in the ELN, GTF2IRD1, and FKBP6 genes has been reported in three WBS patients.[166]

4. Parvulins

Pars are a PPIase subfamily, which show no significant sequence homology with other PPIases[12] and show no affinity for immunosuppressant drugs. There are two human Pars, Pin1 and Pin14. To date, only Pin1 is linked to CVDs (*Table 1*).

4.1 Pin1

The PPIase domain of Pin1 is a rare example of high specificity in substrate recognition as binding requires a 'phospho-X-Pro' a.a. sequence, where phospho-X may be phospho-serine (p-Ser) or phospho-threonine (p-Thr).[167] Pin1 is a nuclear protein, and it is involved in cell cycle progression[167,168] and in the control of oncogenic pathways.[169]

In particular, Lv *et al.*[170,171] provided *in vitro* evidence on the involvement of Pin1 signalling in VSMC cell cycle progression and apoptosis (*Figure 4*). Since post-injury VSMC apoptosis may limit neointima formation, these results underline a potentially critical role of Pin1 in restenosis after endovascular damage. Recent data have shown that reduced Pin1 expression in VSMCs treated with nectandrin B (a potent eNOS activator) blocks cell proliferation through stimulation of the adenosine monophosphate-activated protein kinase pathway.[172] In 2008, the interaction between Pin1 and inducible nitric oxide synthase (iNOS), an important endothelial inflammation mediator, was discovered. Given the high sequence homology between iNOS and eNOS, Ruan *et al.*[173] demonstrated the phosphorylation-dependent interaction of Pin1 with eNOS, resulting in Pin1-induced eNOS inactivation due to conformational changes. This inactivation was proposed to be mediated by either direct impairment of the eNOS catalytic site or indirectly by making eNOS more or less susceptible to phosphorylation/dephosphorylation and enzyme degradation.[173] Thus, Pin1 activity can be easily considered as an 'on-off' switch where the activity of downstream proteins, such as phosphatases, depend on its function.[174] Ruan *et al.* showed impaired NO production due to increased Pin1; however, Chiasson *et al.*[175] uncovered a concerted down-regulation of NO and Pin1. Furthermore, treatment with juglone (a specific Pin1 inhibitor) or Pin1 gene deletion caused both hypertension and endothelium dysfunction (phosphorylated eNOS and decreased NO production) in mice.[175] Moreover, Paneni *et al.* have recently shown that $Pin1^{-/-}$ diabetic mice were protected against endothelial impairment in a hyperglycaemic setting. Pin1 expression and activity increased specifically in EC during hyperglycaemia, which plays a key role in triggering diabetic vascular disease. Indeed, Pin1 facilitates $p66^{Shc}$ mitochondrial translocation, inducing ROS production, while impairing NO availability.[176] Recently, it has been noted that $Pin1^{-/-}$ mice were protected from pressure overload-induced cardiac hypertrophy. However, surprisingly, cardiomyocytes overexpressing Pin1 also displayed resistance to hypertrophy.[177] To reconcile these paradoxical findings, the study found that Pin1 overexpression reduces MEK activation via inhibitory Raf^{Ser259} autophosphorylation, thus leading to an overall decrease in hypertrophic signalling. Recently, statins have been shown to exert their pleiotropic antihypertrophic effect partly through Pin1 inactivation.[178] Given these experimental findings, it can be suggested that Pin1 may play a significant role in CVD by acting as a regulator of NOS and hypertrophic cell signals. However, more studies are necessary to elucidate a putative strategy for Pin1-targeted drug therapy.

5. Conclusion and clinical perspectives

PPIases are a class of proteins that play a central role in multiple biological processes, such as protein folding, trafficking, and assembly, as well as

intracellular calcium handling, chemotaxis, and cell cycle progression. In particular, there is a vast amount of information on individual members of this family of proteins in the development of several CVDs, such as vascular stenosis, hypertension, atherosclerosis, cardiac hypertrophy, arrhythmias, ischaemic and non-ischaemic cardiomyopathy, and HF. The mechanisms underlying this involvement are related to their strong association with key functional regulators of the cardiovascular system, including eNOS, scavenger receptors, calcineurin, RyR, inositol trisphosphate receptor, and mTOR. In spite of the recent advances on the role of PPIases in the cardiovascular field, several aspects related to PPIases pathophysiological function *in vitro* and *in vivo* remain poorly understood. Therefore, a detailed analysis of their interaction with critical molecular partners and/or receptors in addition to characterization of the signalling pathways may shed light on this protein family.

It is important to point out that some controversies exist between the different classes of PPIases. For instance, while Cyps and Pin1 loss prevents several CVD, FKBP12.6 deficiency leads to AF and cardiac arrhythmias. Even within the same subfamily, some contrasting results have come to light depending on cardiac disease type. An example is offered by CypD knockdown which provides cardioprotection following I/R injury while a maladaptive cardiac phenotype is evident in HF. Another point that should be considered regarding the extracellular PPIases is the dose-dependent effect. Specifically, studies in cultured ECs have shown that exogenously administered CypA at low concentrations enhances cell proliferation, capillary-like structure development, migration, invasive properties as well as MMP-2 secretion. In contrast, at high concentrations, CypA inhibits HUVEC migration and viability.[179]

In light of these considerations, future investigations should be focused on finding inhibitors targeting specific PPIases and in well-characterized disease models. The achievement of the drug specificity for homogenous protein families is a very difficult task and requires a concerted effort between medicinal chemistry as well as of the specific biochemical and pharmacological experts. Indeed, currently many efforts are focused on the development of novel PPIase inhibitors by intelligent structure-based drug design methodologies.

To date, various drugs targeting these proteins have been discovered comprising FK506, sirolimus/rapamycin, cyclosporine, and tacrolimus.[180] Several FKBP-binding macrocyclic drugs, everolimus, zotarolimus, and temsirolius are in Phase III trials as targets for cell proliferation, immunosuppression, and anti-cancer effects.[181]

One of the problems associated with these inhibitors, however, is their off-target effects, particularly and not surprisingly, non-deliberate immunosuppression. Thus, concerted efforts to generate compounds lacking immunosuppressive activity have resulted in varied outcomes. In particular, Debio 025 (Alisporivir) and NIM81182–84 have shown great promise in multiple therapeutic areas.[182–184] Similarly, the development of cell impermeable, non-immunosuppressive CSA analogues has permitted the inhibition of extracellular CypA in mouse models of inflammation.[185]

Finally, because many of the PPIase family members are secreted, they might hold great promise to be a valuable biomarkers for diagnostic/prognostic tests for cardiovascular-related diseases.

It is muted that the development of agents that selectively inactivate PPIases or block the binding to their molecular targets or modulating the secretory pathways may be an appealing approach to fully elucidate the pathological mechanisms and provide treatments for CVDs, pathologies with a huge global impact in the world.

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