C

Cyclophilin

Suchismita Roy[1], Prabhjeet Singh[2], Sneh Lata Singla-Pareek[3] and Ashwani Pareek[1]
[1]School of Life Sciences, Jawaharlal Nehru University, New Delhi, India
[2]Department of Biotechnology, Guru Nanak Dev University, Amritsar, India
[3]Plant Stress Biology, ICGEB, New Delhi, India

Synonyms

Cyclophilin-like domain (CLD); Immunophilin; Peptidyl prolyl cis trans isomerase; PPIase; Rotamase

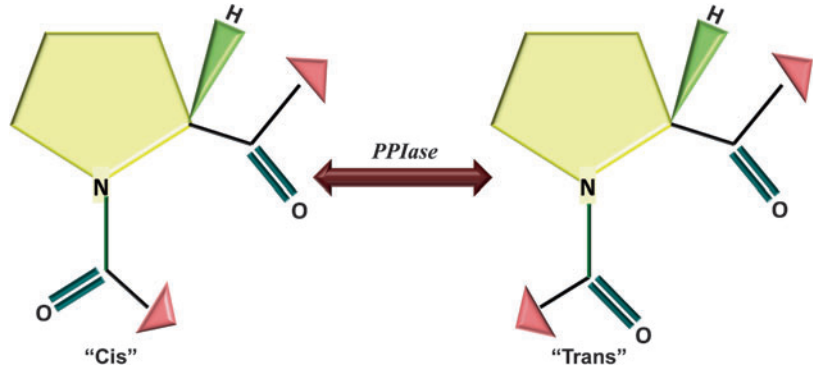
Historical Background

The first cyclophilin (Cyp/PPIases: EC 5.2.1.8) was isolated more than three decades ago as an intracellular receptor of the immunosuppressive drug cyclosporine A (CsA) from the bovine thymocytes (Handschumacher et al. 1984). It was not until 1989, its PPIase activity was elucidated. Cyclophilins comprise a ubiquitous set of proteins which is present across diverse genera of organisms. The single domain cyclophilin has a single cyclophilin-like domain (CLD), whereas multidomain cyclophilins also possess additional domains such as tetratricopeptide repeat (TPR), RNA recognition motif (RRM), tryptophan aspartate domain (WD40), coiled-coil domain (CCD), and internal repeats domain (RPT). Cyclophilins are involved in a myriad of physiological cellular processes, such as protein trafficking and maturation, receptor complex stabilization, apoptosis, receptor signaling, RNA processing, immune response, spliceosome assembly, miRNA activity, and also RISC assembly (Kumari et al. 2013). Notably, 22 cyclophilins have been reported from human genome, of which seven are major ones, including hCypA, hCypB, hCypC, hCypD, hCypE, hCyp40, and hCypNK.

Cyclophilins: Structure

The first structure of human cyclophilin revealed it to possess eight antiparallel β strands (Kumari et al. 2013). These secondary structures form a right-handed β barrel-shaped structure with an α-helix at either end. This conformation of CypA forms closed β barrel, preventing CsA or proline-containing substrate peptide from binding to its hydrophobic core. The smallest cyclophilin is CypA of 17 kDa size, which contains only the PPIase domain and is localized in the cytosol. Other cyclophilins have unique sequences which target them to specific organelles such as hCypB, and hCypC are directed towards the endoplasmic reticulum (ER), hCypD is directed to the mitochondria, whereas hCypE/hCypF/hCypG are nucleus targeted. The interaction of CsA with

S. Choi (ed.), *Encyclopedia of Signaling Molecules*,
DOI 10.1007/978-1-4614-6438-9_101549-1



Cyclophilin, Fig. 1 Pictorial representation of the PPIase activity of cyclophilins in general. The interconversion between the *cis* and *trans* forms of the peptide bonds around the proline residue is catalyzed by cyclophilins and other peptidyl-prolyl isomerases (PPIases)

CypA at the outer surface is a hydrophobic interaction mediated through the seven aromatic and other hydrophobic residues present in the hydrophobic core. The active site of cyclophilin family members include the invariant catalytic arginine residue at position 55 and a highly conserved mixture of hydrophobic, aromatic, and polar residues comprising of Phe60, Met61, Gln63, Ala101, Phe113, Trp121, Leu122, and His126 (Davis et al. 2010). These residues are well conserved across all PPIase domains and are believed to participate in either the catalysis or substrate/ligand-binding activities (Davis et al. 2010).

Mechanism of Action: Protein Folding and PPIase Activity

The peptide bonds of newly synthesized or folded proteins tend to occur in either *cis* or *trans* conformations; the dihedral angles for the rotation about the CN bond are tightly clustered around 180 ° (*trans*) and 0° (*cis*). In *trans* state, the side chains are opposite to each other and are sterically most favored (Kumari et al. 2013). Proline, because of its unique structure, has an inbuilt capability either to adopt a *cis* or a *trans* state. Therefore 6.7% of all Xaa-Pro peptide bonds takes up the *cis* conformation (Fischer et al. 1984). The *cis* to *trans* transition is imperative for the final protein maturation since *cis*-proline introduces bends within the protein, hence, decreasing the protein stability. The relative large energy barrier ($\Delta G = 14–24$ kcal/mol) makes the *cis-trans* isomerization a slow and rate-limiting process (Kumari et al. 2013). The PPIase activity of several cyclophilins (and also FK506-binding proteins) stabilizes this *cis-trans* transition, lowers the activation energy of the stabilized protein product, and accelerates the isomerization process (Fischer et al. 1984). This process generally happens during the slow isomerization steps as represented in Fig. 1.

PPIases are considered as classical enzymes as they are not ATP dependent for their enzymatic properties and the reaction follows Michaelis-Menten first order kinetics (Fischer et al. 1984). This isomerization is essential for domain assembly and folding of other proteins. Using NMR and molecular simulation studies, Camillonia et al. (2014) proposed an electrostatic mechanism for the functioning of cyclophilins. They reported the development of an electrostatic field in the catalytic site by the PPIases which triggers the electric dipole associated with the substrate, especially carbonyl group of the amino acid preceding the proline residue, thus causing a rotation of the associated peptide bond between the two amino acids (Camillonia et al. 2014).

Cyclophilins as Signaling Molecules

Cyclophilins play diverse roles as signaling molecules, controlling a myriad of cellular pathways. Table 1 gives a summary of extensively studied cyclophilins and the associated signaling pathways.

Cyclophilin, Table 1 Cyclophilins and their associated signaling pathways

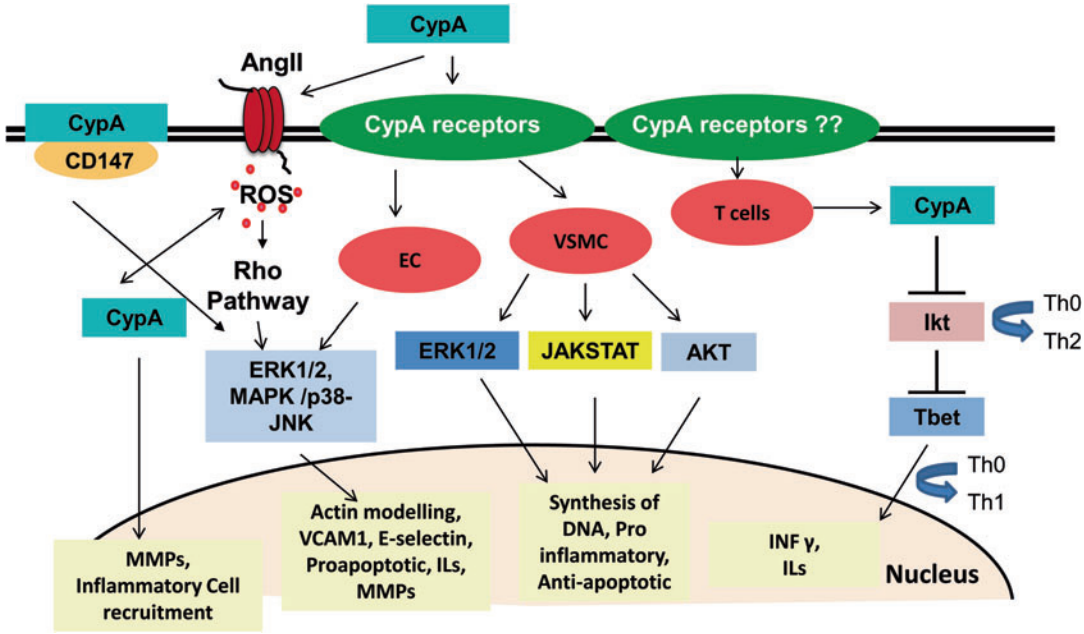
Cyclophilin	Receptor/signaling pathway	Effect	References
CypA	Interleukin-2 tyrosine kinase	Positive regulation of Th1 and inhibition of Th2 differentiation	Brazin et al. 2002
	CD174, ERK activation	Adhesion of monocytes/macrophages	Yang et al. 2007
	Calcineurin, NF-kB	Inhibition of phosphatase activity, fibroblast proliferation	Soe et al. 2011
	ERK1/2	Vascular smooth muscle cells (VSMC) proliferation	Soe et al. 2011
	MAPK/p38-JNK signaling	Stimulation of endothelial cells (EC) apoptosis and inflammation	Kim et al. 2015
	AKT signaling	Adhesion of platelets and thrombus development	Seizer et al. 2015
	Abl Crk activation	Stimulation for cell migration	Saleh et al. 2016
	Prolactin signaling	Phosphorylation of JAK2	Syed et al. 2003
CypB	Glycosaminoglycans	Adhesion of T cells to the extracellular matrix	Allain et al. 2002
	Interferon regulatory factors 3 (IRF3)	Activation of IRF3 by its phosphorylation	Obata et al. 2005
	Stat3 signaling	Survival of multiple myeloma cells	Bauer et al. 2009
	p300 E4	CHOP ubiquitination	Jeong et al. 2014
CypC	Osteopontin	Regulates in vitro migration and invasive properties of cancer	Mi et al. 2007
	US2-dependent degradation pathway	US2-dependent degradation of major histocompatibility complex class I (MHCI)	Chapman et al. 2015
CypD	MPTP complex	Regulation of mitochondrial permeability Transition pore (mPTP)	Baines et al. 2005
	Bcl 2	Inhibits cytochrome c release, antiapoptotic	Eliseev et al. 2009
	p53, PARP1	Necrosis	Ying and Padanilam 2016
Cyp40	Aryl hydrocarbon receptor (AhR) signaling pathway	Formation of AhR/Arnt heterodimer	Luu et al. 2008

CypA-Mediated Signaling

CypA is known to have both intracellular and extracellular signaling properties. CypA has a biphasic effect as a signaling molecule. hCypA promotes proliferation of cells and initiates cellular migration at low concentrations, whereas at higher concentration, it causes cytotoxic effects on the tumorogenic cells. hCypA regulates the T-cell-specific interleukin-2 tyrosine kinase (Itk) (Brazin et al. 2002). Itks have an important aspect in the development of thymocytes and are required for intracellular signaling events leading to the activation of T-cells. Itks have conserved Src homology 2 (SH2), Src homology 3 (SH3), and kinase domains. CypA binds to the SH2 domain of Itks which result in its structural changes and alteration of ligand specificity. Mutational studies have shown that alteration of proline residue in the SH2 domain disrupts the interaction between Itk and CypA protein, which is

imperative for enhanced production of type 2 (Th2) cytokines (produced by Th2 helper cells). NMR studies suggest that cyclophilin-bound Itk acts as a monomer in its native form causing the proline-rich region to come in proximity with the SH3 binding pocket as an interface of intramolecular interaction. CypA-Itk protein complex gets activated by phosphorylation of the 180th Tyrosine residue of the SH3 domain (Brazin et al. 2002). The C-terminus of the Itk SH2 domain undergoes a conformational change in the presence of CypA that structurally hinder its kinase catalytic site, thus making it inactive. Asparagine and proline residues at 286-287 position are responsible for *cis/trans* isomerization of the SH2 domain which leads to conformational change in the C terminus of the Itk SH2 domain leading to one-to-one interaction into the Itk protein kinase domain. Release of CypA might occur, by the dimerization of Itk protein which favors the *cis* conformation by binding to the phosphotyrosine residue containing ligand to favor the *trans* conformation This may lead to rearrangement of the C-terminal SH2 domain and subsequent reconformation of the kinase active sites (Brazin et al. 2002). Thorough understanding of these signaling pathways is crucial in light of the suggested use of CsA in organ transplantation.

CD147 is a cell-surface receptor for CypA, and it is an essential component in the CypA-initiated signaling cascade that is involved in the extracellular receptor kinases (ERK), chemotactic movements of the leucocytes, and induction of matrix metalloproteinases (MMP)-related pathways (Yurchenko et al. 2002). Pro180/Gly181 residues of the CD147 extracellular domain are critical for CypA-specific signaling pathway (Yurchenko et al. 2002). This cascade forms a part of the major inflammatory processes. It also causes pulmonary hypertension by activation of extracellular signal-regulated kinases (ERK1/2) pathway. This leads to subsequent release of several chemokines or cytokines and related growth factors, such as PDGF-BB. (Yurchenko et al. 2002). CypA acts both as a paracrine and autocrine factor and triggers its release in the extracellular space upon stimulation of oxidative or inflammatory processes in case of apoptosis. CypA is also known to regulate apoptosis signaling-regulating kinase 1 (ASK1). ASK1 is a member of MAPK kinase (MAP3K) family as well as Jun amino-terminal kinases (JNK) and p38/MAPK pathways (Kim et al. 2015). CypA negatively regulates phosphorylation of the serine residue at the 966th position of ASK1 protein thus causing reduction of ASK1 protein by affecting other downstream protein kinases involved in the p38 and JNK signaling cascade. ASK1 causes the activation of protein-like caspase-3 leading to apoptosis as a cellular stress response. Comparative proteomic studies have identified CypA as a potential downstream target of protein kinase B (Akt) as well. This study confirmed that CypA is a downstream effector of the phosphatidylinositide 3-kinase (PI3K)/Akt signaling pathway (Seizer et al. 2015). Extracellular CypA is known to activate platelets via EMMPRIN/CD147 and PI3K/Akt signaling. This pathway regulates adhesion of the platelets thrombus development (Seizer et al. 2015). CypA was found to be highly phosphorylated in response to interleukin-6 treatment, which was consistent with the accumulation of phosphorylated Akt, suggesting that CypA is phosphorylated by Akt, the downstream effector of the PI3K/Akt pathway (Lin et al. 2015). CypA is also implicated in retinoic acid-induced neuronal signaling and differentiation (Song et al. 2004). CypA also modulates prolactin receptor signaling (PRLR) (Syed et al. 2003) through functional interaction of the receptor (Syed et al. 2003). In vitro binding studies have shown a direct interaction of CypA with PRLR in breast epithelial cell lines (T47D) and Chinese hamster ovary transfectants which exhibited overexpression of PRLR protein. Interestingly, co-immunoprecipitation assay also revealed a positive association of CypA with Janus-activated kinase 2 protein (Jak2). Subsequently, it was reported that overexpression of CypA inhibited PRL-induced Rac activation, while simultaneously prolonging the rate of phosphorylation of Jak2 (Syed et al. 2003). This study established that CypA is a tumorigenic factor and also serves

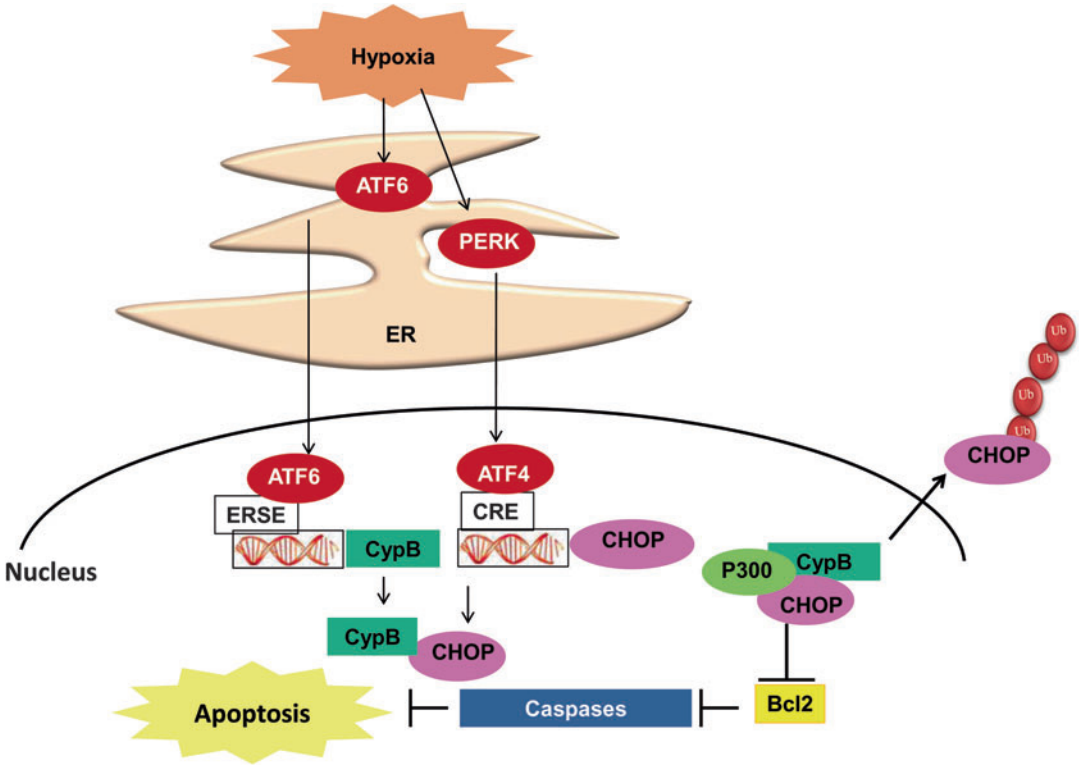


Cyclophilin, Fig. 2 Schematic representation CypA-mediated signaling pathways. CypA-mediated signaling cascade effects endothelial cells (EC), T cells, and vascular smooth muscle (VSMC). CypA interacts with proteins as Angiotensin II (Ang II) and liberates ROS; this in turn determines the release of CypA from VSMC. CypA triggers VSMC signaling pathways such as AKT, ERK1/2, and JAKSTAT pathway. Extracellular CypA contributes to the recruitment of inflammatory cells and activation of matrix metalloproteinase (MMPs) that degrade the extracellular matrix. CypA induces ROS formation by a positive feedback loop. CypA induces inflammation of endothelial cells (EC) by enhancing adhesion and expression of other genes and decreasing eNOS expression. In EC, CypA activates proinflammatory causing enhanced expression of vascular cell adhesion molecule-1(VCAM-1) and lectin-like proteins as E-selectins. CypA also increases the apoptosis of ECs. In T cell targeted signaling response, CypA binds to Itk which is an inhibitor of T-bet, the T helper type 1 (Th1) specific transcription factor. CypA acts as a positive regulator of Th1 profile promoting differentiation of Th0 cells into Th1 lymphocytes which ultimately regulates the expression of interferons (IFs) and interleukins (ILs) (Figure modified from Soe et al. 2011)

as a potential target for PPI inhibitors in oncogenic signaling pathway. A schematic representation of some of the CypA-mediated signaling pathways is given in Fig. 2.

CypB-Mediated Signaling

CypB induces chemotaxis and integrin-mediated adhesion of T cells to the extracellular matrix (ECM) in vitro. Importantly, this effect appears to be targeted predominantly to memory $CD4^+$ T cells, suggesting that CypB might recruit specific populations of T cells into infected tissues *in vivo*, thus regulating the inflammatory response. It therefore appears that CypA and CypB use different classes of group-specific antigens (GAG) molecules for binding, or that the affinity of CypA for GAG is much lower than that of CypB. CypB is known to interact with interferon-regulatory factor-3 (IRF-3), which promotes the activity of interferon as soon as it is translocated into the nucleus. *RNAi*-mediated silencing of CypB indicated the suppression of virus-induced IRF-3 phosphorylation and other related events which ultimately resulted in the inhibition of interferon activity (Obata et al. 2005). CypB mainly phosphorylates IRF-3 (Obata et al. 2005). CypB signaling involves the activity of the C/EBP-homologous protein (CHOP) transcription factor, which is one of the well-studied stress-induced ER-localized proapoptotic molecule causing cell death. It was reported that the CypB and p300 interaction is due



Cyclophilin, Fig. 3 Schematic representation of CypB-mediated signaling. CypB overexpression inhibits hypoxia-induced apoptosis via ER stress-dependent signaling cascade. CypB, CHOP, and P300 protein interaction promotes the ubiquitination of CHOP protein. This process suppresses hypoxia-induced cell death. CypB also causes activation of transcription factor 6 (ATF6) in hypoxic conditions which in turn affects the expression of CypB (Figure modified from Jeong et al. 2014)

to the N-terminal region of the CHOP protein that leads to the ubiquitination of the latter leading to hypoxia-induced apoptosis (Jeong et al. 2014). CypB expression is associated with the activation of transcription factor 6 (ATF6) which is also hypoxic condition mediated. ATF6 influences the expression of CypB by adhering to a specific ATF6-responsive region in the promoter region of CypB. Signal transducer and activator of transcription 3 (Stat3) is an important modulator of cytokines of type interleukin-6 (IL6) (Bauer et al. 2009). CypB also contributes to Stat3 signaling and survival of these multiple myeloma cells (Bauer et al. 2009). CypB causes transactivation of Stat3 towards a Stat3-specific target promoter and is responsible for the survival of multiple myeloma cells (Bauer et al. 2009). A schematic representation of the CypB-mediated signaling pathways is given in Fig. 3.

CypC-Mediated Signaling

Signaling cascades of CypC is mediated through its interaction with CypC-associated protein (CypCAP), a secreted glycoprotein, which modulates the activation of macrophages by regulating the nuclear factor of activated T protein (NFAT), endotoxin signaling, and the expression of metalloproteinase-13. CypCAP is speculated to be involved in the defense mechanisms of the host as it is upregulated both in the tumorigenic cells and also by viral infections, such as HIV and HCV. CypC forms a complex with the COOH-terminal fragment of early T-lymphocyte activation protein (ETA1)/osteopontin (Mi et al. 2007). Osteopontin is a secreted glycoprotein that mediates cell-matrix interactions and cellular signaling through binding with CD44 receptors and transmembrane proteins as integrin (primarily $\alpha v\beta 3$). It helps in cell adhesion, chemotaxis,

macrophage-directed interleukin-10 suppression, stress-dependent angiogenesis, and prevention of apoptosis (Mi et al. 2007). This CypC-osteopontin protein complex adheres to the cell surface receptor CD147 causing subsequent activation of Akt1/2 signaling and MMP-2 in 4T07 murine breast cancer cell line. CypC-osteopontin complex also regulates migration and invasive properties of cancerous breast cell lines (Mi et al. 2007). CypC is involved in the ER dependent degradation of the major histocompatibility complex class I (MHCI) by the active participation of the US2 protein (Chapman et al. 2015). CypC was co-immnunoprecipitated with the immunoinvasive protein US2 and with the class I molecule HLA-A2. Chapman et al. (2015) also reported that the role of CypC is concentration dependent, as its overexpression or deficiency both disturbs the degradation of class I molecules (Chapman et al. 2015).

CypD-Mediated Signaling

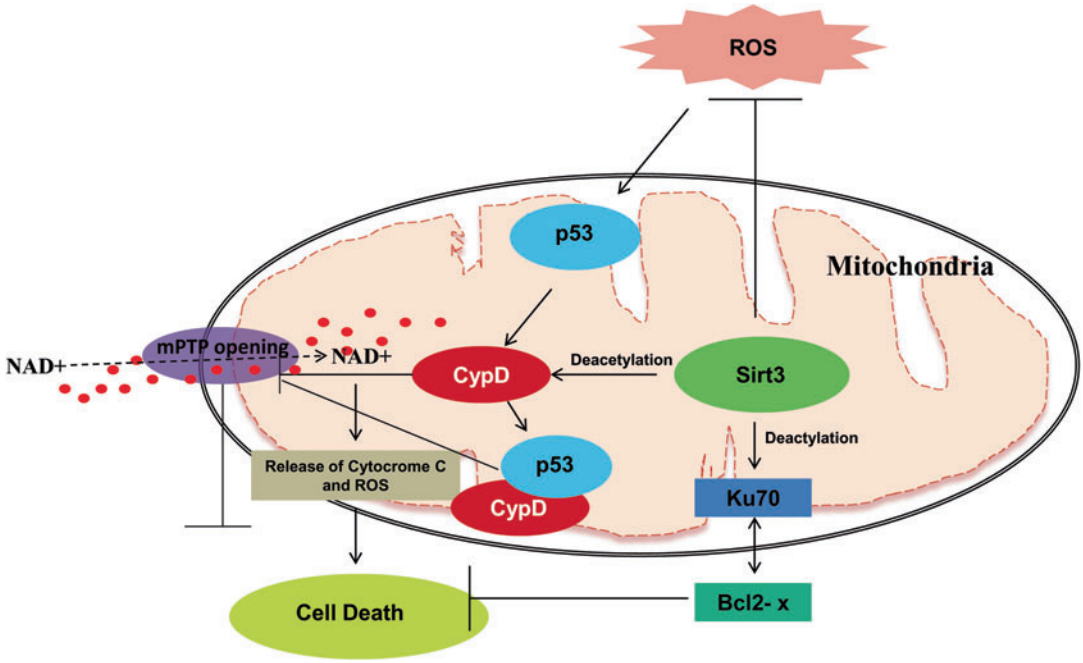
CypD plays a fundamental role in maintaining the overall energy homeostasis in cells and is crucial for necrotic signaling. CypD regulates extramitochondrial signaling in normal as well as tumorigenic cells. This signaling is responsible for transcriptional modulation of a chemokine receptor signature molecule and activation of the pleiotropic inflammatory mediator, such as signal transducer and activator of transcription 3 (STAT3). It was shown that CypD null mutants were highly resistant to cell death by increased cytosolic Ca^{2+} concentration and ROS. Translocation of p53 protein to the mitochondria in response to salinomycin drug treatment resulted in its complex formation with CypD. This complex hinders the mitochondrial permeability transition pore (mPTP) formation and programmed cell death (Baines et al. 2005). ROS and Ca^{2+}, the most prominent mediators of permeability transition, increase the probability of MPTP opening via activation of CypD and ATP synthasome complex leading to necrosis. Cell death via necrosis involves crosstalk of molecules, such as p53, PARP1, and CypD. In oxidative stress, CypD is also known to regulate p53 protein and trigger mitochondrial pore formation followed by necrosis (Yang et al. 2016). Studies relating to CypD support the role of interorganelle signaling in a regulatory network poised to affect broad cellular homeostatic responses. The CypD-mediated signaling pathways are summarized in Fig. 4.

Cyp40-Mediated Signaling

Cyp40 is involved in aryl hydrocarbon receptor (AhR) signaling pathway. Through this pathway, which is Hsp90-independent, Cyp40 promotes the formation of AhR/Arnt/DRE complex which involves the heterodimerization of AhR/Arnt protein that binds to dioxin response element (DRE) (Luu et al. 2008). The linker region comprising of amino acids residues from 186-215 position of Cyp40 is mainly responsible for this signaling mechanism. Cpr7, a homologue CyP40, is essential for the glucocorticoid receptor signaling in yeast. The activities of two heterologous Hsp90-dependent signal transducers expressed in yeast, glucocorticoid receptor, and pp60 (v-src) kinase were adversely affected by cpr7 null mutations.

Cyclophilins: Relevance in Disease and Therapeutics in Human

Broad range physiological functions are valid targets for therapeutic intervention through cyclophilins. During the last two decades considerable insight has been gained regarding the CypA-, CypB-, and CypD-related signaling processes due to their involvement in specific cell functions and disease pathogenesis. A variety of protein-folding processes depend on the PPIase and/or chaperone-like activities of these immunophilins. CypA mechanism is involved with diseases such as atherosclerosis, rheumatoid arthritis, and endothelial dysfunction. It also aids in the enhanced production by macrophages following lipopolysaccharide stimulation, suggesting its role also as an inflammatory mediator. CypA also acts as a mediator of oxidative stress-induced tissue damage, similar to the effects caused by Rho-kinase inhibitors -



Cyclophilin, Fig. 4 Intracellular CypD-mediated signaling. Overdose of mitochondrial calcium (Ca^{2+}, *red circles*) causes CypD-mPTP coupling which leads to prolonged mitochondrial permeability transition pore (mPTP) opening and higher Ca^{2+} ion release into the cytoplasm, favoring cell death as in case of cardiac arrest. This is also regulated by Sirt3 proteins. CypD also initiates transient mitochondrial permeability transition, which in turn causes an increase in intramitochondrial NAD^+ content. NAD^+ increase causes deacetylation of Sirt3 protein affecting other mitochondrial protein targets, like CypD, to modulate metabolism and cell death. SIRT3 causes deacetylation of Ku70 protein to sequester Bcl2-associated protein X away from the mitochondria-inhibiting apoptosis. On the onset of ROS, stress inducible transcription factors gets activated such as p53, which interacts with CypD causing MPTP opening and cell death and necrosis (Figure modified from Baines et al. 2005, Matsushima and Sadoshima 2015, Yang et al. 2016)

Y27632 and simvastatin. These significantly reduce the secretion of CypA from vascular smooth muscle (VSMCs) (Soe et al. 2011). Rho-kinase is a potent therapeutic target in cardiovascular diseases and inhibition of Rho-kinase reduced AngII-induced abdominal aortic aneurysm formation, atherosclerosis, pulmonary hypertension (Soe et al. 2011), and cardiac hypertrophy. CypA is also involved in the regulation of Ca^{2+} ions in the platelets and thus plays an important role in controlling thrombosis of the artery. CypA also regulates endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) generation and thus controls blood pressure level. By inhibiting the cycle that enhances ROS generation through CypA autocrine/paracrine signaling pathway, there is a hope to develop a novel therapeutic target for controlling cardiovascular diseases. CypD maintains mitochondrial membrane permeability by regulating transition pore complex formation, in case of cell death induced by concentration change in Ca^{2+} and ROS, and causes cardiac ischemia-perfusion injury (Baines et al. 2005). CypD thus stands out as a potential therapeutic protein in tissue death and myocardial infarction-related diseases. Increase in Ca^{2+} leads to the persistent opening of mitochondrial pore followed by PCD, which happens in case of neuronal diseases (Baines et al. 2005). Loss of CypD causes a change towards glycolytic pathway via upregulation of transcriptional effectors related to the metabolism of glucose and enhanced glucose uptake which leads to higher amount of ATP liberation. CypD mutations also lead to defects in mitochondrial TCA cycle intermediates, leading to reduced amount of acetyl CoA, defective

pattern of fumarate and malate accumulation, and defect in fatty acid β-oxidation-like processes. Inhibition of CypD is also a promising strategy against bone loss.

Cyclophilins are also involved in the pathogenesis of varied liver diseases. Extracellular CypA and CypB are potential lymphotactic agents (Austin et al. 2015). Both CypA and CypB cyclophilins interact with CD147 on the membrane of T cells. Drugs targeting either Cyp or CD147 show a marked anti-inflammatory response in animal models of acute or chronic lung diseases, portraying a therapeutic clue. CD147 also serves as a receptor for virus-associated CypA. Expression of CD147 on the cell surface requires the involvement of Cyp60 protein. CypA also gets incorporated into HIV-1 virions, by associating with the polyprotein precursor of virion structural proteins GAG. A very small part of the HIV-1 capsid protein which bears four conserved prolines has been shown to be important for incorporation of CypA into virions. CypJ is also involved in cancer as CypJ upregulation causes upregulation of transcripts of several drug resistance-related genes, thus displaying a potential role in chemotherapeutics. Expression of CypJ gene may also be correlated with the development of human glioma cells, which in turn might control the conformation of a proapoptotic protein apoptin in tumorous cells (Austin et al. 2015). Investigation on extracellular CypA receptors of vascular cell components will contribute to the development of novel strategies against therapies for cardiovascular diseases. CypB expression is associated with development of malignancy of breast cancer. When CypB was present in the conditioned medium of the breast carcinoma cell line MDA-MB231, it enhanced chemotactic movement of the mesenchymal stromal cells derived from the bone marrow (Austin et al. 2015). Isomerase activity of CypA, CypB, and cyclophilin 40 have been shown to be essential for replication of hepatitis C virus (HCV) as well. Cyclophilin inhibitors are potent as replication inhibitors of several life-threatening RNA viruses such as HCV, HIV, SARS corona virus, and influenza virus. Some nonimmunosuppressive cyclosporin derivatives are available in the market such as Alisporivir (Debio-025; Debiopharm, Novartis) and SCY-635 (Scynexis Inc.) for the treatment of hepatitis C infection (Austin et al. 2015). CsA itself has also shown some promise in new therapeutic implementations, for example, in case of treatment of brain injury. Preclinical research has suggested the utility of these or other cyclophilin inhibitors in treatment of diverse diseases such as Alzheimer's disease, cardiovascular disease, muscular dystrophy, and respiratory disease to represent a few in the prevailing scenario.

Summary

Cyclophilins form a ubiquitous set of proteins, which are involved in complex cell signaling processes. hCypA was initially identified as an interacting partner of the immunosuppressive drug CsA having PPIase activity, and much later, it was identified as the cellular signaling component. Over the past 25 years of cyclophilin research in humans and other animal model systems, this protein has been reported to regulate signaling cascades such as ERK signaling, ASK1 signaling, etc. Other cyclophilins such as CypB, CypC, and CypD are also involved in signaling processes. CypA and CypB, because of similar structures, have the same receptors such as CD147. Further studies are required to understand the role of different cyclophilins in regulating signal transduction pathways through identification of interacting partners. Current research on different cell lines and animal models has provided plethora of evidences supporting the crucial function of cyclophilins in several human diseases. It is believed that further elucidations of the role of cyclphilin will provide a better understanding of the molecular mechanisms underlying these diseases and will help develop potential pharmacological therapies for drug targeting.

References

Allain F, Vanpouille C, Carpentier M, Slomianny MC, Durieux S, Spik G. Interaction with glycosaminoglycans is required for cyclophilin B to trigger integrin-mediated adhesion of peripheral blood T lymphocytes to extracellular matrix. Proc Natl Acad Sci U S A. 2002;99:2714–9.

Austin C, Davis JB, Fliri HG, Ford RL, Steadman A. Prolyl Isomerases – Old Proteins as New Therapeutic Targets: Selcia Ltd, Essex, UK. 2015;1–12. https://www.selcia.com

Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, Hambleton M, Brunskill EM, Sayen MR, Gottlieb RA, Dorn GW, Robbins J, Molkentin JD. Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death. Nature. 2005;434:658–62.

Bauer K, Kretzschmar AK, Cvijic H, Blumert C, Loffler D, Brocke-Heidrich K, Schiene-Fischer C, Fischer G, Sinz A, Clevenger CV, et al. Cyclophilins contribute to Stat3 signaling and survival of multiple myeloma cells. Oncogene. 2009;28:2784–95.

Brazin KN, Mallis RJ, Fulton DB, Andreotti AH. Regulation of the tyrosine kinase Itk by the peptidyl-prolyl isomerase cyclophilin A. Proc Natl Acad Sci USA. 2002;99:1899–904.

Camillonia C, Sahakyana AB, Holliday MJ, Isernc NG, Zhangd F, Eisenmesserb EZ, Vendruscolo M. Cyclophilin A catalyzes proline isomerization by an electrostatic handle mechanism. Proc Natl Acad Sci USA. 2014;111:10203–8.

Chapman DC, Stocki P, DB W. Cyclophilin C participates in the US2-mediated degradation of major histocompatibility complex class I molecules. PLoS One. 2015; doi:10.1371/journal.pone.0145458.

Davis TL, Walker JR, Campagna-Slater V, Finerty Jr PJ, Paramanathan R, Bernstein G, MacKenzie F, Tempel W, Ouyang H, Lee WH, Eisenmesser EZ, Dhe-Paganon S. Structural and biochemical characterization of the human cyclophilin family of peptidyl-prolyl isomerases. PLoS Biol. 2010;8:e1000439.

Eliseev RA, Malecki J, Lester T, Zhang Y, Humphrey J, Gunter TE. Cyclophilin D interacts with Bcl2 and exerts an anti-apoptotic effect. J Biol Chem. 2009;284:9692–9.

Fischer G, Bang H, Mech C. Determination of enzymatic catalysis for the cis-trans-isomerization of peptide binding in proline-containing peptides. Biomed Biochim Acta. 1984;43:1101–11.

Handschumacher RE, Harding MW, Rice J, Drugge RJ, Speicher DW. Cyclophilin: a specific cytosolic binding protein for cyclosporin A. Science. 1984;226:544–7.

Jeong K, Kim H, Kim K, Kim SJ, Hahn BS, Jahng GH, Yoon KS, Kim SS, Ha J, Kang I, Choe W. Cyclophilin B is involved in p300-mediated degradation of CHOP in tumor cell adaptation to hypoxia. Cell Death Differ. 2014;21:438–50.

Kim H, Oh Y, Kim K, Jeong S, Chon S, Kim D, Jung MH, Pak YK, Ha J, Kang I, Choe W. Cyclophilin A regulates JNK/p38-MAPK signaling through its physical interaction with ASK1. Biochem Biophys Res Commun. 2015;464:11–27.

Kumari S, Roy S, Singh P, Singla-Pareek SL, Pareek A. Cyclophilins: proteins in search of function. Plant Signal Behav. 2013;8:e22734.

Lin ZL, Wu HJ, Chen JA, Lin KC, Hsu JH. Cyclophilin A as a downstream effector of PI3K/Akt signalling pathway in multiple myeloma cells. Cell Biochem Funct. 2015;33(8):566–74.

Luu TC, Bhattacharya P, Chan WK. Cyclophilin-40 has a cellular role in the aryl hydrocarbon receptor signaling. FEBS Lett. 2008;582:3167–73.

Matsushima S, Sadoshima J. The role of sirtuins in cardiac disease. Am J of Physiol Heart and Circ Physiol. 2015;309(9):H1375–89.

Mi Z, Oliver T, Guo H, Gao C, Kuo PC. Thrombin-cleaved COOH-terminal osteopontin peptide binds with cyclophilin C to CD147 in murine breast cancer cells. Cancer Res. 2007;67(9):4088–97.

Obata Y, Yamamoto K, Miyazaki M, Shimotohno K, Kohno S, Matsuyama T. Role of cyclophilin B in activation of interferon regulatory factor-3. J Biol Chem. 2005;280:18355–60.

Saleh T, Jankowski W, Sriram G, Rossi P, Shah S, Lee K, Cruz LA, Rodriguez AJ, Birge RB, Kalodimos CG. Cyclophilin A promotes cell migration via the Abl-Crk signaling pathway. Nat Chem Biol. 2016;12:117–23.

Seizer P, Ungern-Sternberg SN, Schönberger T, Borst O, Münzer P, Schmidt EM, Mack AF, Heinzmann D, Chatterjee M, Langer H, Malešević M, Lang F, Gawaz M, Fischer G, May AE. Extracellular cyclophilin A activates platelets via EMMPRIN (CD147) and PI3K/Akt signaling, which promotes platelet adhesion and thrombus formation in vitro and in vivo. Arterioscler Thromb Vasc Biol. 2015;35:655–63.

Soe NN, Bradford MN, Berk C. Cyclophilin A: a mediator of cardiovascular pathology. Korean Soc Hypertens. 2011;17:133–47.

Song J, Lu YC, Yokoyama K, Rossi J, Chiu R. Cyclophilin A is required for retinoic acid-induced neuronal differentiation in p19 cells. J Biol Chem. 2004;279:24414–9.

Syed F, Rycyzyn MA, Westgate L, Clevenger CV. A novel and functional interaction between cyclophilin A and prolactin receptor. Endocrine. 2003;20:83–90.

Yang Y, Lun N, Zhou J, Chen ZN, Zhu P. Cyclophilin A upregulates MMP-expression and adhesion of monocytes/macrophages via CD147 signalling pathway in rheumatoid arthritis. Rheumatology. 2008;47:1299–310.

Ying Y, Padanilam BJ. Regulation of necrotic cell death: 604 p53, PARP1 and cyclophilin D-overlapping pathways of regulated necrosis? Cell Mol Life Sci. 2016;73:2309–24.

Yurchenko V, Zybarth G, O'Connor M, Dai WW, Franchin G, Hao T, Guo H, Hung HC, Toole B, Gallay P, Sherry B, Bukrinsky M. Active site residues of cyclophilin A are crucial for its signaling activity via CD147. J Biol Chem. 2002;277:22959–65.