



## Review Article

# Cyclophilins: The Structure and Functions of an Important Peptidyl-prolyl Isomerase

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**Abstract:** Cyclophilins are a subgroup of highly conserved protein family immunophilins which are peptidyl-prolyl isomerases that interconvert between the cis and trans positions. They can act as chaperones in maintaining conformational quality control of proteomes. They are structurally conserved throughout evolution and have been found in mammals, plants, insects, fungi, and bacteria. They share a common fold architecture consisting of 8 antiparallel beta sheets and two alpha helices that pack against the sheets. They exist in the cellular compartment of most tissues and encode special functions. Intracellular Cyclophilins are secreted from cells in response to inflammatory stimuli and can mediate intercellular communication. Pro-inflammatory signals may be stimulated by extracellular Cyclophilin. Overexpression of Cyclophilins can contribute to pathological conditions. Cyclophilins are involved in the pathogenesis of viral infection, neurodegenerative diseases, ageing and cancer. Exhibiting several molecular functions, Cyclophilins can bind to cyclosporine and calcium-dependent ser/thr Calcineurin and has been used to describe the immunosuppressive action of cyclosporine. Cyclophilin can stabilize the cis-trans conformation transition state and speed up isomerization steps in protein folding. This process is important in the assembly of multiple domain proteins. Their existence as foldases and molecular chaperones enable them to be able to assist in the covalent folding or unfolding and the assembly or disassembly of other macromolecular structures.

**Keywords:** Cyclophilin, Peptidyl-prolyl Isomerase, Immunosuppressive, Isomerization

## 1. Introduction

Cyclophilins are a subgroup of large immunophilins protein family. Immunophilins are cytosolic peptidyl-prolyl isomerases that interconvert between the cis and trans positions endogenously. Multiple sequence alignment, structural analyses of peptidylprolyl isomerases and other studies have revealed their biological diversity and functions. The peptidyl-prolyl cis-trans isomerase family include the cyclosporine-binding cyclophilins (CyPs) and FK506-binding proteins (FKBPs). The Cyclosporine (CsA) and FK506 or rapamycin are immunosuppressive drugs. A binary complex,

CsA/CypA and FK506/FKBP are formed when the CsA and FK506 bind to their cognate immunophilins. The CyPs and FKFBPs both exhibit the peptidyl-prolyl isomerases or rotamase activity and generally accelerates the changes in conformation between the cis and trans forms of the Xaa-Pro peptide bond during the folding of a substrate protein in-vitro [1]. Meanwhile, the enzyme functions in various situations including signaling, mitochondrial function, chaperone activity, stress response, RNA splicing, regulation of kinase activity [2, 3]. The Parvulins which show irreversible inhibition to juglone (5-hydroxy-1, 4-naphthoquinone). Parvulins [Par 10] was isolated from E-coli [4] and it has a

homologue SurA which is essential for E-coli during the stationary phase [5].

Sequence alignments analysis of the Cyp and FKBP from different phyla show that their PPIase activity site and macrolide binding cavity amino acid residues remain well preserved in the majority of them but their sequences diverge which suggests that the spatial structures and functions of each group of PPIases remain conserved [6]. Cyclophilins stabilize the cis/trans transition state and accelerate isomerization, a process regarded not only common only in protein folding but also during the assembly of multi-domain proteins [7].

Cyclophilins have been found in plants, mammals, insects, bacteria and fungi. *Saccharomyces cerevisiae* has eight Cyps [8]. *Drosophila* has more than 9 [6], *Caenorhabditis elegans* has 16 Cyclophilins [9] The human genome encodes 17 unique Cyps; eight localized to the cytoplasm or are secreted, one associate with mitochondria and eight are found in the nucleus [10]. Plants have more Cyps than any eucaryotes [11, 12] with *Arabidopsis thaliana* and *Oryza sativa* having the highest numbers of Cyps with 35 AtCyps and 28 OsCyps [13].

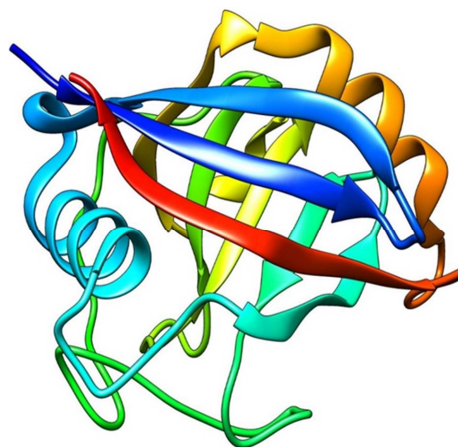
Cellular distribution of Cyps in most tissues encode unique functions. Cyp-A and Cyp-40 are cytosolic and Cyp-B and Cyp-C has been found in the ER protein secretory pathway as found in mammals because of their amino-terminal signal sequence [6]. Cyp-D has a signal sequence which directs it to the mitochondria [14]. The largest Cyp found is the human CypNK, which is located in the cytosol [15]. The human Cyp40 have long carboxyl-terminal (TPR) repeats; they associate functionally with homologs of heat-shock proteins and other protein chaperones. Regardless of their origin, Cyps structural conservation throughout evolution and the PPIase activity of members underlines the importance of their enzymatic reaction. We summarized our current understanding of the structure and molecular functions of this protein in this review.

## 2. Structure of Cyclophilins

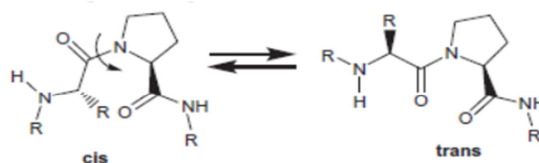
Immunophilins are not of the same sequence and structure. Cyclophilin and FKBP differ in sequence and structure but both possess conserved isomerase domain. CypA has eight  $\beta$  barrels with an alpha helix lies at either end. The central core is formed by four  $\beta$  sheets ( $\beta_3$ ,  $\beta_4$ ,  $\beta_5$ ,  $\beta_6$ ) and is a uniquely closed type that proline containing substrate nor CsA can bind to the hydrophobic core, implying that it is not evolutionarily linked to other  $\beta$  barrel structures. The substrate or CsA and peptides bind to the hydrophobic residues at the outer surface of CypA. While FKBP has five  $\beta$  strands wrapped around a short alpha-helix forming a conical shape with a hydrophobic groove to which FK506 and PPIase substrates bind. Aside from the FK506-binding domain, FKBP's also have tetratricopeptide repeat domains (TTR), calmodulin binding and transmembrane motifs [16]. The difference that exists in their sequence and structures doesn't prevent substrates and the inhibitory

immunosuppressants compete for binding to the PPIase active site. The short alpha helix turn of Cyp contain active site residue Trp21 found in the  $\beta_6/\beta_7$  loop region. The active sites also contain never-changing catalytic Arg55, Phe60, Gln63, 101, Phe113, Trp121, Leu122 and His 126. Arg 55 has a double function by anchoring the proline oxygen and activating the proline amide of the isomeric peptide bond [17]. There exist sites of minor diversity among the family members at the Phe60, Met61, and His126 positions, the most striking correlation between cyclosporine binding, tetrapeptide identity, and active site residues is found at the Trp121 position [18]. Tryptophan or histidine at this position is permissive for cyclosporine binding while other naturally occurring residues at this position (tyrosine and glutamic acid) can abrogate cyclosporin binding [19].

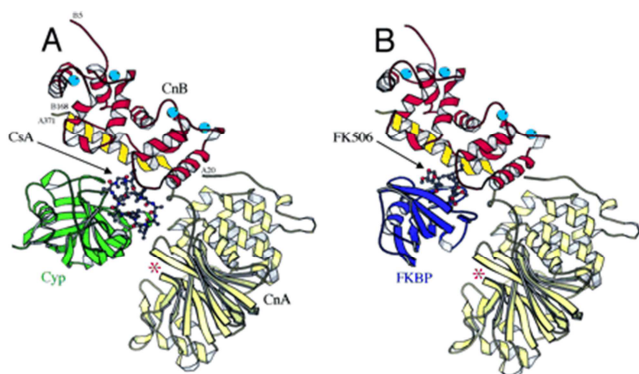
The surface of the PPIase domains near the active site has two pockets contributes to binding, the specificity of substrate and turnover. The S1 pocket where the target proline in a substrate, P1 binds have Phe113 at the base of the pocket and Phe60, Met 60, Leu122 and His126. The base of the S2 pocket is defined by the main-chain atoms of the  $\beta_5/\beta_6$  loop, the chemical identities of residues found in this region do not have much influence on the S2 pocket [18]. Structural divergence is pronounced at the S2 pocket throughout the Cyclophilin family. The loop regions linking the secondary structural elements also have some structural differences. The  $\beta_1/\beta_2$  loop region has a deletion, Ala111/Pro16 in CypA which alters the  $\beta$  sheet length along with the loop between them. While the  $\alpha_1/\beta_3$  loop, the Thr41/Gly50. Inference can be made from the sequence and structural diversity in this region for different binding partners [20].



**Figure 1.** The beta-barrel structure OF Human Cyclophilin A (PDB 2CPL).



**Figure 2.** The cis/trans isomerization of a peptide bond N-terminal to proline.



**Figure 3.** Human Cn (PDB ID 1AUI) and human Cyclophilin (PDB ID 2RMA).

(A) The Cyp/CsA/Cn ternary complex (Left) (B) The FKBP/FK506/Cn complex (Right). CsA and FK506 are depicted in ball-and-stick representations; CnA is in yellow (with the CnB-binding segment in dark yellow); CnB, red; Cyp, green; FKBP, blue; and Ca<sup>2+</sup> ions, cyan balls. The Cn active-site cleft is shown with an asterisk [21]

### 3. Molecular Functions

#### 3.1. Immunosuppressive Action

Cyclophilins play an important role in regulating the immune response. They are mediator of immunosuppression by cyclosporine. Cyclosporine, CsA is a cyclic decapeptide that has been used as an immunosuppressant and widely used in humans to prevent organ transplant rejection. The CsA binds with sub-nanomolar affinity to CypA via contacts within the hydrophobic pockets and it inhibits the PPIase activity but not significant for immunosuppression. A ternary complex had to be formed between Cyclosporine, Cyclophilin and Calcineurin [22]. Calcineurin which is a calcium and calmodulin-dependent serine/threonine protein phosphatase. Calcineurin activates nuclear factor of activated T-cell cytoplasmic (NFATc) [23]. The formation of CsA-CypA blocked T-cell activation, resulting in the reduced expression of pro-inflammatory cytokines and an overall decrease in the immune response.

The binding of cyclosporine and cyclophilin makes the charges and hydrophobic surfaces of the drug-protein complex become congruent while the binding point of cyclosporine and cyclophilin on the calcineurin is the interface between the catalytic and regulatory subunits. Cyclosporine binding calcineurin results in blockage of dephosphorylation of the NFATC and gene expression encoding cytokines and other proteins involved in immune are inhibited [24]. Amino acids within the cyclophilin that are crucial to cyclosporine binding have been identified and found to be conserved within 15 mammalian cyclophilins which suggest that many are potential targets for the drug.

FK506 is another immunosuppressive compound structurally un-similar to cyclosporine but it can bind to and inhibits calcineurin, only as part of a complex of the FKBP family of PPIases. The ternary structure of FKBP/FK506/Cn complex can be used to describe their mechanism of inhibition [21].

#### 3.2. Cyclophilin in Protein Folding

Cyclophilins have specific roles in protein folding. They act as both chaperones and foldases. Foldases are molecular catalysts that accelerate the slow step non-covalent folding of proteins in an ATP-dependent manner (by arranging the di-sulphide bonds introduced by di-sulphide isomerases or isomerization of prolyl peptide bonds by PPIases [25] Folded proteins have peptide bonds in two conformations, cis and trans, and the torsional angles (dihedral angle) for the rotation about the C-N bond is tightly clustered around 0° (cis) and 180° (trans). Cyclophilins stabilize the cis-trans conformation transition state and speed up isomerization steps in the folding of proteins. This process is also important in the assembly of multiple domain proteins [26].

Cyp40 chaperoning activity is capable of maintaining the protein in a folding-competent state with efficiency comparable to that of hsp90. The molecular chaperoning activity of Cyp40 was not suppressed by CsA, which indicates that it may be separate from its peptidyl-prolyl cis-trans isomerase activity [27]. Studies in yeast and mammals have shown that the Cyp40 protein has both PPIase and protein chaperone activity and it binds to HSP90 via its TPR domain [19].

Cyclophilins structural conservation throughout evolution and the PPIase activity of all members underlines the importance of this enzymatic reaction. Unlike chaperones, PPIases are classical enzymes. Their enzymatic properties are based on Michaelis-Menten kinetic studies and do not require energy in the form of ATP. Studies have shown that conformational folding steps and prolyl isomerization are mutually interdependent

#### 3.3. Cyclophilin in the HIV Life Cycle

Retroviruses encode three gene products, Gag protein is one of the gene products. The Gag protein primarily control HIV assembly and it is subject to cleavage by the viral protease to yield the internal structural proteins of mature virions. Cyclophilin A is among the host proteins incorporated into HIV virions and it enhances viral infectivity, [28]. Cyclophilin A engaged with the virions at the N-terminal CA domain via interactions with a proline-rich stretch found on the loop [29]. The CA loop emerges from an alpha-helical domain that diminishes towards the C-terminal end and play vital role during assembly. This suggest that cyclophilin primary binding site may lie across several subunits in a capsid protein oligomer. CypA was suggested to function to accelerate isomerization as a result of cis and trans conformations of Pro-90 which are in slow exchange in free CA and thereby overcome a kinetic block to cone arrangement and disassembly [30]. The isomerization of the Gly89 - Pro90 of the capsid is catalyzed by CypA which suggest its role in maturation or disassembly [31]. Cyclophilin can reduce the infectivity of the virus if there is a disruption in the CypA-Capsid protein association formed from the binding of loop Pro 90 in the capsid with the hydrophobic binding pocket of Cyp [32].

Cyclophilin binds to Gag and mature capsid in different ways which suggest role in post-assembly events which appears that the proline isomerase activity of CypA is important for replication. The isomerase activity of CypA may promote uncoating in a non-enzymatic manner. A side-to-side model for assembly of the CA strips formed during CypA binding to CA suggests an alternative mechanism in which the sequence-specific binding of CypA destabilizes capsid CA-CA interactions, thus facilitating core disassembly [29]. The strips of CA seen in the crystal are formed by the association of CA molecules through two different interfaces, both of which exhibit 2-fold symmetry. CypA binding loops are located at the top edge of CA strips, and it appears that binding of CypA sterically inhibits interaction between the strips. CypA may destabilize the core and reduce the cooperativity of disassembly by introducing a series of minor dislocations between the associated strips of CA molecules.

### 3.4. RNA Binding and Splicing

Cyclophilins can act as foldases or chaperones. They possess peptidyl-prolyl isomerases (PPIase) activity, which is inhibited by cyclosporine A (CsA). Their PPIase activity makes them be able to accelerate protein folding *in vivo* [1]. A ribosome-associated PPIase was also identified as the trigger factor [33] and it assists the folding of newly synthesized proteins by binding to nascent polypeptides when they emerge from the ribosomal exit tunnel. RNA-binding cyclophilin, hCyp33 was found in human T-cells having an RNA-binding domain with 84 amino-acids residues in its N-terminus, a cyclophilin domain with 139 amino acids residues in its C-terminus and a connective part with 78 amino acids residues between these two domains [34]. The C-domain was found to have the PPIase activity which was detected from its crystal structure. Human Cyp33 binds (hCyp33) specifically to mRNA, which contains a connected sequence AAUAAA and a polyA tail after this sequence. The binding of hCyp33 to mRNA stimulates the PPIase activity of hCyp33 [34]. This reflected in the PPIase activity of hCyp33 by the acceleration of the cis/trans conversion rate which almost fit the first-order reaction [35]. RNA-binding proteins are involved in splicing, modification and transport of RNA after transcription in eukaryotic cells. RNA-bound proteins can provide a signal for localization of RNA in a cell. Considered together with the fact that hCyp33 exists in both the nuclear matrix and nuclear membrane fractions in T cells, the binding of hCyp33 to mRNA may be concerned in internal cell-physiological functions. It has been reported that hCyp33 could be involved in nuclear pre-mRNA processing [36].

Human Cyp33 binding affinity to AAUAAA is very strong and it indicates that it is possible that hCyp33 is not involved in intron removal during the process of splicing, but binds to the region of AAUAAA and participates in polyA tail assembly. The fact that the binding capacity of hCyp33 to poly-A and poly-U is much higher than to poly-C and poly-G. A critical point is the meaning of the combination of

RNA-binding activity and PPIase activity in this protein. It is also possible that hCyp33 is concerned with the transport of mRNA or signal transport in cells.

Four out of eight nuclear cyclophilins have effect on splicing chemistry and assembly but not directly involved in splicing [37]. It was suggested that spliceosomal proteins and cyclophilins tight interaction may help to anchor proteins to each other in the midst of the dynamic conformational rearrangements that occur at the RNA and protein level during the splice cycle, in order to keep them oriented productively within the ever-changing splicing machinery alternatively cyclophilins and other highly-ordered protein-protein interaction domains within the spliceosome act to ensure proper stoichiometry and/or prevent off-target interactions of the large numbers of disordered proteins of the spliceosome.

### 3.5. Cyclophilin in Signalling

Cyclophilin A can be expressed intracellularly and is usually expressed in response to inflammatory stimuli. The mechanism of CypA-mediated signaling is unknown but the CypA signalling cascade is dependent on cell surface receptor, CD147 and heparans which represent the binding sites for CypA on cell surface. The association of CypA with CD147 can increase the level of phosphorylated extracellular signal-regulated kinases, ERKs. The rotamase activity of CypA is essential for its signaling process as it interacts with the Pro180 and Gly181 of the CD147 [38]. The CD147 are expressed by tumour cells stimulating fibroblasts to produce very collagenase activity thereby linking to the possible roles of CypA in metalloproteinase induction [39]. Also the CD147 activity regulates the intercellular adhesion pathways through an intracellular signaling-mediated mechanism [40].

CT-10 Regulated Kinase, Crk are expressed in every tissues and are overexpressed in human cancers. The Crk stimulates the activity of Abl, a kinase that can interact with epidermal growth factor receptor (EGFR) kinase thereby mediating oncogenic signaling. CypA binds to Crk at the phosphorylation site Gly220 and Pro221. The Crk phosphorylation site exhibit heterogeneity and so CypA being a PPIase catalyzes the cis-trans isomerization at the site. The binding of CypA to CrkII proteins results in inhibition of the phosphorylation process that shuts down signaling by CrkII [41].

## 4. Conclusion

Cyclophilins are highly conserved protein family and cytosolic binding proteins of the immunosuppressive drug cyclosporine A. They play pivotal roles within the cells and have been found to play important roles in protein folding, cell signaling. Cyclophilins overexpression contributes to pathological conditions. Cyclophilins are involve in pathogenesis of viral infection, neurodegenerative diseases, aging and cancer. The interaction of the Gag capsid (CA) protein and Gag sequences can have effect on viral infectivity within cells. They are unusually expressed in several cancer

types as they can promote cancer cell proliferation, anti-apoptotic process, drug resistant in different cancer cells. Cyclophilins mechanism in the progression of cancer requires a cascading with other proteins and pathways. Cyclophilins can therefore be a target that needs to be studied in cancer therapy. Cyclophilins being a peptidyl prolyl isomerase employs similar binding to small molecules with the FKBP and can suggest new strategies for drug binding.

## Abbreviations

PPIase	Peptidyl-prolyl isomerases
Cyp	Cyclophilin
FKBP	FK506-binding proteins
CsA	Cyclosporine A

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