World J Microbiol Biotechnol (2017) 33:164
DOI 10.1007/s11274-017-2330-6

REVIEW

# Microbial cyclophilins: specialized functions in virulence and beyond

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Received: 24 May 2017 / Accepted: 5 August 2017 / Published online: 8 August 2017


**Abstract** Cyclophilins belong to the superfamily of peptidyl-prolyl *cis*/*trans* isomerases (PPIases, EC: 5.2.1.8), the enzymes that catalyze the *cis*/*trans* isomerization of peptidyl-prolyl peptide bonds in unfolded and partially folded polypeptide chains and native state proteins. Cyclophilins have been extensively studied, since they are involved in multiple cellular processes related to human pathologies, such as neurodegenerative disorders, infectious diseases, and cancer. However, the presence of cyclophilins in all domains of life indicates a broader biological importance. In this mini-review, we summarize current advances in the study of microbial cyclophilins. Apart from their anticipated role in protein folding and chaperoning, cyclophilins are involved in several other biological processes, such as cellular signal transduction, adaptation to stress, control of pathogens virulence, and modulation of host immune response. Since many existing family members do not have well-defined functions and novel ones are being characterized, the requirement for further studies on their biological role and molecular mechanism of action is apparent.

**Keywords** Chaperone · Cyclophilin · Cyclosporin · Function · Gene distribution · Immunomodulation · Pathogenesis · Peptidyl-prolyl *cis*/*trans* isomerase · Stress tolerance · Structure · Virulence

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## Introduction

Cyclophilins, FK506-binding proteins, and parvulins, collectively referred to as PPIases, catalyze the slow interconversion between the *cis* and *trans* isomers of the N-terminal amide bond of the amino acid proline, which often represents a rate-limiting step in biochemical reactions (Wang and Heitman 2005). The first discovered cyclophilin was of mammalian origin, and it catalyzed the interconversion of the *cis* and *trans* conformers of the peptide bond preceding a proline residue while it was also the intracellular receptor for the immunosuppressive cyclosporin A (CsA) (Fischer et al. 1989; Takahashi et al. 1989). Since then, extensive structural and functional study on human cyclophilins has shown their involvement in many biological processes, including protein folding and trafficking, while their association with various pathological conditions, like cancer, neurodegenerative disorders, and viral infections, has led to the design of selective drugs with possible therapeutic applications (Davis et al. 2010; Nigro et al. 2013; Schiene-Fischer et al. 2013; Blair et al. 2015; Hopkins and Gallay 2015).

Genome wide analyses have shown the ubiquitous presence of cyclophilin genes in all living organisms, but the number of genes in different organisms varies significantly; usually, eukaryotes encode numerous cyclophilins, whereas prokaryotes only a few (Wang and Heitman 2005). The identified cyclophilins are either small single-domain proteins or large multi-domain ones that contain one or more additional unrelated domains (Pemberton 2006; Krücken et al. 2009). Cyclophilins participate in the folding of newly synthesized proteins and induce conformational changes in mature ones (Schiene and Fischer 2000; Schiene-Fischer et al. 2013). They are involved in various cellular processes, such as signal transduction, stress response, and cell

growth and death, and they have been related to pathogens virulence (Ünal and Steinert 2014; Bukrinsky 2015; Gutiérrez-Aguilar and Baines 2015; Ratajczak 2015; Vasudevan et al. 2015; Geisler et al. 2016). This mini-review focuses on microbial cyclophilins and their multitude of functions, which renders them intriguing enzymes awaiting further investigation.

## Cyclophilin gene distribution among microbes

Bacteria usually possess only a few cyclophilin genes, some of which show high similarity to eukaryotic homologues (Hayano et al. 1991; Göthel et al. 1996; Manteca et al. 2006). Fungi and Apicomplexa parasites possess more cyclophilin genes, similarly to higher eukaryotes (Pemberton 2006; Krücken et al. 2009). Cyclophilins have also been identified in Dinoflagellata, oomycetes, archaea, and viruses (Nagashima et al. 1994; Gan et al. 2009; Ponmani et al. 2015). Many microbes contain a novel group of PPIases that are characterized by simultaneous existence of a cyclophilin and an FK506-binding domain in the same protein (Adams et al. 2005; Barik 2017).

## Cyclophilin protein structure and prolyl isomerase and chaperone functions

Most microbial cyclophilins, of those whose structure has been solved so far, are monomeric and characterized by the presence of a fold that is formed by one β-barrel with eight antiparallel β-strands and one α-helix at each side, showing high similarity to the prototypic member of the cyclophilin family, the human CypA (Clubb et al. 1994; Edwards et al. 1997; Christoforides et al. 2012; Trivedi et al. 2013b). The presence of minor and major variations of this fold, such as insertions, large extensions, dimerization by 3D domain swapping, and divergence of the active site (Henriksson et al. 2004; Limacher et al. 2006; Thai et al. 2008; Ulrich and Wahl 2014; Jakob et al. 2016), suggests diverse physiological functions. For instance, the recently characterized AquaCyps fold into two domains, and they differ regarding their oligomerization state, even though they show major structural similarities. Furthermore, they utilize distinct sets of active site residues, which is consistent with differences in catalytic efficiency and substrate specificity (Jakob et al. 2016).

The initial function attributed to cyclophilins was participation in protein folding. Even though the mechanism is still under investigation, it is assumed that they accelerate the spontaneous prolyl isomerization by lowering the free energy barrier via preferential binding to and stabilization of the transition state configuration of the substrate (Ladani et al. 2015). The thermophilic GeoCyp has been used for studying the role of protein motions in substrate recognition and catalysis (Holliday et al. 2015), and it showed remarkable similarity for in vitro binding and catalytic functions to the prototypical human CypA (Eisenmesser et al. 2005; Doshi et al. 2012).

Many cyclophilins possess chaperone activity (Dimou et al. 2011; Zhang et al. 2013; Pandey et al. 2016), which in some cases is independent of the prolyl isomerase activity. For instance, *Leishmania donovani* CyP2 disaggregates adenosine kinase complexes by an isomerase independent chaperone function (Chakraborty et al. 2004; Mukherjee et al. 2013), and yeast Cpr7 enhances [Ure3] prion fibrillation independently to its prolyl isomerase activity (Kumar et al. 2015). Furthermore, the negative effect of the cytoplasmic cyclophilin of *Escherichia coli* on biofilm formation and swarming and swimming motility depends on its prolyl isomerase activity only in the first two instances (Skagia et al. 2017a).

## Cyclophilins and CsA sensitivity

The study of microbial cyclophilins enabled the understanding of the immunosuppressive mechanism of action of CsA, which expanded the field of organ transplantation (Tropschug et al. 1989; Liu et al. 1991a). CsA also has antifungal activity mediated by inhibition of calcineurin by the cyclophilin-drug complex in a way essentially identical to its immunosuppressive action (Breuder et al. 1994). Recovery from the division arrest induced by the mating pheromone is sensitive to CsA (Foor et al. 1992). Protozoan parasite cyclophilins have been implicated in the antiparasitic activity of CsA (Bell et al. 2006; Yau et al. 2010). Although bacterial cyclophilins are less sensitive to CsA (Liu et al. 1991b; Compton et al. 1992), a few enzymes with higher identity to eukaryotic homologues show CsA binding and inhibition (Pahl et al. 1992; Göthel et al. 1996).

## Multiple roles of cyclophilins in microbial cellular physiology and stress tolerance

Prolyl isomerases show greater specificity for their protein targets than other chaperones, and even though many cyclophilin interaction partners have been identified, the functional significance of the interaction is not always clear. Certain proteins, like DnaK, Pta, and AccC, interact with the cytoplasmic cyclophilin of *Azotobacter vinelandii* (Dimou et al. 2011, 2012a, b). In yeast, Cpr3 accelerates protein refolding after mitochondrial import (Matouschek et al. 1995), and Cpr6 and Cpr7 interact with the intact ribosome (Tenge et al. 2015). *Neurospora crassa* CyP40-type

cyclophilin binds to a growth and thiamine regulated protein (Faou and Tropschug 2003). *Plasmodium falciparum* cyclophilins interact with the HSP70 (Leneghan and Bell 2015), and a *Trypanosoma brucei* cyclophilin associates with a protein involved in ribosomal RNA maturation (Droll et al. 2010). *Mycobacterium tuberculosis* PpiA interacts with a number of host substrates involved in iron storage, signal transduction, and immune responses, probably acting as an effector mimic of host cyclophilins (Bhaduri et al. 2014).

Expression of many cyclophilin genes is induced in response to various stresses, such as cold and heat shock and antibiotic, antiparasitic, pharmaceutical, and pollutant treatment, suggesting a possible function in stress tolerance (Graumann et al. 1996; Iida et al. 1997; Joseph et al. 1999; Kim et al. 2011; Ponmani et al. 2015; Singh and Dubey 2016). A range of microbial cyclophilins in bacteria, yeast, human cell lines, and plants improves the survival under stress (Kim et al. 2010a, b, 2017; Trivedi et al. 2013a, b; Rêgo et al. 2015; Pandey et al. 2016; Thomloudi et al. 2017). Furthermore, disruption of *Saccharomyces cerevisiae* CYP1 decreased the survival of cells after heat shock (Sykes et al. 1993), and disruption of *L. donovani* CYP40 resulted in reduced virulence due to defects in stress resistance (Yau et al. 2014, 2016). In *Trypanosoma cruzi*, the mitochondrial TcCyP22 cyclophilin is involved in the regulated cell death induced by oxidative stress (Bustos et al. 2017).

Several studies with bacterial cyclophilin mutants suggest that cyclophilins are not essential for growth, since the deletion strains display no distinct phenotype under standard growth conditions (Herrler et al. 1994; Kok et al. 1994; Kleerebezem et al. 1995; Pissavin and Hugouvieux-Cotte-Pattat 1997; Trémillon et al. 2012). The only cyclophilin that it has been suggested to be essential for bacterial growth is *rotA* from *Synechococcus* sp. (Hassidim et al. 1992). There are some studies, however, that propose a role for bacterial cyclophilins during special growth conditions. In *E. coli*, deletion of the cytoplasmic cyclophilin *ppiB* eliminated growth inhibition by a putative growth inhibitor from the T7 bacteriophage and also resulted in increased motility and biofilm formation ability (Molshanski-Mor et al. 2014; Skagia et al. 2016). In addition, either deletion or overexpression of *E. coli ppiB* resulted in mild or severe cell filamentation, respectively, suggesting a role for it in cell division (Skagia et al. 2017b). The cytoplasmic PpiB deletion mutant of *Legionella pneumophila* exhibits reduced growth at 17 °C and attenuated invasion of *Acanthamoeba castellanii* (Schmidt et al. 1996; Söderberg and Cianciotto 2008).

The eight cyclophilins of *S. cerevisiae* have non-essential functions probably mediated via regulation of a few unique partner proteins (Dolinski et al. 1997). Cpr1 is implicated in sporulation, where it governs the meiotic transcriptional program (Arévalo-Rodríguez et al. 2000; Arévalo-Rodríguez and Heitman 2005); nuclear export of the zinc-finger-containing Zpr1p protein (Ansari et al. 2002); and the function of Vid22p in the import of fructose-1,6-bisphosphatase into intermediate transport vesicles (Brown et al. 2001). Cpr6 and Cpr7 interact with and regulate the activity of the Hsp90 chaperone (Duina et al. 1996; Tesic et al. 2003), and Cwc27 has been identified within the essential Myb-related Cdc5p complex, which has been implicated in pre-mRNA splicing (Ohi et al. 2002). In addition, Cpr7 inhibits the replication of *Tomato bushy stunt* tombusvirus by binding to the RNA-binding domain of the replication protein p33 (Lin et al. 2012). *Schizosaccharomyces pombe* Cyp2 interacts with the SNW/SKIP transcription co-regulator Snw1 (Skruzný et al. 2001). Overexpression of *Podospora anserina* CypD results in accelerated ageing due to increased autophagy-dependent degradation of mitochondrial and cytosolic proteins (Brust et al. 2010; Kramer et al. 2016).

## Particular roles of cyclophilins in microbial pathogenesis

A possible function of microbial cyclophilins in host infection was suggested in several gene expression studies that have shown upregulation of the expression of various cyclophilin genes during infection (Gan et al. 2009; Cabral et al. 2011; Singh et al. 2014; Williams et al. 2014; Lim et al. 2016). Furthermore, several genes within the gene cluster responsible for CsA biosynthesis in *Tolypocladium inflatum*, including an hCypA homologue, are upregulated in response to insect hemolymph, which is consistent with a role in fungal pathogenesis (Bushley et al. 2013).

Many studies indicate a direct role of cyclophilins in bacterial pathogenesis, since diverse bacteria display reduced infectivity or survival in the host in the absence of a cyclophilin (Delpino et al. 2009; Reffuveille et al. 2012). *Yersinia pseudotuberculosis* lacking the periplasmic cyclophilin *ppiA*, along with other PPIase genes, is attenuated in mice infections (Obi et al. 2011). Deletion of both *Brucella abortus* cyclophilins resulted in a mutant that displayed reduced virulence in mice and defective survival within HeLa cells (Roset et al. 2013). *Streptococcus pneumoniae* SlrA cyclophilin contributes to the pneumococcal virulence in the first stage of infection (Hermans et al. 2006), and the homologous lipoprotein PpiA suppresses the phagocytosis of *S. gordonii* and *S. mutans* by macrophages, playing an important role in the evasion of the host immune response (Mukouhara et al. 2011; Cho et al. 2013). *M. tuberculosis* cyclophilins are immunogenic proteins that enhance persistence within the host by subverting its stress

response (Pandey et al. 2017). An intracellular cyclophilin is required for folding and activity of the *Staphylococcus aureus* secreted nuclease, which is transported across the cell membrane, along with other virulence factors, by the Sec secretion system in a denatured state (Wiemels et al. 2016).

There is growing evidence that the fungal cyclophilins, particularly the human CypA homologues, are involved in the infection of both animal and plant hosts (Wang et al. 2001; Viaud et al. 2002; Shenton et al. 2012; Singh et al. 2017). In *Cryphonectria parasitica*, deletion of *cyp1* resulted in reduced virulence when the fungus was inoculated in chestnut stems (Chen et al. 2011). A hypovirus mediated *cyp1* downregulation possibly contributes to the hypovirulence of *C. parasitica* following a hypovirus infection (Wang et al. 2016). The BCP1 cyclophilin deletion mutant of *Botrytis cinerea* causes altered symptoms in bean and tomato leaves (Viaud et al. 2003). Transient silencing of the CYC1 cyclophilin gene in *Puccinia triticina* compromised growth and sporulation resulting in disease suppression in wheat (Panwar et al. 2013). Deletion of either of two particular cyclophilin genes as well as simultaneous deletion of all eleven cyclophilin genes in *Beauveria bassiana* resulted in decreased virulence in insect bioassays (Zhou et al. 2016). In addition, the CypB of *B. bassiana* is involved in its asexual development, dimorphic transition, stress tolerance, and virulence (Chu et al. 2017).

Many fungal cyclophilins are major allergens (Pellon et al. 2014; Buldain et al. 2016), and some cyclophilins of Apicomplexa parasites can modulate the immune response of their intermediate host via sophisticated mechanisms promoting their transmission. *Toxoplasma gondii* TgCyp18 acts like a chemokine mimic (Aliberti et al. 2003; Yarovinsky et al. 2004), and it regulates the proliferation and migration of host cells (Ibrahim et al. 2010, 2014). In addition, it can inhibit the infectivity of human immunodeficiency viruses by co-receptor antagonism (Golding et al. 2003). The CypA homologue of *Schistosoma japonicum* is immunomodulatory as well (Han et al. 2012; Li et al. 2013), and a secreted cyclophilin from *T. cruzi* neutralizes its vector's antimicrobial peptide trialysin promoting its own survival (Kulkarni et al. 2013).

## Conclusions and future directions

Overall, it has now become evident that microbial cyclophilins are involved in diverse biological processes ranging from cellular signal transduction to virulence (Fig. 1). However, until we identify the protein substrates of these enzymes and understand their mechanism of action, we cannot fully appreciate their possible biological functions or their potential use as therapeutic targets. More studies are also required in order to understand whether the presence of multiple prolyl isomerases in most microbes provides a functional redundancy among them. In vivo analysis of additional mutant microbes, structural characterization of more cyclophilins with diverse sizes and localization patterns, and characterization of cyclophilins protein interactome are some of the areas that deserve further attention in future studies in order to better understand how alterations in protein conformation mediated by cyclophilins affect cell biology under physiological and stress conditions.

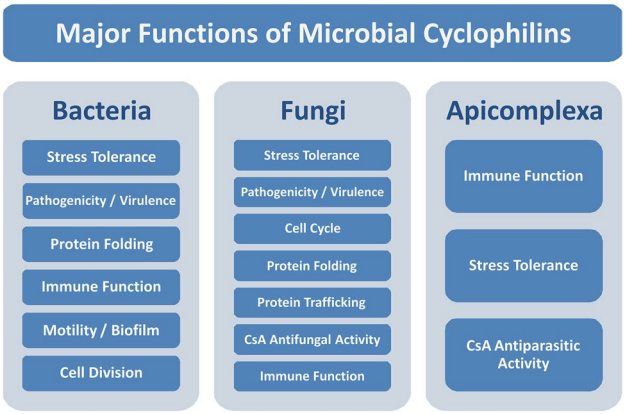


**Fig. 1** The most important biological processes in which various microbial cyclophilins have been implicated (see the text for references)

**Acknowledgements** We apologize to the colleagues whose work we could not cite due to space limitations.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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