Purification and characterization of Cyclophilin: a protein associated with protein folding in *Salmonella Typhimurium*

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Abstract

*Salmonella Typhimurium* (ST) is a Gram-negative zoonotic pathogenic bacterium that causes infectious disease in humans as well as in animals. It causes foodborne diarrheal or gastrointestinal illness and fever called salmonellosis, which is a leading cause of millions of deaths worldwide. *Salmonella enterica* serovar Typhimurium (S. Typhimurium) during its pathogenesis take away the actin cytoskeleton of their host cells and this is the crucial step of its infection cycle. Cyclophilin A, a type of peptidyl-prolyl isomerase that’s encoded by the *ppiA* gene in ST, plays pleiotropic roles in maintaining bacterial physiology. In this investigation, the proteomic characterization of the peptidyl-prolyl cis–trans isomerase- A (Cyclophilin A) from *Salmonella Typhimurium* is reported. Cyclophilin A (CypA) protein from *Salmonella Typhimurium* proved to be highly conserved and homologous protein sequence compared to other organisms. This protein was expressed in *Escherichia coli* followed by its purification in a recombinant form protein exhibited a characteristic PPIases activity (\(V_{\text{max}} = 0.8752 \pm 0.13892 \ \mu\text{moles/min}, \ K_{\text{m}} = 0.9315 \pm 0.5670 \ \mu\text{M}\) in comparison to control. The mass spectrometry analysis of Cyp A protein-peptide showed a highest sequence similarity with the cyclophilin protein of *Salmonella*. PPIases proteins (enzyme) data suggest that Ppi-A has roles in the protein folding that may be contributing to the virulence of *Salmonella* by isomerization of protein outline. These results suggest an active and vital role of this protein in protein folding along with regulation in *Salmonella Typhimurium*.

Keywords  *Salmonella Typhimurium* · PPIases · STPpiA · Cyclophilin · CypA · Cyclosporine

Introduction

*Salmonella enterica* serovar Typhimurium (ST) is one of the most common pathogenic Gram-negative, non-typhoidal bacteria causing foodborne diarrheal and salmonellosis disease in humans. *Salmonella Typhimurium* is one of the widespread causative agents of human salmonellosis in the world and is among the top five most detected pathogens for each major food from animal origin (Rabsch et al. 2001). As per CDC zoonotic diseases database, human salmonellosis causing by *Salmonella Typhimurium* is one of the most frequent disease worldwide (Sabirovic et al. 2010). The global burden of foodborne *Salmonella* estimated around 93.8 million cases reported worldwide, out of which the disease claims 0.15 million lives (Majowicz et al. 2010). The common virulence strategy of the *Salmonella* genus is adhesion, invasion, intracellular replication and bacterial dissemination from the intestinal cells of the host. The ability of bacteria to sense and respond to unfavourable changes
in the host environment is important for their survival and infection (Foster and Spector 1995).

Peptidyl-prolyl isomerase (PPIases) a family of evolutionarily conserved enzymes, initially discovered in eukaryotes, catalyzes a diverse process required for protein folding at proline residues, which accelerates the rate of exchange between cis and trans isomers (Fischer et al. 1998). The catalysis of the cis–trans isomerization of peptidyl-prolyl bonds facilitated by the PPIases enzyme (Lang et al. 1987). PPIase includes four different families distinct in their amino acid sequence based on drug resistance and homology. These are cyclosporin A (CsA)-binding proteins, cyclophilins, the FK506 and rapamycin binding proteins, FKBP, parvulins which do not bind immunosuppressant drugs (Fischer et al. 1998, Schiene-Fischer et al. 2013). Members of the cyclophilin family are also called immunophilins because of their involvement in the intermediate effects of immunosuppressive drugs, Cyclosporine A (Hamiton and Steiner 1998).

Peptidyl-prolyl isomerase protein is ubiquitously distributed in almost all living organisms, from bacteria, plants to humans. Bacterial PPIases have homologs with membrane-associated lipoproteins which involved in post-translocation secretion, protein folding and stability (Sarvas et al. 2004, Unal and Steinert 2014). Salmonella Typhimurium has identified peptidyl-prolyl cis–trans isomerase called “rotamase” a homolog of human cyclophilins. Protein Cyclophilin A (CypA), widespread with higher abundance in the cytoplasm (Dimou et al. 2017), is a secretory protein that belongs to a family of evolutionary protein preserved cis–trans isomases (PPIases) that catalyze protein folding at prolyl amino acid and cellular trafficking (Nigro et al. 2013). The PPIases, especially cyclophilin, are highly abundant proteins, while Cyclophilin account for about 0.4% of the dry mass of cellular proteins. Cyclophilin has been classified as an immunophilin and has a variety of intracellular functions, including intracellular signalling, protein trafficking, and the regulation of other proteins activity (Koletsky et al. 1986). Cyclophilin shows enzymatic activity required for optimal protein folding and also plays a vital role in multiple bacterial systems like the stress response, infectivity and virulence factors. Cyclophilin binds with high affinity to the clinically important immunosuppressive agent cyclosporin A (CsA) (Moochhala and Renton 1986).

These PPIase play an important role in protein conformation, which occurs during biological conditions like refolding of denatured proteins (Schiene-Fischer and Yu 2001). PPIase enzymes were initially thought to be limited to folding proteins only, but recent research established their role in other biological functions like signal transduction (Walsh et al. 1992), intracellular trafficking (Wintermeyer et al. 1995), gene transcription (Hanes 2015), cell cycle regulation (Baum et al. 2009), refolding of aggregated proteins (Zhang et al. 2013), regulation of reactive oxygen species (ROS) (Linard et al. 2009), apoptosis (Ding and Nam Ong 2003), proliferation and transformation (Zhu et al. 2015) and function as a molecular timer (Lu et al. 2007). Expression of Cyclophilin has been shown to be induced in the various stresses like heat shock, low temperature, salt stress, and pathogens (Chou and Gasser 1997).

In the bacterial membrane envelope, PPIases also play various essential biological functions. In Salmonella, SurA protein (PPIase type protein), found in the outer membrane, plays a key role in maintenance of the maturation of outer membrane proteins and resistance to various stress agents (like ROS and RNS), as this protein sustains the outer membrane protein biogenesis and assembly (Behrens-Kneip 2010). Other protein like SurA from E. coli, Shigella flexneri, and Salmonella Typhimurium also helps in cell adhesion and invasion (Sydenham et al. 2000). In E. coli, PpiB also controls cell division by modulating the function of various proteins which are directly or indirectly associated with the cell division (Skagia et al. 2017). In this study, the role of Peptidyl-prolyl cis–trans isomerase—A type of cyclosporin is explored. Enzyme activity of the expressed and purified recombinant STPpiA was analyzed and identity was confirmed by the mass spectrometry sequencing. Finally, it was demonstrated that STPpiA is an active type protein that illustrates the function of PPIases, which could be a regulator to facilitate the survival and virulence factors of bacteria. Furthermore, the exact biological role and effects of the STPpiA function in Salmonella systems remain a challenge for future studies. The findings of this study facilitated a better understanding of the pathogenesis of Salmonella Typhimurium and led to an elucidation of the different mediators of the pathogenic mechanism resulting in the Salmonella Typhimurium infection.

**Materials and methods**

**Bacterial strains and plasmids**

The E. coli strain DH5α and T7 Express lys γ were used for cloning and protein expression purposes. E. coli strains were cultured in Luria broth (LB). Kanamycin (sigma) was added, where necessary, to LB medium at a concentration of 30 μg/mL.

**Expression and purification of STPpiA proteins**

The recombinant clone PpiA_pET28c construct and conformation was done by double digestion and PCR amplification of STPpiA from the recombinant clone PpiA_pET28c plasmid. The recombinant PpiA_pET28c construct was transformed into competent E. coli T7 Express lys cells. Finally, 50 μl of the re-suspended pellets were plated on kanamycin...
(30 μg/ml) plus chloramphenicol (10 μg/ml) containing LB agar plate and incubated at 37 °C overnight.

The isolated colonies were inoculated and grown overnight in LB broth containing antibiotics at 37 °C at 180 rpm. The cultures were diluted (1:100) in fresh media and grew at 37 °C, 180 rpm (~3½ hrs) to an OD600 of 0.5. About one ml of this culture was removed in a 1.5 ml tube as an un-induced culture. The remaining culture was induced using isopropyl-β-D-thiogalactopyranoside (IPTG) final concentration 1.0 mM. Both un-induced and induced cultures were incubated at 30 °C, 180 rpm overnight, the cells were harvested by centrifugation 7000 × g at 4 ºC, and the pellet was stored at −80 ºC.

The recombinant protein STPpiA was purified using the Ni–NTA affinity chromatography (Qiagen). The bacterial pellet was thawed on ice and suspended in a 10 ml chilled lysis buffer containing 50 mM sodium phosphate pH 8.0, 150 mM sodium chloride and 10 mM final imidazole concentrations. Lysozyme at a final concentration of 1 mg/ml was added to the suspension and incubated on ice for 30 min. The cells were also lysed by 15 cycles of sonication in ice. Each cycle has a 45 s pulse of amplitude 48 Hz and a 45 s gap before the next pulse. PMSF (1 mg/ml final concentration) as protease inhibitor was added to the cell suspension. The lysate was centrifuged (10,000 g, 4 ºC, 15 min) and the supernatant was filtered through a 0.45 μm syringe filter. The Ni–NTA column was equilibrated with 20 volumes of lysis buffer. The cell-free supernatant obtained by centrifugation was loaded in the Ni–NTA column. The unbound proteins from column were removed by washing with 50 mM sodium phosphate (pH 8.0), 150 mM sodium chloride and 40 mM imidazole. The protein bound to the Ni–NTA column was eluted with an elution buffer containing 50 mM sodium phosphate (pH 8.0), 150 mM sodium chloride and 200 mM imidazole. The fractions were analysed by spectrophotometer at 280 nm, and high absorbance peak fractions were pooled and dialyzed against 50 mM sodium phosphate (pH 7.5) buffer at 4 °C. The purity of eluted fractions was then analysed by SDS-PAGE and total protein was estimated by Bradford’s total protein assay method using the BSA as standard. Finally obtained protein samples were stored at −80 ºC for further experiments.

**Western blotting of recombinant proteins**

After the purification, STPpiA protein was resolved on SDS-PAGE followed by transferring onto polyvinylidene difluoride (PVDF) (0.2 μM) membrane (200 mA for 2 h). The PVDF membrane was blocked with 5% skimmed milk in PBST (w/v) overnight at 4 ºC. After that the membrane was washed with PBS and 0.05% Tween 20 (v/v) solution. After washing with PBST, the membrane was incubated with a 1:1000 dilution mouse anti-His antibody at 37 ºC for 3 h. After washing, the blot was incubated with 1:15,000 alkaline phosphatase-conjugated anti-rabbit IgG at 37 ºC for 2 h, which acted as the secondary antibody. The blotted membrane was developed using enzyme substrates like 5-bromo-4-chloro-3'-indolyphosphate and nitro-blue tetrazolium chloride.

**Identification of proteins by mass spectrometry**

The purified STPpiA protein was resolved on SDS–PAGE and was stained with CBB stain. After destining with 10% methanol and 10% acetic acid solution, the protein band was cut carefully and digested by trypsin followed by LC–MS, MS/MS was done to record mass spectrum (MS). The mass spectrometric data were analysed manually and with the

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Fig. 1  a Induction and purification of recombinant PpiA protein expression following:- Lane M is the molecular weight marker (Bio-Rad) Lane 1- uninduced culture, Lane 2- induced culture by IPTG (1 mM), Lane CL- column load, Lane FT- flow though, Lane 5–7 are eluted protein fraction. The expressed STPpiA (~ 24 kDa) protein bands marked by the arrow. b Western blot analysis of His-tag purification of STPpiA protein. M is protein ladder markers and recombinant STPpiA band is marked by the arrow
help of the MASCOT search engine (www.matrixscience.com). The highest score peptides sequences were submitted to NCBI protein BLAST.

**PPIases enzyme activity by recombinant proteins**

In the present study, various assays were devised to measure PPIases activity based on Fisher 1990 (Fischer and Schmid 1990). The assay is based on the little difference in absorbance determined for the cis and trans isomers of Suc-Ala-Xaa-Pro-Phe-4-nitroanilide. To estimate enzyme activity we use substrate concentration from 0.25 to 10 mM N-succinyl-alal-alal-pro-phe-p-nitroanilidiné as test peptide, assay buffer [50 mM HEPES (pH 7.8) and 150 mM NaCl prechilled] and 300 µg of the recombinant PPIase protein to make the final volume to 1 ml. The reaction was initiated by the addition of chymotrypsin (500 µg/ml) and the change in absorbance at 390 nm was monitored using a spectrophotometer (Perkin-Elmer Lambda Bio20) for 3 min at 25 °C. The enzyme kinetic analysis and the relation between velocity (v) substrate concentrations (S) were done through theMichaelis–Menten equation.

**Results**

**Purification of recombinant proteins STPpiA**

The expression of recombinant protein STPpiA was done using the transformed PpiA_pET28c plasmid into the T7 Express lys γ strain of E. coli. The induction of the recombinant STPpiA protein was confirmed by SDS-PAGE followed by CBB R-250 staining as shown in Fig. 1A. The full-length recombinant STPpiA protein was purified from the PpiA_pET28 containing E. coli culture using affinity chromatography by using nickel-NTA resin. A highly purified preparation of STPpiA was recovered by eluting the column with 500 mM imidazole. The recombinant STPpiA protein had an apparent size of ~24 kDa on SDS-PAGE gel (Fig. 1A), reacted with anti-His antibody and showed ~24 kDa on western blot (Fig. 1B). A single band with good intensity was observed on the membrane suggesting the recombinant STPpiA protein with Histidine-tag. The size of the detected band was ~24 kDa with a Histidine Tag (~3 kDa), which predicted the molecular weight for STPpiA protein as ~21 kDa.

**Identification of proteins by mass spectrometry**

After the molecular weight confirmation by SDS-PAGE and Western blot analysis, the purified recombinant STPpiA was verified by using proteomic analysis with liquid chromatography-mass spectrometry. The full mass spectrum, as shown in Fig. 2a and peaks were marked with corresponding peaks of STPpiA peptides (Fig. 2a, b). The LC–MS and MS/MS were subjected to the MASCOT database search and identified the target protein band with a higher significance score. The result showed the identification of some Cyclophilin A-type PPIases isoforms. The peptide sequence coverage observed was more than 41%. Detailed peptide coverage information is provided in bold (Fig. 3). The LC–MS analyse strongly suggests the presence of recombinant STPpiA protein. These peptides matched the original sequence from NCBI, authenticating the protein identification. (Fig. 3a). Perfectly matching LCMS data of peptides with NCBI sequence also suggest the appropriate identification of the protein (Fig. 3b).

**Enzymatic activity of the purified STPpiA protein**

After the confirmed identification of the protein by LC–MS and MS/MS analysis, we determined the functional (enzymatic) activity of this purified and dialyzed recombinant protein. The velocity (v) of an enzyme-catalyzed reaction was observed to be hyperbolically related to the substrate concentration (S) through the well-known equation of Michaelis–Menten [v = V_{max} (S)/(K_{m} + (S))]. The purified STPpiA protein exhibited PPIases enzymatic activity with V_{max} = 0.8752 ± 0.13892 µmoles/min, K_{m} = 0.9315 ± 0.5670 µM comparison to control (Fig. 4). The purified protein found to be a first-order rate constant, and the presence of purified STPpiA showed an increase with an increase in the protein concentration (Table 1), thus, implying that the STPpiA specifically contributed to the observed PPIases activity.

**Discussion**

*Salmonella* Typhimurium is one of the major serovars commonly isolated from the human gastrointestinal tract that causes gastrointestinal infection. The PPIases proteins are associated with a broad range of pathogenic bacteria. The initial function known to cyclophilin was participation in protein folding only. Among the PPIases, CypA appears to play a pivotal role in the proper protein folding in many...
**Fig. 3** a Amino Acid sequence of STPpiA: residues 1–190. The total length of this protein is 163 amino acids, whereas the STPpiA protein covers more than 41% amino acid residues. b Basic local alignment of peptide sequence acquire from MS: mass spectrometry acquire peptides were subjected for NCBI BLAST analysis. BLAST result showed higher similarity with PPIases proteins.
biological conditions. Studies showed that CypA expression to several cellular processes that require action polymerization and cytoskeletal remodelling (Calhoun 2008, Saleh et al. 2016). Some research study also showed that Cyclophilin protein plays a role as an antifungal, antiviral, and antioxidant agents (Wong et al. 2010). The recombinants from of Cyclophilin from *Pyropiayoensis* express and purified in *E. coli* showed cell proliferation (Jung et al. 2019). Some studies showed that PPIases are play vital role for proteins function/folding in bacterial/viral infection and diseases (Theuerkorn et al. 2011, Unal and Steinert 2014, Zhang et al. 2014). In the pathogenic *Brucella* cyclophilins are also playing a vital role in virulence and survival in the host cells (Roset et al. 2013). PPIases also play an important role in the secretion of virulence factor. In *E. coli* are combined protein Cyclophilin from *Trypanosoma cruzi* expressed and the purified recombinant protein exhibited PPIases activity (Bua et al. 2001). Some bacterial cyclophilins, also play important chaperone activity in different environmental conditions (Dimou et al. 2011, Pandey et al. 2016) which are disposing of independent cis–trans activity.

In this study, we have characterized Cyclophilin A protein from *Salmonella* that showed high protein peptides sequence homology to CyPs from other organisms and demonstrated the PPIase activity of recombinant protein exhibited by artificial enzyme substrate in vitro. Earlier finding on bacterial cyclophilins showed *cypA* gene have PPIase as well as chaperone activity and its role in many biological processes,

**Table 1** STPpiA protein enzymatic activity $V_m$ and $K_m$ calculation

| STPpiA protein | Hanes plot | Lineweaver-Burk plot | Eadie-Hofstee plot | Hyperbolic regression analysis |
|----------------|------------|----------------------|--------------------|-------------------------------|
| $V_m$          | 0.9429     | 1.0053               | 0.8508             | $0.8752 \pm 0.13892$          |
| $K_m$          | 1.2567     | 1.3082               | 0.8615             | $0.9315 \pm 0.5670$           |
like cellular signal transduction, adaptation to stress, control of pathogens virulence, and modulation of host immune response during the infection (Dimou et al. 2017). Our previous finding has showed that Salmonella Typhimurium cyp-A gene also have high sequence similarities with other virulence bacteria (Manoj et al. 2016, Kumawat et al. 2020). Another study showed that ppiA gene that is highly conserved among all Salmonella genomes, has a critical role in the growth of Salmonella Typhimurium in the examined stress conditions, and may play a role in its responses and virulence (Kumawat et al. 2020). Thus, this study will help to understand the importance of Cyclophilin protein in Salmonella Typhimurium which may be involved in various biological activities. This will lead to know how Salmonella regulates virulence factors. Some previous study has confirmed that cyclophilin A protein plays a role in modulating virulence of bacterial species resulting in attenuation in vivo (Wang et al. 2001, Roset et al. 2013, Dimou et al. 2017, Bzdyl et al. 2019). However biological functions of Salmonella CyPA, their natural substrate and their role in host-parasite relationships are still unclear. PPIases proteins enzyme data suggest that Ppi-A has roles in the protein folding that may be contributing to the virulence of Salmonella by isomerization of protein outline.

Peptidyl-prolyl cis–trans isomerisation showed more specificity for their protein targets than other chaperones, the purposeful importance of the interplay isn’t always frequently clear. In this study, we performed recombinant form of STPpiA protein expression and purified in vivo. The proteomic analysis of recombinant form STPpiA proteins showed the significant acceleration of peptidyl-prolyl cis–trans isomerisation, a rate-limiting step in protein folding. Possibly these PPIAase enable the survival of ST under uncomplimentary conditions. Other PPIases protein activity data suggest that PPIase plays role in the protein folding that may be contributing to the survival of Salmonella. In conclusion, The findings of the present study demonstrate that CypA is an active cellular protein which has the critical role in salmonella infection. Therefore, CypA may be a potential therapeutic target for salmonellosis. Furthermore, experimental studies are also required to assess how alterations in protein conformation mediated by PpiA affect cell, during infections caused by Salmonella, which in turn could prove beneficial for the development of potential therapeutic and prophylactic candidates against this infection.

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References

Baum N et al (2009) The prolyl cis/trans isomerase cyclophilin 18 interacts with the tumor suppressor p53 and modifies its functions in cell cycle regulation and apoptosis. Oncogene 28:3915–3925. https://doi.org/10.1038/onc.2009.248

Behrens-Kneip S (2010) The role of SurA factor in outer membrane protein transport and virulence. Int J Med Microbiol 300:421–428. https://doi.org/10.1016/j.ijmm.2010.04.012

Bua J, Aslund L, Pereyra N, Garcia GA, Bontempi EJ, Ruiz AM (2001) Characterisation of a cyclophilin isofrom in Trypanosoma cruzi. FEMS Microbiol Lett 200:43–47. https://doi.org/10.1111/j.1574-6968.2001.tb10690.x

Bzdyl NM et al (2019) Peptidyl-prolyl isomerase ppiB is essential for proteome homeostasis and virulence in Burkholderia pseudomallei. Infect Immun 87:e00528-e1519

Calhoun CC (2008) Cellular functions of cyclophilin A in actin stability and cyclosporine A induced-gingival overgrowth. University of California, Los Angeles.

Chou JT, Gasser CS (1997) Characterization of the cyclophilin gene family of Arabidopsis thaliana and phylogenetic analysis of known cyclophilin proteins. Plant Mol Biol 35:873–892.

Dimou M, Venieraki A, Liakopoulos G, Kouri ED, Tampakaki A, Katinakis P (2011) Gene expression and biochemical characterization of Azotobacter vinelandii cyclophilins and Protein Interaction Studies of the cytoplasmic isoform with dnaK and lpxH. J Mol MicrobiolBiotechnol 20:176–190. https://doi.org/10.1159/000329486

Dimou M, Venieraki A, Katinakis P (2017) Microbial cyclophilins: specialized functions in virulence and beyond. World J MicrobiolBiotechnol 33:164. https://doi.org/10.1007/s11274-017-2330-6

Ding WX, Nam Ong C (2003) Role of oxidative stress and mitochondrial changes in cyano bacteria-induced apoptosis and hepatotoxicity. FEMS Microbiol Lett 220:1–7. https://doi.org/10.1016/S0378-1097(03)00100-9

Fischer G, Schmid FX (1990) The mechanism of protein folding. Implications of in vitro refolding models for de novo protein folding and translocation in the cell. Biochemistry 29:2205–2212. https://doi.org/10.1021/bi00461a001

Fischer G, Tradler T, Zarnt T (1998) The mode of action of peptidyl prolyl cis/trans isomerases in vivo: binding vs. catalysis. FEBS Lett 426:17–20. https://doi.org/10.1016/S0014-5793(98)00242-7

Foster JW, Spector MP (1995) How Salmonella survive against the odds. Annu Rev Microbiol 49:145–174

Hamilton GS, Steiner JP (1998) Immunophilins: beyond immunosuppression. J Med Chem 41:5119–5143. https://doi.org/10.1021/jm980307x

Hanes SD (2015) Prolyl isomerases in gene transcription. Biochem Biophys Acta 1850:2017–2034. https://doi.org/10.1016/j.bbagen.2014.10.028

Jung JH, Choi JW, Lee MK, Choi YH, Nam TJ (2019) Effect of Cyclophilin from Pyropia Yezoensis on the proliferation of intestinal epithelial cells by epidermal growth factor receptor/Erk signaling pathway. Mar Drugs. https://doi.org/10.3390/md17050297

Koletsy AJ, Harding MW, Handschumacher RE (1986) Cyclophilin: specialized functions in virulence and beyond. World J MicrobiolBiotechnol 20:176–190. https://doi.org/10.1159/000329486

Kumin M, Singh PK, Rananaware SR, Ahlawat S (2020) Comparative evaluation of structure and characteristic of peptidyl-prolyl cis-trans isomerase proteins and their function in Salmonella Typhimurium stress responses and virulence. Folia Microbiol 65:161–171

Lang K, Schmid FX, Fischer G (1987) Catalysis of protein folding by prolyl isomerase. Nature 329:268–270. https://doi.org/10.1038/329268a0
Linard D, Kandlbinder A, Degand H, Morsonme P, Dietz KJ, Knoops B (2009) Redox characterization of human cyclophilin D: identification of a new mammalian mitochondrial redox sensor? Arch Biochem Biophys 491:39–45. https://doi.org/10.1016/j.abb.2009.09.002

Lu KP, Finn G, Lee TH, Nicholson LK (2007) Prolyl cis-trans isomerization as a molecular timer. Nat Chem Biol 3:619

Majowiez SE et al (2010) The global burden of nontyphoidal Salmonella gastroenteritis. Clin Infect Dis 50:882–889. https://doi.org/10.1086/650733

Manoj K, Neeraj AM, Lall OV, Sushma, (2016) Cloning and Sequencing of Peptidyl-prolylcis-trans Isomerase A (PPIase A) of Salmonella Typhimurium. J Vet Public Health 13:115

Moochhala SM, Renton KW (1986) Inhibition of hepatic microsomal drug metabolism by the immunosuppressive agent cyclosporin A. BiochemPharmacol 35:1499–1503. https://doi.org/10.1016/0006-2952(86)90115-2

Nigro P, Pompilio G, Capogrossi MC (2013) Cyclophilin A: a key player for human disease. Cell Death Dis. https://doi.org/10.1038/cdddis.2013.410

Pandey S et al (2016) Mycobacterium tuberculosis peptidyl-prolyl isomerases also exhibit chaperone like activity in vitro and in vivo. PLoS One. https://doi.org/10.1371/journal.pone.0150288

Rabsch W, Tschapee H, Baumler AJ (2001) Non-typhoidal salmonellosis: emerging problems. Microbes Infect 3:237–247. https://doi.org/10.1016/s1286-4579(01)01375-2

Reffuveille F et al (2012) Involvement of peptidylprolyl cis/trans isomerase as a biocatalysis perspective of conformational dynamics in proteins. Top Curr Chem 328:35–67. https://doi.org/10.1007/10.000478588

Sydenham M, Douce G, Bowe F, Ahmed S, Chatfield S, Dougan G (2000) Salmonella enterica serovar typhimurium surA mutants are attenuated and effective live oral vaccines. Infect Immun 68:1109–1115

Theuerkorn M, Fischer G, Schiene-Fischer C (2011) Prolyl cis/trans isomerase signalling pathways in cancer. CurrOpinPharmacol 11:281–287. https://doi.org/10.1016/j.coph.2011.03.007

Unal CM, Steinert M (2014) Microbial peptidyl-prolyl cis/trans isomerases (PPIases): virulence factors and potential alternative drug targets. Microbiol Mol Biol Rev 78:544–571. https://doi.org/10.1128/MMBR.00015-14

Walsh CT, Zydowsky LD, McKeon FD (1992) Cyclosporin A, the cyclophilin class of peptidylprolyl isomerases, and blockade of T cell signal transduction. J Biol Chem 267:13115–13118

Wang P, Cardenas ME, Cox GM, Perfect JR, Heitman J (2001) Two cyclophilin A homologs with shared and distinct functions important for growth and virulence of Cryptococcus neoformans. EMBO Rep 2:511–518. https://doi.org/10.1038/embo-reports.kve109

Wiemels RE et al (2017) An intracellular peptidyl-prolyl cis/trans isomerase is required for folding and activity of the Staphylococcus aureus secreted virulence factor nuclease. J Bacteriol. https://doi.org/10.1128/JB.00453-16

Wintermeyer E, Ludwig B, Steinert M, Schmidt B, Fischer G, Hacker J (1995) Influence of site specifically altered Mip proteins on intracellular survival of Legionella pneumophila in eukaryotic cells. Infect Immun 63:4576–4583

Zhang XC, Wang WD, Wang JS, Pan JC (2013) PPIase independent arginine kinase refolding. FEBS Lett 587:666–672. https://doi.org/10.1016/j.febslet.2013.01.028

Zhang Xl, Si BW, Fan CM, Li HJ, Wang XM (2014) Proteomics identification of differentially expressed leaf proteins in response to Setosphaeria turcica infection in resistant maize. J Integr Agric 13:789–803

Zhu Y et al (2015) Helicobacter pylori FKBP-type PPIase promotes gastric epithelial cell proliferation and anchorage-independent growth through activation of ERK-mediated mitogenic signaling pathway. FEMS Microbiol Lett. https://doi.org/10.1093/femsle/fnv023

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