

Cyclophilin: A Versatile Chaperone of Biological System

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The functional cellular proteome machinery depends on the protein folding and unfolding within the cell. The primary amino acid sequence and the chaperone activity play a significant role in proper protein folding [1]. Chaperone interacts with nascent polypeptide and helps in proper folding and formation of stable protein complexes [2]. Molecular chaperone prevents inappropriate inter- and intra-molecular interactions among polypeptides. Immunophilins are the receptors for immunosuppressant drug consist of two large groups of proteins called 'cyclophilins' (receptors for cyclosporine A, CYPs) and FK506-binding proteins (FKBPs). Cyclophilins are ubiquitous proteins found to be present in all organisms ranging from bacteria to mammals [3]. Cyclophilins are involved in a wide range of cellular processes like protein folding, protein complex stabilization, cell division, protein trafficking, cell signalling, transcriptional regulation, pre-mRNA splicing and stress tolerance [4,5].

Cyclophilin are known as peptidyl-prolyl isomerase (PPIase) having PPIase domain which is conserved among all species. The peptidyl-prolyl isomerase (E.C. 35.1.2.8) is involved in catalysis of cis-trans isomerisation of proline residues [3]. The exact molecular mechanism and biological function of the PPIase activity of cyclophilin still remains unclear. All cyclophilins having conserved PPIase domain with the exception of some multi-domain cyclophilin proteins comprised of domains like WD domain (of CYP71 in Arabidopsis, LOC_Os08g44330 in Rice), leucine (Leu) zipper and phosphatase binding domain (in thylakoid lumen-localized cyclophilin TLP40) [6]. The Arabidopsis cyclophilin CYP38 does not display any PPIase activity despite of having a PPIase domain. CYP38 is essential for the proper folding of D1 protein and CP43 of photosystem II and correct assembly of the oxygen evolving complex [7]. It has been reported that Arabidopsis with mutated CYP38 is susceptible against photoinhibition. WD40 domain containing CYP71 in Arabidopsis plays a key role in gene repression and organogenesis and acts as a histone remodelling factor which ultimately leads to chromatin based gene silencing [8]. The tetratricopeptide repeat (TPR) motif containing CYP40 in mammals interacts with hsp-90, indicating the crucial role played by these proteins in signalling [9]. All cyclophilins contain conserved cyclophilin-like domain (CLD) of approximately 109 amino acids. Cyclophilins were known to be ubiquitous proteins found in all systems such as mammals, plants, fungi and bacteria. These proteins are highly conserved with respect to PPIase activity from the evolutionary point of view. There are 28 and 35

cyclophilins in rice and Arabidopsis respectively [4]. In humans, 7 major cyclophilins have been reported- hCyp18 (CypA), hCyp22 (CypB), hCypC, hCypD, hCyp40 (hCypE) and hCypNK (identified in natural killer cells). In *Saccharomyces cerevisiae*, 8 cyclophilins have been identified, named Cpr1-Cpr8 [4] whereas, in *Drosophila*, 9 cyclophilins have been identified. The crystal structure of AtCyp38 and PiCypA from *Arabidopsis thaliana* and *Piriformospora indica* respectively, showed that it is a monomeric single domain protein and forms a canonical cyclophilin fold comprising two α -helices and eight β -strands [5,7]. Eight β -strands form a flattened cylinder with β -barrel-like fold where two helices sit on the top and bottom of the barrel. The molecular structure of the proline residue allows the Xaa-Pro peptide bond (where Xaa is any amino acid residue) to adopt a 'cis' conformation [10]. Cyclophilins are ubiquitous proteins which consist of peptidyl-prolyl cis/trans isomerase (PPIase) activity and perform important

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functions in protein folding [8]. The PPIase domain has two typical binding sites for each residue of the signature motif, pSer/Thr-Pro. Three important residues of the PPIase domain, Lys63, Arg68 and Arg69, form an active triad sack that is particularly binding to the phosphate group. The exclusion of any of these residues immensely diminishes the activity of the enzyme, but does not completely stop the isomerization activity. The elementary step in the catalysis of the cis/trans isomerisation of a peptidyl-prolyl bond is a reduction in the double bond character of the C-N bond.

The relative expression of Cyclophilin has been shown to be upregulated by both biotic and abiotic stresses including HgCl₂, viral infection, salicylic acid, salt stress, heat and cold shock, light, drought, wounding, fungal infection, abscisic acid and methyl jasmonate [11]. The endoplasmic reticulum-localized cyclophilin AtCyp5 is expressed in young stems (prominently in apical meristem) and it is induced by cold stress and high salt stress, but not by heat stress. The expression of cyclophilins in beans has been reported to be induced in response to salicylic acid, ethephon and plays a vital role in defense response mechanisms.

The expression of cyclophilin ThCy in wheat was reported to be induced by high salt, abscisic acid, H₂O₂ and heat shock [11]. A cyclophilin protein PiCypA from fungus *Piriformospora indica* was found to be causing resistance against high salt when heterologously expressed in the tobacco plant [5]. Recently, it has been reported that the transcript level of a Golgi body-localized OsCYP21-4 upregulates in response to various abiotic stresses and the phytohormone abscisic acid [12]. Arabidopsis cyclophilin gene AtCyp20-3 expression is upregulated by high light intensity. PCypB, a chloroplast-localized cyclophilin in fava beans is induced in response to heat shock [11]. Drought stress-responsive cyclophilin OsCYP18-2 from rice interacts with ski-interacting protein (SKIP), a transcriptional co-regulator and spliceosomal component [13]. Therefore, it can be concluded that cyclophilins are universally present in all organisms and are involved in a wide range of crucial cellular processes. Future investigations of molecular structure and signalling of cyclophilins could provide further insights into the mechanism involved in stress resistance and processes in biological system.

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