Prefoldin, a jellyfish-like molecular chaperone: functional cooperation with a group II chaperonin and beyond

Muhamad Sahlan^{1,2} · Tamotsu Zako³ · Masafumi Yohda^{4,5}

Received: 14 December 2017 / Accepted: 23 January 2018 / Published online: 9 February 2018

© International Union for Pure and Applied Biophysics (IUPAB) and Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

Prefoldin is a hexameric molecular chaperone found in the cytosol of archaea and eukaryotes. Its hexameric complex is built from two related classes of subunits and has the appearance of a jellyfish: its body consists of a double beta-barrel assembly with six long tentacle-like coiled coils protruding from it. Using the tentacles, prefoldin captures an unfolded protein substrate and transfers it to a group II chaperonin. The prefoldin-group II chaperonin system is thought to be important for the folding of newly synthesized proteins and for their maintenance, or proteostasis, in the cytosol. Based on structural information of archaeal prefoldins, the mechanisms of substrate recognition and prefoldin-chaperonin cooperation have been investigated. In contrast, the role and mechanism of eukaryotic PFDs remain unknown. Recent studies have shown that prefoldin plays an important role in proteostasis and is involved in various diseases. In this paper, we review a series of studies on the molecular mechanisms of archaeal prefoldins and introduce recent findings about eukaryotic prefoldin.

Keywords Molecular chaperone · Prefoldin · Chaperonin

Introduction

Prefoldin (PFD) was first discovered by Cowan et al. and Geissler et al. based on its ability to capture an unfolded actin or to contribute to tubulin maturation (Geissler et al. 1998; Vainberg et al. 1998). PFD binds specifically to a eukaryotic cytosolic chaperonin (chaperonin containing TCP-1 (CCT)/

TCP-1 ring complex (TRiC)) and transfers target proteins to it. Eukaryotic PFDs are composed of six different subunits. The genes encoding the yeast homologs of PFD subunits PFD2–PFD6 (*GIMI–5*) were identified in a screen for genes that are lethal in combination with a mutant γ -tubulin (Geissler et al. 1998). Sequence alignment has shown the existence of PFDs in archaea. Archaeal PFDs are composed of two kinds of subunits: two α subunits and four β subunits. Eukaryotic PFD3 and PFD5 subunits are homologous to the archaeal α subunit, while the others are homologous to the archaeal β subunit. Archaeal PFDs are molecular chaperones capable of stabilizing a range of nonnative proteins and releasing them for subsequent chaperonin-assisted folding (Leroux et al. 1999; Okochi et al. 2004; Okochi et al. 2002). In contrast, PFD homologs have not been found in Eubacteria. Chaperonins (CPNs) are ubiquitous, double-ring-shaped molecular chaperones that capture unfolded proteins in their cavities and assist in their folding in an ATP-dependent manner (Hartl and Hayer-Hartl 2002; Horwich et al. 2007). CPNs are subdivided into group I and group II (Gutsche et al. 1999; Horwich et al. 2007). Group I CPNs are present in bacteria and in the organelles of eukaryotes, mitochondria, and chloroplasts. Eukaryotic cytosolic CPN (CCT/TRiC) and archaeal CPN belong to group II CPNs. Unlike group I CPNs, group II CPNs do not require a GroES-like co-chaperonin but have a

This article is part of a Special Issue on ‘Biomolecules to Bio-nanomachines - Fumio Arisaka 70th Birthday’ edited by Damien Hall, Junichi Takagi and Haruki Nakamura.

✉ Masafumi Yohda
yohda@cc.tuat.ac.jp

¹ Department of Chemical Engineering, Universitas Indonesia, Depok, Indonesia

² Research Centre for Biomedical Engineering, Faculty of Engineering, Universitas Indonesia, Depok, Indonesia

³ Department of Chemistry and Biology, Graduate School of Science and Engineering, Ehime University, Matsuyama, Ehime, Japan

⁴ Department of Biotechnology and Life Science, Tokyo University of Agriculture and Technology, 2-4-16 Naka-cho, Koganei, Tokyo 184-8588, Japan

⁵ Institute of Global Innovation Research, Tokyo University of Agriculture and Technology, Koganei, Tokyo, Japan

built-in lid that is composed of a helical protrusion in the apical domain (Ditzel et al. 1998; Iizuka et al. 2004; Meyer et al. 2003; Shomura et al. 2004). CCT/TRiC adopts a complex structure composed of eight different subunits. Archaeal CPNs consist of one or two different subunits. As described below, PFDs interact and function with group II CPNs in a cooperative manner. Thus, it is reasonable to think that PFDs coevolved with group II CPNs.

It has been almost 20 years since the discovery of PFD. The importance of PFD in proteostasis in the cytosol has been widely recognized. However, there has been little advancement in the study of eukaryotic PFDs due to the complexity of eukaryotic PFDs and their partner CCT/TRiC. Thus, the functional and structural characterization of PFDs has primarily advanced by studying the archaeal system. In this article, we review studies on the structures and functional mechanisms of PFDs, especially from a biophysical point of view. In addition, we introduce recent findings about eukaryotic PFD.

Structure of Prefoldin

The crystal structures of archaeal PFDs from *Methanobacterium thermoautotrophicum* (*Methanobacterium* PFD) and from *Pyrococcus horikoshii* OT3 (*Pyrococcus*PFD) have been determined to be 2.3 and 3.0 Å resolutions, respectively (Siegert et al. 2000; Ohtaki et al. 2008). The quaternary structure of prefoldin is a hexamer composed of two α and four β subunits. Strikingly, PFD resembles a jellyfish (Fig. 1): its body consists of a double-barrel assembly with six long tentacle-like coiled coils protruding from it. Each of the α and β subunits contains two or one central β -hairpins, respectively; these are N- and C-terminally flanked by coiled-coil helices. The coiled-coil helices of each subunit assemble into an anti-parallel conformation. Each coiled-coil tentacle is fully solvated, and its polar and charged side chains are almost exposed to the solvent. The average B-factor of the coiled-coil region of each subunit is much higher than that of

the β barrel assembly region; the coiled-coil tentacles have few inter-subunit interactions within the hexameric complex, indicating that each individual coiled coil is highly flexible. This flexibility should be favorable for widening the central cavity and capturing a variety of nonnative proteins.

Martin-Benito et al. analyzed the structure of a eukaryotic PFD by electron microscopy at a relatively low resolution (Martin-Benito et al. 2002). The structure of eukaryotic PFDs is similar to that of archaeal PFDs, with the six arms protruding from the base of the oligomer. Recently, crystallization of human PFD was reported (Aikawa et al. 2015). Although X-ray diffraction data were collected to 4.7 Å resolution, the structure was not determined.

Substrate recognition sites of prefoldin

The substrates of eukaryotic PFDs are mainly nascent cytoskeletal proteins (Hansen et al. 1999; Vainberg et al. 1998). Simons et al. have shown that eukaryotic PFDs use the distal ends of different but overlapping sets of subunits to form stable binary complexes with different target proteins, namely, actin and α - and β -tubulin (Simons et al. 2004). A three-dimensional reconstruction of a eukaryotic PFD complexed with an unfolded actin molecule revealed that the PFD-bound target protein adopts a defined conformation that crosses the PFD cavity and seems to interact with the tips of tentacles (Martin-Benito et al. 2002).

Archaeal PFDs have been shown to prevent the aggregation of various proteins (Iizuka et al. 2008; Leroux et al. 1999; Lundin et al. 2004; Okochi et al. 2004; Okochi et al. 2002). Generally, molecular chaperones interact with the hydrophobic surfaces of unfolded proteins of various sequences, sizes, and shapes. Hydrophobic grooves exist in the coiled coils of both the α and β subunits of archaeal PFDs. Since the hydrophobic grooves face the central cavity, they are thought to be involved in binding nonnative substrates. The hydrophobic residues in the hydrophobic groove of the α subunit do not face one another in an orderly way, unlike those of the β subunit. Thus, the hydrophobicity of the groove of the β subunit is higher than that of the α subunit, indicating that the β subunit is essential for binding non-native proteins. Electron microscopic images have shown that *Pyrococcus* PFD stabilizes an unfolded protein by interacting at the distal regions of the tentacles, suggesting a different mechanism from that of eukaryotic PFDs, which encapsulates its substrate inside the cavity (Martin-Benito et al. 2007).

Lundin et al. have analyzed the substrate-binding properties of *Methanobacterium* PFD by introducing mutations at the coiled-coil tips of the PFD (Lundin et al. 2004). These authors proposed that while substrate binding depends on the spatial arrangement of residues that are generally intrinsic to coiled coils, PFDs have evolved with additional features that are specific to their chaperone

Fig. 1 Crystal structure of *Pyrococcus* prefoldin. Overall structure of the $\alpha_2\beta_4$ hexameric complex of *Pyrococcus* PFD showing side and bottom views. α subunits and β subunits are shown in red (α subunit), green, and blue (β subunit). Reproduced with permission from Ohtaki et al. 2008

activities. Okochi et al. performed a systematic mutational study to elucidate the substrate-binding site of *Pyrococcus* PFD (Okochi et al. 2004). It was found that both the N- and C-terminal ends of the β subunit were critical for interactions with unfolded proteins. Of the eight C-terminal amino acid residues (Ala110-Leu111-Arg112-Pro113-Pro114-Thr115-Ala116-Gly117-COOH) of the β subunit, the hydrophobicity of Leu111 was found to be important for the interaction. However, its contribution was only marginal.

Molecular dynamics (MD) simulation studies of non-native protein binding to substrates by *Pyrococcus* PFD have been reported (Ohtaki et al. 2008). MD simulations indicated that at high temperatures, the residues of the coiled-coil regions on both α and β subunits showed greater flexibility when compared to those of the β -assembly region. Thus, the β assembly contributes to the maintenance of the width of the central cavity and the overall unique structure of PFD. In addition, short segments in the connecting linkers between the α -helical and β -assembly regions exhibited even higher flexibility, suggesting that these regions play the role of a “hinge” and allow flexible movements by the coiled coils of all subunits.

The docking simulations of *Pyrococcus* PFD with a denatured insulin model demonstrated that the β subunit makes a noticeable positional change and that the hydrophobic groove at the distal region stabilizes hydrophobic interactions with a denatured protein (Ohtaki et al. 2008). The hydrophobic groove is formed by Val8, Leu12, Leu15, Leu103, Ile107, and Leu111 of the β subunit (Fig. 2). As expected, site-directed mutagenesis analyses showed that these residues of the β subunit play an essential role in non-native substrate binding. Among these residues, Ile107 seems to be a critical residue. Thus, Ile107 of the β subunit, in addition to being involved in direct substrate binding, may also serve as a central core in the formation of the hydrophobic region. The α subunit modulates the shape and width of the central cavity to accommodate various substrates.

It was also shown that *Pyrococcus* PFD exhibits refolding activity for a denatured lysozyme at temperatures relatively lower than physiologically active temperatures (Zako et al. 2010). A study of this interaction using the Biacore system suggested that the weak affinity for *Pyrococcus* PFD at lower temperatures prevents aggregation and may facilitate the refolding of denatured lysozyme, whereas at higher temperatures, the refolding of lysozyme is prevented due to the higher affinity for *Pyrococcus* PFD. Thus, it is plausible that the affinities of the interactions between molecular chaperone proteins and denatured substrate proteins could modulate the refolding processes of the substrates. This result also implies that PFD might be able to contribute to the folding of some cellular proteins whose affinity for PFD is weak or under conditions of relatively lower temperatures than physiological temperatures.

Cooperation between PFD and group II CPN

It was thought that PFD delivers a substrate protein to a group II CPN through a direct interaction. Martin-Benito et al. showed the three-dimensional reconstruction of a symmetric complex formed between CCT and PFD, with PFD bound to each of the CCT rings (Martin-Benito et al. 2002). This finding confirmed the physical interaction between PFD and CCT. PFD interacted with two specific subunits in each of the CCT rings, which were placed in a 1,4 arrangement. The two PFD-binding subunits from one ring interacted with the corresponding pair in the opposite ring through their equatorial domains, suggesting a model for the phasing of the two rings of CCT.

Using the hyperthermophilic archaeal CPN-PFD system, a kinetic study of the interaction between PFD and a group II CPN was carried out. The kinetics of the reaction between *Pyrococcus* PFD and *Pyrococcus* CPN were studied by surface plasmon resonance using the Biacore system (Okochi et al. 2004). Both N- and C-terminal ends of the β subunit of *Pyrococcus* PFD were found to be critical for interactions with *Pyrococcus* CPN. The dissociation constant, K_D , gradually increased with the deletion of five to seven amino acids from the C-termini. Thus, the binding site for CPN is adjacent to that of an unfolded protein, which may correlate with the effective handover of a substrate to a group II CPN.

A single-molecule imaging study showed that substrate proteins captured by *Pyrococcus* PFD were delivered to CPN. Importantly, PFD cannot re-capture the substrate protein once it has been captured by CPN, suggesting that substrate delivery is irreversible (Zako et al. 2005).

The detailed localization of the interaction site was performed by the comparison of *Pyrococcus* and two *Thermococcus* group II CPNs (α and β) (Fig. 3) (Zako et al. 2006). The three group II CPNs share high sequence identity, but their interactions with *Pyrococcus* PFD are significantly different. Glu250 and Glu256 residues of the helical protrusion regions of *Pyrococcus* CPN and *Thermococcus* β CPN (CPN β) are responsible for the relatively stronger binding to *Pyrococcus* PFD than *Thermococcus* α CPN (CPN α), whose 250th and 256th residues are Lys. Since the putative CPN-binding sites at the distal ends of *Pyrococcus* PFD are rich in basic residues, electrostatic interactions seem to be important for binding. Importantly, the transfer rate of a denatured GFP from PFD to CPN correlated with the affinities between PFD and CPN.

Recently, it was revealed that the C-terminal region of group II CPN is also responsible for the interaction with PFD (Zako et al. 2016). The C-terminal truncation mutants of CPN β showed a reduced interaction with PFD (Table 1) and a decrease in the transfer efficiency of the denatured substrate protein from PFD and subsequent CPN-dependent refolding. Similar to those of other

Fig. 2 Amino acid residues responsible for the interactions of *Pyrococcus* PFD with substrate and chaperonin. **a** The overall structure of α and β subunits. The hydrophobic residues (α Leu11, α Leu14, α Val131, α Val138, β Leu8, β Leu12, β Leu15, β Leu103, and β Ile107) in the distal region of each subunit are in CPK representation. **b** The structure of the hydrophobic grooves of the α and β subunits at the distal region of the coiled coil. The hydrophobic residues are shown as ball-and-stick models. Reproduced with permission from Ohtaki et al. 2008

CPNs, the structure of the C-terminal amino acid residues was disordered. The high mobility of this region was confirmed by NMR analysis (Kurimoto et al. 2007). Thus, the C-terminal region should protrude into the cavity of CPN. Of the six C-terminal amino acids (Phe-Gly-Ser-Asp-Leu-Asp), the last two, Asp and Leu, appear to be the most important for binding to PFD. It is plausible that the *Pyrococcus* PFD β subunit could interact with the C-terminal region of CPN, i.e., the PFD β subunit simultaneously interacts with the apical domain and the C-terminal region of CPN β (Fig. 4).

Diversity of new archaeal PFDs

Genome analysis revealed that the hyperthermophilic archaeon *Thermococcus kodakaraensis* KOD1 has two pairs of prefoldin subunit genes (*TK1005* and *TK1121* for α subunits and *TK0643* and *TK1122* for β subunits) (Danno et al. 2008). *TK1005* and *TK1121* encode α subunits, and *TK0643* and *TK1122* are genes that encode β subunits. *TK1005* and *TK0643* are located at different loci and are commonly found in both *Thermococcus* and *Pyrococcus* sp. *TK1121* and

TK1122 are tandemly arranged on the genome. *TK1005* and *TK0643* were expressed at all examined temperatures. In contrast, *TK1121* and *TK1122* were specifically expressed under heat-stress conditions at 93 °C. *Thermococcus* spp. have two pairs of CPN genes encoding CPN α and CPN β (Fujiwara et al. 2008; Yoshida et al. 2001). CPN β was significantly more abundant with increasing temperature (maximum at 93 °C), whereas CPN α was not. *Thermococcus* CPN formed a hetero-oligomer with variable subunit composition; CPN β may be better suited to higher temperatures than CPN α . CPN β is highly homologous to *Pyrococcus* CPN.

Functional characterizations of the PFD complexes of the two pairs of PFD subunits were performed using those of *Thermococcus* sp. strain KS-1 (Iizuka et al. 2008). The canonical subunits (*TK1005* and *TK0643*) are named PFD α 1 and PFD β 1, and the heat stress-induced subunits (*TK1121* and *TK1122*) are named PFD α 2 and PFD β 2. There are four different recombinant prefoldin complexes composed of two pairs of prefoldin subunits (PFD α 1, PFD α 2, PFD β 1, and PFD β 2) that form $\alpha_2\beta_4$ heterohexamers and that can protect several proteins from forming aggregates. However,

Fig. 3 Two important amino acid residues for the interaction of the helical protrusion regions of the apical domain of chaperonin with *Pyrococcus* PFD. **a** Amino acid sequence alignment of the helical protrusion regions (246–276 aa) of *Pyrococcus* CPN, *Thermococcus* CPNβ, and CPNα. The two amino acid residues at the 250th and 256th positions, which have opposite electric charges between CPNα and *Pyrococcus* PFD and CPNβ, are highlighted. Amino acid residues conserved in CPNα are marked by asterisks. **b** Structure of the CPNα subunit. The apical, intermediate, and equatorial domains are colored

blue, yellow, and red, respectively. Lys250 and Lys256 are shown by the CPK model. The coordinates are from the Protein Data Bank code 1Q3S. **c** Effects of mutations in Lys250 and Lys256 on the affinity for *Pyrococcus* PFD. *Pyrococcus* PFD was immobilized on a Biacore biosensor chip. Sensorgrams of CPNα, CPNαK256E, CPNαK250E, CPNαK250E/K256E, and CPNβ are shown for comparison. The largest SPR signal value of CPNαK250E/K256E at 300 s was taken as 100%. Reproduced with permission from Zako et al. 2006

immunoprecipitation experiments suggested that PFDα1-β1 and PFDα2-β2 are physiologically relevant complexes, while the others are artifacts (Danno et al. 2008). Interestingly, there is a difference in their interactions with CPNs. In all cases, PFD-containing PFDβ1 exhibited higher affinities to PFDs. PFDβ2 lacks the terminal region of the coiled coil, which is thought to contribute to the interaction with CPN. PFDα2-β2 did not interact with CPNα, but a significant interaction was observed with CPNβ. Thermodynamic studies showed that the interaction between PFD and CPN is entropy driven. Among the four combinations of PFD–CPN interactions, the difference in entropy upon binding of CPNβ to PFDα2-β2 was the largest, and the affinity significantly increased at higher temperatures (Sahlan et al. 2010). Thus, it is reasonable

to think that PFDα2-β2 cooperates with CPNβ under heat stress conditions.

A filamentous PFD (γ PFD) was discovered in the hyperthermophilic archaeon *Methanocaldococcus jannaschii* (Whitehead et al. 2007). The γ PFD, which is upregulated over 20-fold in response to heat shock, is homologous to the α PFD of *M. jannaschii*. This homolog did not assemble with either an α or β subunit, but it formed a long filamentous structure that was shown to have chaperone activity in vitro. Transmission electron microscopy (TEM) measurements revealed that the lengths of the γ PFD filaments vary from 200 nm to over 2 μm, whereas the width of the filaments, as deposited on mica or carbon support grids, are uniform, at 8.4 ± 0.4 nm. Based on the TEM observations and the homology model with the α subunit of the crystal structure of the α₂β₄ PFD complex, a potential model can serve to explain the orientation of γ PFD on the surface (Whitehead et al. 2009).

Table 1 Dissociation constants between PFDα1β1 and CPNβ variants

Analyte	K_D (M)	Relative K_D
Wild type	$5.0 \pm 0.53 \times 10^{-8}$	1.0
CPNβTc1	$7.1 \pm 2.2 \times 10^{-8}$	1.4
CPNβTc2	$1.1 \pm 0.27 \times 10^{-7}$	2.1
CPNβTc6	$1.4 \pm 0.31 \times 10^{-7}$	2.8

The dissociation constants (K_D) were calculated by steady-state affinity determination method. Errors obtained by the fitting were shown. Reproduced with permission from Zako et al. 2016

Perspective

The molecular chaperone system of hyperthermophilic archaea is very simple compared with those of other organisms. Within hyperthermophilic archaea, only the following six kinds of chaperones have been identified so far: group II CPN, PFDs, small heat shock proteins, peptidyl-prolyl *cis-trans*-isomerases, AAA proteins, and NAC. These archaea

Fig. 4 Schematic images for the complex of PFD and group II chaperonin. **a** Total view of the PFD-CPN complex. Only half a ring of CPN is shown. **b** The interaction sites between the CPN monomer and the prefoldin β subunit is shown

lack the Hsp70 chaperone system as well as Hsp90 and Hsp100, though these are thought to be indispensable chaperones in all other organisms. Therefore, the PFD-CPN system could be responsible for the *de novo* folding and maintenance of various proteins. Archaeal PFDs are able to capture various unfolded proteins due to their six tentacles and transfer the proteins to archaeal group II CPN for productive folding. As described above, the details of the mechanisms for substrate recognition and substrate transfer of archaeal PFDs were revealed.

In contrast, the role and mechanism of eukaryotic PFDs remain unknown. The cooperation of eukaryotic PFDs and CCT/TRiC in the folding of cytoskeletal proteins is evident. However, there are only a few reports on the substrates of eukaryotic PFDs. Recent studies have shown that eukaryotic prefoldins are connected to phenomena that are not directly linked to the cytoskeleton, such as protein aggregation. Eukaryotic PFDs play a role in quality control against protein aggregation, and dysfunction of prefoldin is one of the causes of neurodegenerative diseases (Abe et al. 2013). This role of PFD explains its protective effect against polyglutamine toxicity and the accumulation of aggregated pathogenic huntingtin (Tashiro et al. 2013). Human PFD also inhibits amyloid- β fibrillation and contributes to the formation of non-toxic amyloid- β aggregates *in vitro*, which is consistent with its upregulation in a murine model for Alzheimer's disease (Sorgjerd et al. 2013). Several studies have also shown the role of PFD in a number of cancers. It has been shown that PFD4 expression is a prognostic factor in breast and colorectal tumor and cancer cells (Miyoshi et al. 2010). An array comparative genomic hybridization (CGH) study identified PFD2 as a biomarker of bladder cancer cells (Lopez et al. 2013). Unconventional prefoldin RPB5 interactor (URI) contributes to the resistances of cervical, colorectal, and gastric cancer cells to drugs, and to cell survival (Gu et al. 2015; Hu et al. 2016; Lipinski et al. 2016). PFD1 was also involved in the

progression of colorectal and lung cancer (Wang et al. 2017; Wang et al. 2015).

Further study of eukaryotic PFDs is expected to reveal proteostasis in the cytosol and provide new insights into PFDs as potential therapeutic target proteins in aggregation diseases and various cancers.

Acknowledgements This work partly supported by grants-in-aids for scientific research (JP16H04572, JP16H00753 and JP15J08261) from the Ministry of Education, Science, Sports, and Culture of Japan and the World Class Professor Program (No. 168.A10/D2/KP/2017) from Ministry of Research, Technology and Higher Education of the Republic of Indonesia.

Compliance with ethical standards

Conflict of interest Muhamad Sahlan declares that he has no conflict of interest. Tamotsu Zako declares that he has no conflict of interest. Masafumi Yohda declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

- Abe A et al (2013) Prefoldin plays a role as a clearance factor in preventing proteasome inhibitor-induced protein aggregation. *J Biol Chem* 288: 27764–27776. <https://doi.org/10.1074/jbc.M113.476358>
- Aikawa Y, Kida H, Nishitani Y, Miki K (2015) Expression, purification, crystallization and X-ray diffraction studies of the molecular chaperone prefoldin from *Homo sapiens*. *Acta Crystallogr F Struct Biol Commun* 71:1189–1193. <https://doi.org/10.1107/S2053230X15013990>
- Danno A et al (2008) Expression profiles and physiological roles of two types of prefoldins from the hyperthermophilic archaeon *Thermococcus kodakaraensis*. *J Mol Biol* 382:298–311. <https://doi.org/10.1016/j.jmb.2008.07.032>
- Ditzel L, Lowe J, Stock D, Stetter KO, Huber H, Huber R, Steinbacher S (1998) Crystal structure of the thermosome, the archaeal chaperonin and homolog of CCT. *Cell* 93:125–138

- Fujiwara S, Aki R, Yoshida M, Higashibata H, Imanaka T, Fukuda W (2008) Expression profiles and physiological roles of two types of molecular chaperonins from the hyperthermophilic archaeon *Thermococcus kodakarensis*. *Appl Environ Microbiol* 74:7306–7312. <https://doi.org/10.1128/AEM.01245-08>
- Geissler S, Siegers K, Schiebel E (1998) A novel protein complex promoting formation of functional alpha- and gamma-tubulin. *EMBO J* 17:952–966. <https://doi.org/10.1093/emboj/17.4.952>
- Gu J et al (2015) URI expression in cervical cancer cells is associated with higher invasion capacity and resistance to cisplatin. *Am J Cancer Res* 5:1353–1367
- Gutsche I, Essen LO, Baumeister W (1999) Group II chaperonins: new TRiC(k)s and turns of a protein folding machine. *J Mol Biol* 293:295–312. <https://doi.org/10.1006/jmbi.1999.3008>
- Hansen WJ, Cowan NJ, Welch WJ (1999) Prefoldin-nascent chain complexes in the folding of cytoskeletal proteins. *J Cell Biol* 145:265–277
- Hartl FU, Hayer-Hartl M (2002) Molecular chaperones in the cytosol: from nascent chain to folded protein. *Science* 295:1852–1858. <https://doi.org/10.1126/science.1068408>
- Horwich AL, Fenton WA, Chapman E, Farr GW (2007) Two families of chaperonin: physiology and mechanism. *Annu Rev Cell Dev Biol* 23:115–145. <https://doi.org/10.1146/annurev.cellbio.23.090506.123555>
- Hu X et al (2016) URI promotes gastric cancer cell motility, survival, and resistance to adriamycin in vitro. *Am J Cancer Res* 6:1420–1430
- Iizuka R, So S, Inobe T, Yoshida T, Zako T, Kuwajima K, Yohda M (2004) Role of the helical protrusion in the conformational change and molecular chaperone activity of the archaeal group II chaperonin. *J Biol Chem* 279:18834–18839. <https://doi.org/10.1074/jbc.M400839200>
- Iizuka R et al (2008) Functional characterization of recombinant prefoldin complexes from a hyperthermophilic archaeon, *Thermococcus* sp. strain KS-1. *J Mol Biol* 377:972–983. <https://doi.org/10.1016/j.jmb.2008.01.070>
- Kurimoto E et al (2007) Dynamics of group II chaperonin and prefoldin probed by (^{13}C) NMR spectroscopy. *Proteins* 70:1257–1263
- Leroux MR et al (1999) MtGimC, a novel archaeal chaperone related to the eukaryotic chaperonin cofactor GimC/prefoldin. *EMBO J* 18:6730–6743. <https://doi.org/10.1093/emboj/18.23.6730>
- Lipinski KA, Britschgi C, Schrader K, Christinat Y, Frischknecht L, Krek W (2016) Colorectal cancer cells display chaperone dependency for the unconventional prefoldin URI1. *Oncotarget* 7:29635–29647. <https://doi.org/10.18632/oncotarget.8816>
- Lopez V et al (2013) Identification of prefoldin amplification (1q23.3-q24.1) in bladder cancer using comparative genomic hybridization (CGH) arrays of urinary DNA. *J Transl Med* 11:182. <https://doi.org/10.1186/1479-5876-11-182>
- Lundin VF, Stirling PC, Gomez-Reino J, Mwenifumbo JC, Obst JM, Valpuesta JM, Leroux MR (2004) Molecular clamp mechanism of substrate binding by hydrophobic coiled-coil residues of the archaeal chaperone prefoldin. *Proc Natl Acad Sci U S A* 101:4367–4372. <https://doi.org/10.1073/pnas.0306276101>
- Martin-Benito J et al (2002) Structure of eukaryotic prefoldin and of its complexes with unfolded actin and the cytosolic chaperonin CCT. *EMBO J* 21:6377–6386
- Martin-Benito J et al (2007) Divergent substrate-binding mechanisms reveal an evolutionary specialization of eukaryotic prefoldin compared to its archaeal counterpart. *Structure* 15:101–110. <https://doi.org/10.1016/j.str.2006.11.006>
- Meyer AS, Gillespie JR, Walther D, Millet IS, Doniach S, Frydman J (2003) Closing the folding chamber of the eukaryotic chaperonin requires the transition state of ATP hydrolysis. *Cell* 113:369–381
- Miyoshi N et al (2010) Abnormal expression of PFDN4 in colorectal cancer: a novel marker for prognosis. *Ann Surg Oncol* 17:3030–3036. <https://doi.org/10.1245/s10434-010-1138-5>
- Ohtaki A et al (2008) Structure and molecular dynamics simulation of archaeal prefoldin: the molecular mechanism for binding and recognition of nonnative substrate proteins. *J Mol Biol* 376:1130–1141. <https://doi.org/10.1016/j.jmb.2007.12.010>
- Okochi M, Yoshida T, Maruyama T, Kawarabayashi Y, Kikuchi H, Yohda M (2002) Pyrococcus prefoldin stabilizes protein-folding intermediates and transfers them to chaperonins for correct folding. *Biochem Biophys Res Commun* 291:769–774
- Okochi M et al (2004) Kinetics and binding sites for interaction of the prefoldin with a group II chaperonin: contiguous non-native substrate and chaperonin binding sites in the archaeal prefoldin. *J Biol Chem* 279:31788–31795. <https://doi.org/10.1074/jbc.M402889200>
- Sahlan M et al (2010) Thermodynamic characterization of the interaction between prefoldin and group II chaperonin. *J Mol Biol* 399:628–636. <https://doi.org/10.1016/j.jmb.2010.04.046>
- Shomura Y, Yoshida T, Iizuka R, Maruyama T, Yohda M, Miki K (2004) Crystal structures of the group II chaperonin from *Thermococcus* strain KS-1: steric hindrance by the substituted amino acid, and inter-subunit rearrangement between two crystal forms. *J Mol Biol* 335:1265–1278
- Siebert R, Leroux MR, Scheufler C, Hartl FU, Moarefi I (2000) Structure of the molecular chaperone prefoldin: unique interaction of multiple coiled coil tentacles with unfolded proteins. *Cell* 103:621–632
- Simons CT, Staes A, Rommelaere H, Ampe C, Lewis SA, Cowan NJ (2004) Selective contribution of eukaryotic prefoldin subunits to actin and tubulin binding. *J Biol Chem* 279:4196–4203. <https://doi.org/10.1074/jbc.M306053200>
- Sorgjerd KM et al (2013) Human prefoldin inhibits amyloid-beta (A β) fibrillation and contributes to formation of nontoxic A β aggregates. *Biochemistry* 52:3532–3542. <https://doi.org/10.1021/bi301705c>
- Tashiro E et al (2013) Prefoldin protects neuronal cells from polyglutamine toxicity by preventing aggregation formation. *J Biol Chem* 288:19958–19972. <https://doi.org/10.1074/jbc.M113.477984>
- Vainberg IE, Lewis SA, Rommelaere H, Ampe C, Vandekerckhove J, Klein HL, Cowan NJ (1998) Prefoldin, a chaperone that delivers unfolded proteins to cytosolic chaperonin. *Cell* 93:863–873
- Wang P et al (2015) PFDN1, an indicator for colorectal cancer prognosis, enhances tumor cell proliferation and motility through cytoskeletal reorganization. *Med Oncol* 32:264. <https://doi.org/10.1007/s12032-015-0710-z>
- Wang D et al (2017) Prefoldin 1 promotes EMT and lung cancer progression by suppressing cyclin a expression. *Oncogene* 36:885–898. <https://doi.org/10.1038/onc.2016.257>
- Whitehead TA, Boonyaratankornkit BB, Holtrig V, Clark DS (2007) A filamentous molecular chaperone of the prefoldin family from the deep-sea hyperthermophile *Methanocaldococcus jannaschii*. *Protein Sci* 16:626–634. <https://doi.org/10.1110/ps.062599907>
- Whitehead TA, Je E, Clark DS (2009) Rational shape engineering of the filamentous protein gamma prefoldin through incremental gene truncation. *Biopolymers* 91:496–503. <https://doi.org/10.1002/bip.21157>
- Yoshida T, Ideno A, Hiyamuta S, Yohda M, Maruyama T (2001) Natural chaperonin of the hyperthermophilic archaeum, *Thermococcus* strain KS-1: a hetero-oligomeric chaperonin with variable subunit composition. *Mol Microbiol* 39:1406–1413
- Zako T et al (2005) Facilitated release of substrate protein from prefoldin by chaperonin. *FEBS Lett* 579:3718–3724. <https://doi.org/10.1016/j.febslet.2005.05.061>
- Zako T et al (2006) Localization of prefoldin interaction sites in the hyperthermophilic group II chaperonin and correlations between binding rate and protein transfer rate. *J Mol Biol* 364:110–120
- Zako T, Banba S, Sahlan M, Sakono M, Terada N, Yohda M, Maeda M (2010) Hyperthermophilic archaeal prefoldin shows refolding activity at low temperature. *Biochem Biophys Res Commun* 391:467–470. <https://doi.org/10.1016/j.bbrc.2009.11.081>
- Zako T et al (2016) Contribution of the C-terminal region of a group II chaperonin to its interaction with prefoldin and substrate transfer. *J Mol Biol* 428:2405–2417. <https://doi.org/10.1016/j.jmb.2016.04.006>