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The functions and mechanisms of prefoldin complex and prefoldin-subunits

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Abstract

The correct folding is a key process for a protein to acquire its functional structure and conformation. Prefoldin is a well-known chaperone protein that regulates the correct folding of proteins. Prefoldin plays a crucial role in the pathogenesis of common neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and Huntington's disease). The important role of prefoldin in emerging fields (such as nanoparticles, biomaterials) and tumors has attracted widespread attention. Also, each of the prefoldin subunits has different and independent functions from the prefoldin complex. It has abnormal expression in different tumors and plays an important role in tumorigenesis and development, especially c-Myc binding protein MM-1. MM-1 can inhibit the activity of c-Myc through various mechanisms to regulate tumor growth. Therefore, an in-depth analysis of the complex functions of prefoldin and their subunits is helpful to understand the mechanisms of protein misfolding and the pathogenesis of diseases caused by misfolded aggregation.

Keywords: Prefoldin complex, Prefoldin subunits, Protein folding, Prefoldin-like complex, Neurodegenerative diseases, MM-1, c-Myc

Background

Prefoldin complex was discovered 20 years ago in the domains of eukaryotes and archaea as the property of promoting the assembly of cytoskeletal proteins (actin and tubulin) into corresponding polymers, also known as Gim complex (Genes involved in microtubule biogenesis) [1]. The prefoldin complex helps protein fold correctly and prevents aggregation by providing class II chaperones (Hsp60 molecular chaperones found in archaeobacteria and eukaryotic cytoplasm) with a linear, unnatural

substrate in the cytoplasm [2]. Therefore, the Prefoldin complex plays a role as a chaperone protein [3].

As a cytoplasmic chaperone protein, the prefoldin complex is a hybrid oligomer assembled from six different proteins (six subunits). The prefoldin complex is a multifunctional protein, and its importance has been known. Studies have shown that one subunit of prefoldin affects the protein levels of other subunits [4]. By forming complexes with other constituent subunits, the prefoldin subunit is protected from degradation mediated by the ubiquitin–proteasome system [4]. However, it is unclear how cells regulate the protein level of each subunit, and what is the mechanism to regulate the activity ratio between subunits and their complexes. Studies have found that the absence of specific prefoldin subunits, rather than the prefoldin complex in *Saccharomyces cerevisiae* will alter stress-induced transcription [5]. Therefore, we have reason to believe that each subunit also has different and independent functions from the

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complex, and each prefoldin subunit confers different substrate specificity to the prefoldin complex [6]. In various tumors, the subunit of prefoldin was abnormally expressed. Therefore, it is necessary to understand the role of prefoldin subunits in the development of different diseases (such as tumors).

Therefore, the importance of in-depth analysis of the complex functions of the prefoldin complex and its subunits is self-evident. In this article, we update the latest developments in the functions and mechanisms of the prefoldin complex and prefoldin subunit.

Prefoldin complex

Structure of the Prefoldin complex

Archaeobacteria prefoldin complex is composed of two identical α subunits and four identical β subunits, forming an $\alpha_2\beta_4$ hexamer (Fig. 1) [7]. Eukaryotic prefoldin complex is a heterohexameric complex like a jellyfish-like structure, consisting of six different subunits (PFDN1–6): two α subunits (PFDN3 and PFDN5) and four β subunits (PFDN1, PFDN2, PFDN4, and PFDN6) [8]. From the perspective of spatial structure, “jellyfish” is composed of double beta barrels and six slender tentacle-shaped coils that have hydrophobic amino acid residues at the distal end to bind unnatural proteins [9]. Regardless of archaea or eukaryotes, each alpha subunit terminal junction region of the prefoldin complex contains two beta hairpins, and each beta subunit contains one beta-hairpin [10]. Chaperones, such as prefoldin, triggering factor and Hsp90 all have a clamp-like structure that holds the substrate proteins. The clamp-like structure has a multivalent binding surface and can protect the protein conformers of unnatural proteins until they reach Natural state or transfer to another component of the folding machine [11]. The heterohexameric complex is first composed of two sub-complexes: PFDN2–PFDN3 and PFDN5–PFDN6, and finally assembled by PFDN1 and PFDN4. The prefoldin

subunits are arranged in the clockwise space order of PFDN3–PFDN2–PFDN1–PFDN5–PFDN6–PFDN4.

Function of the prefoldin complex

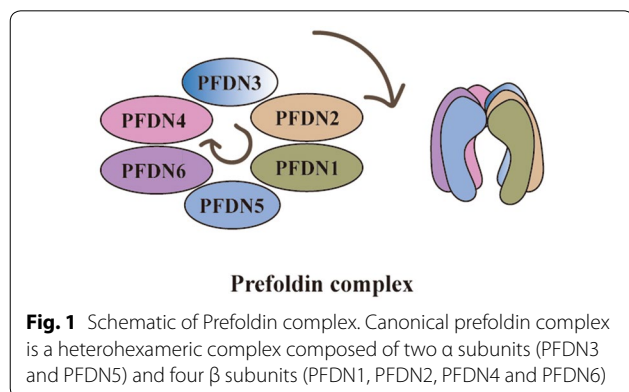
Prefoldin complex acts as chaperone protein in cytoplasm

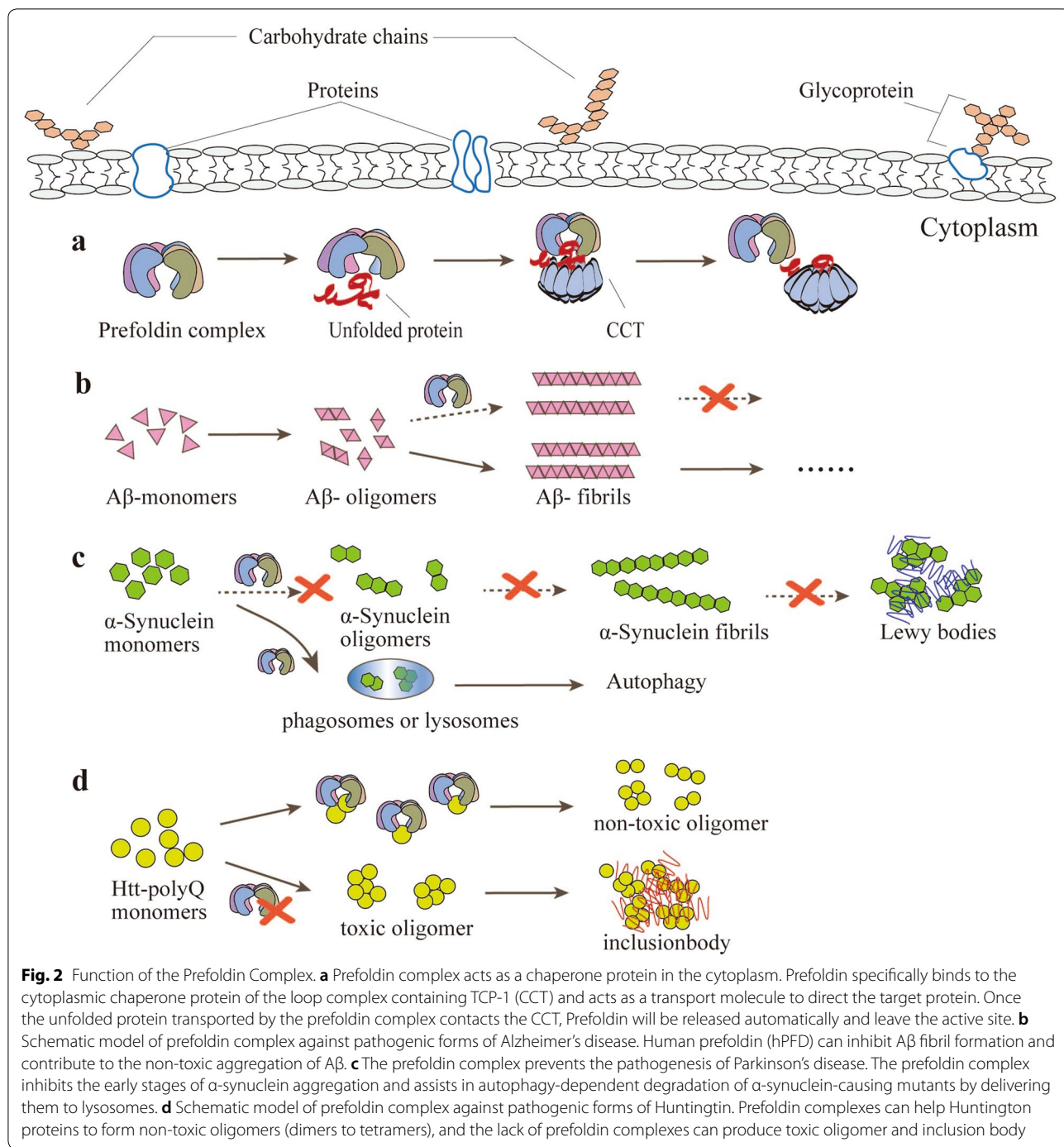
Both actin and tubulin are important components of the eukaryotic cytoskeleton. Due to their high concentration, they are easily self-binding and cannot be folded correctly. Therefore, newly synthesized actin and tubulin require an assistant, and the eukaryotic prefoldin complex can establish the correct tubular assembly for many tubular proteins (such as actin, α/β tubulin). The prefoldin complex specifically binds to the cytoplasmic chaperone protein of TCP-1 (CCT), a loop complex, forming actin molecules and acting as a transport molecule that directs protein accurately, thereby promoting actin and tubulin to be protected from aggregation and folded correctly [12]. Researchers have observed in yeast that in the presence of the prefoldin complex, the CCT folding rate can be increased five times, which may be related to the prefoldin complex that prevents the premature release of newborn proteins [13].

It is well known that chaperone proteins are a class of functional proteins that recognize unnatural, immature, and conformationally unstable proteins and help them to fold, assemble, and transport correctly. After assembly, the chaperone protein is actively separated and does not form part of the protein structure that performs the function. Therefore, once tubulin transported by prefoldin complex contacts CCT, the prefoldin complex is automatically released and leaves the active site due to the high affinity of tubulin for CCT (Fig. 2a). When the prefoldin complex is contacted with CCT, it will lose its affinity for the unfolded target protein [14]. Therefore, prefoldin complex binds only to unnatural unfolded target proteins in the cytosol. Unlike many other chaperone proteins, the substrate binding and release of the prefoldin complex are not related to adenosine triphosphate (ATP) [15].

Prefoldin complex are involved in the pathogenesis of neurodegenerative diseases

The role of prefoldin complex as a chaperone-mediated folding is not limited to cytoskeleton components, but also involved in the assembly of other cytoplasmic complexes and maintains protein function by avoiding protein aggregation and promoting proteolysis and degradation. Recent studies show that prefoldin complexes can promote proteasome degradation of cytosolic proteins with missense mutations by maintaining substrate solubility, which reflects the role of prefoldin complexes in preventing the accumulation of potentially toxic proteins [16]. Studies have shown that the prefoldin complex





is involved in the pathogenesis of neurodegenerative diseases, especially Alzheimer's disease (AD) [17], Parkinson's disease (PD) [18] and Huntington's disease (HD) [19].

Extracellular aggregation of the β-amyloid peptide (Aβ) in the human cerebral cortex and marginal regions is one of the onset features of AD, and the oligomer structure of Aβ is related to its toxicity (Fig. 2b)

[20]. The production of Aβ is a complex self-assembly process. Once abnormality occurs during the assembly process, proteins are abnormally aggregated and misfolded, and Aβ will be abnormally stacked. Chaperone proteins can play a significant role in the breakdown of protein aggregates, and thus chaperone proteins are essential in cell defense (e.g., protein aggregation caused by misfolding inside and outside the cell)

and are also potentially powerful neurodegeneration inhibitors [21]. Previous studies have shown that the expression of chaperone proteins Hsp60, Hsp70, and Hsp90 is enhanced or down-regulated in AD-affected tissues and cells, indicating that Hsp60, Hsp70, and Hsp90 are lively in the development and progression of AD disease [21]. Karin, et al. found that human prefoldin (hPFD) can inhibit the formation of A β fibrils and help the non-toxic aggregation of A β , indicating that prefoldin complex may have a protective effect on AD [17]. Parkinson's disease (PD), also known as tremor paralysis, is a long-term degenerative disease of the central nervous system that mainly affects the motor system [22]. Alpha-synuclein is a pathogenic gene product of familial PD and is the main component of inclusion bodies in PD [23]. Studies have shown that the prefoldin complex not only inhibits the early stages of α -synuclein aggregation but also assists in autophagy-dependent degradation of α -synuclein-causing mutants by delivering them to lysosomes (Fig. 2c) [18]. Huntington's disease (HD), also known as hereditary chorea, is an autosomal dominant hereditary neurodegenerative disease. The main cause of HD is the mutation of the Huntington gene (IT15) on the patient's chromosome 4 leading to the synthesis of the misfolded form of the toxic Huntington protein (mHTT) [24]. Abnormal Huntington protein has many repeated glutamines and is easy to stick and aggregate, eventually leading to the death of nerve cells [25]. Prefoldin complex retains Huntington protein oligomers at the small oligomer stage (dimer to tetramer), thereby inhibiting the aggregation and extension of larger pathogenic Huntington protein oligomers and the formation of inclusion bodies (Fig. 2d) [19, 26].

Besides, the prefoldin complex plays a key role in maintaining neuronal cell activity. Studies have shown that the prefoldin complex activity and the ability to prevent protein aggregation are stronger in neuronal cells than non-neuronal cells: PFDN1-deficient mice show cerebellar neuron loss [27]; missense mutations in PFDN5 can cause neurodegeneration [6]. In *Drosophila*, the prefoldin complex and infertile partners (Pins) synergistically regulate the asymmetric division of neuroblasts and intermediate neural progenitor cells (INPs) by stabilizing tubulin, and hence inhibits neuroblast overgrowth in the brain of *Drosophila* larvae [28].

Although neurodegenerative diseases are currently incurable and treatment aims to improve symptoms, with the in-depth study of the role and mechanism of the prefoldin complex in neurodegenerative diseases, it is expected to develop drugs for the treatment of neurodegenerative diseases that target prefoldin.

Application of prefoldin complex in emerging fields

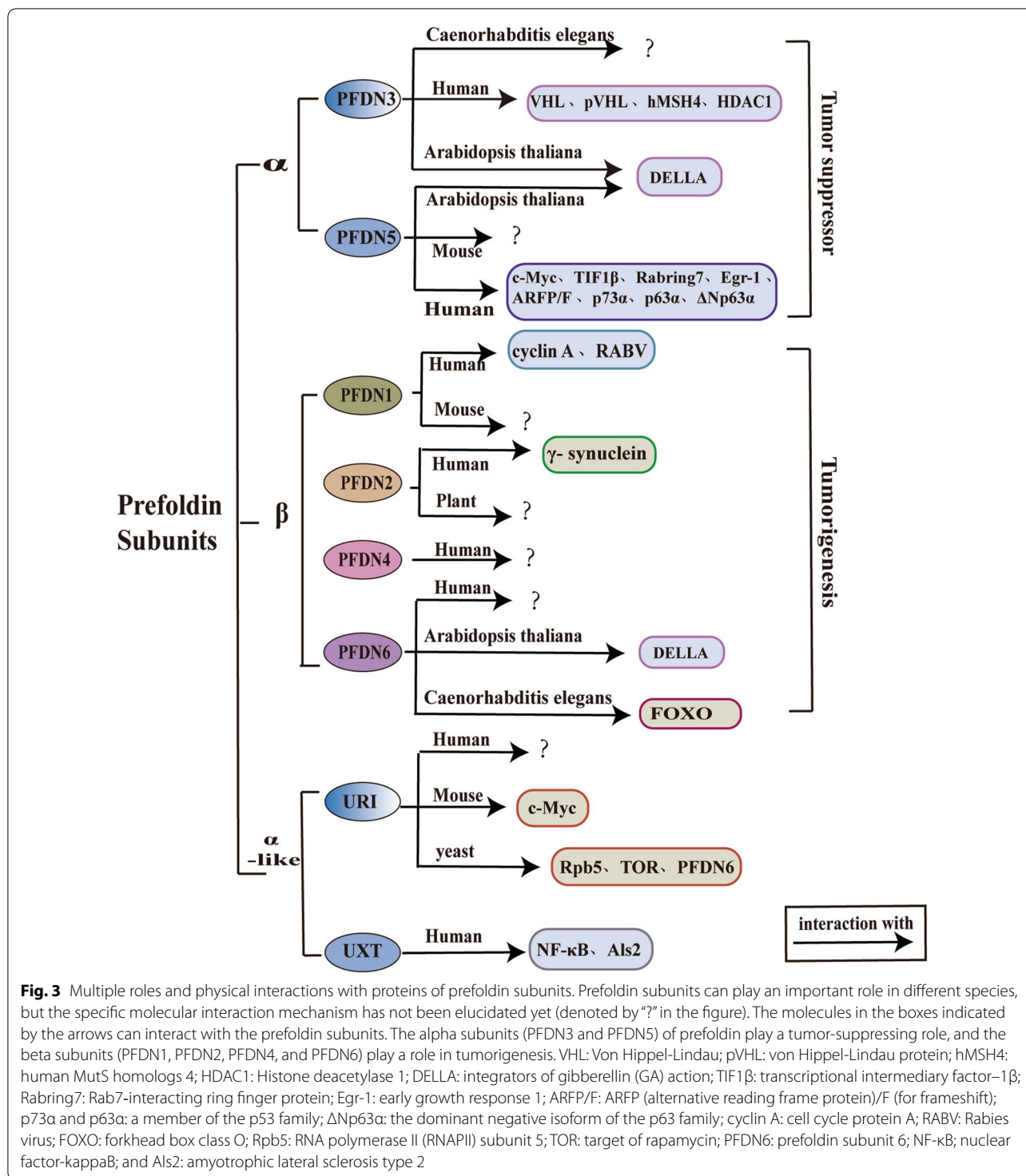
The prefoldin complex does not only play an important role in neurodegenerative diseases but also in emerging fields. Djohan et al. found that the prefoldin complex exists on the surface of gold nanoparticles (AuNPs), and the presence of the prefoldin complex helps to synthesize AuNPs with dispersion stability and particle controllability [29]. Organic solvents are extremely toxic to bacteria, and the accumulation of organic solvents can damage microbial cell membranes, thereby affecting cell structure and functional integrity [30]. Studies have found that *E. coli* cells that highly express prefoldin and class II chaperone proteins are resistant to organic solvents. This is because prefoldin prevents the accumulation of organic solvents in *E. coli* cells by preventing the activity of intramolecular chaperones [31]. Samuel et al. found that from hyperthermophilic archaea γ -prefoldin (γ PFD) functions as a protein component in a novel protein-polymer hybrid hydrogel. The resulting hybrid hydrogel has adjustable mechanical properties and can be used as the design of biological materials (such as tissue culture scaffolds and wound adhesives), as well as multi-step biocatalysis and stem cell culture [32]. γ -prefoldin does not form oligomeric oligomers with α -prefoldin or β -prefoldin but rather forms filaments of a certain size so that it is also known as filamentous protein γ -prefoldin [33]. Nanotechnology is attractive because it uses proteins as templates to locate molecules in a regular pattern with nano-precision, which is necessary to build advanced biomaterials. The filamentous protein γ PFD, through incremental gene truncation, has achieved controllable attachment of filaments in a specific direction on the carbon surface to form oriented filaments, so that it is expected to be used as a biological template [34].

The multiple roles of prefoldin subunits

The prefoldin complex is multifunctional, and its importance is self-evident. It has been found that prefoldin subunits can play different roles in different species and diseases (such as tumors) (Fig. 3), and the abnormal expression of prefoldin subunits occurs in many tumors. Thus it is necessary to have an in-depth understanding of the functions and roles of the prefoldin subunits.

The role of prefoldin subunits in human tumors and other diseases

The study found that the prefoldin subunit can be used as a strong indicator of poor prognosis of gastric cancer (GC), and the results of subgroup analysis in various clinical parameters show that different prefoldin subunits



display different effects the overall survival situation (Table 1) [35].

PFDN1 has been reported to be involved in the development of many types of tumors (such as lung, breast, and colon cancers) [36, 37]. PFDN1 is a

cancer-promoting factor. In lung cancer, PFDN1 inhibits the expression of cyclin A by directly interacting with the cyclin A promoter at the transcription initiation site, thereby suppressing EMT and metastasis of lung cancer [36]; In colon cancer cell lines SW480 and

Table 1 Proteins that physically interact with canonical or prefoldin-like subunits, and research advances in different organisms and diseases

Prefoldin subunits	Function	Organism	Interactor	Disease
β				
PFDN1	Oncogene	Human	Cyclin A [36] RABV [39]	Gastric cancer [35] Lung cancer [36] Colon cancer [37] Nasopharyngeal carcinoma [38]
		Mouse		Lymphocyte development [27] Cytoskeletal defect [27]
PFDN2	Oncogene	Human	γ -Synuclein [42]	Gastric cancer [35] Breast cancer [40] Metastatic urothelial carcinoma [41]
		Plant [65]		
PFDN4	Oncogene	Human		Atherosclerosis [19] Gastric cancer [35, 52] Breast cancer [48, 49] Colon cancer [51] Hepatocellular carcinoma [50] Atopic dermatitis [53]
PFDN6		Human		Gastric cancer [35] Acute lymphocytic leukemia [64]
		<i>Arabidopsis thaliana</i> [76]	DELLA [67]	
		<i>Caenorhabditis elegans</i>	FOXO [77]	
α				
PFDN3/VBP1	Anti-oncogene	Human	VHL [43] pVHL [44] hMSH4 [45] HDAC1 [46]	Gastric cancer [35]
		<i>Arabidopsis thaliana</i>	DELLA [67]	
		<i>Caenorhabditis elegans</i> [66]		
PFDN5/MM1	Anti-oncogene	Human	c-Myc [99] TIF1 β [101] Rabring7 [127] Egr-1 [128] ARFP/F [129] p73 α [133] p63 α [134] Δ Np63 α [135]	Gastric cancer [35] Secondary hyperparathyroidism [54, 55] Colon cancer [60]
		Mouse		Breast cancer [70–73]
		<i>Arabidopsis thaliana</i>	DELLA [67]	
α -like				
URI/Bud27		Human		Cervical cancer [89] Colon cancer [90] Gastric cancer [91]
		Mouse	c-Myc [88]	Hepatocellular carcinoma [85]
		Yeast	Rpb5 [83] TOR [93] PFDN6 [94]	
UXT/Art-27			NF- κ B [95] Als2 [97]	Androgen receptor [96] Centrosome component [98]
γ				
γ -prefoldin				Nanobiotechnology [32–34]

RKO cells, silencing PFDN1 can inhibit the proliferation, invasion, and migration of colon cancer cells, and PFDN1 expression is positively correlated with tumor size and tumor invasion, therefore PFDN1 can be used

as an indicator of poor prognosis of colorectal cancer [37]. In other disease, there is no lack of research on PFDN1. Through the reference gene selection system for nasopharyngeal carcinoma gene expression

research, PFDN1 was found to be one of the candidate genes [38]. Studies have found that in N2a cells infected with rabies virus (RABV), the subcellular distribution of PFDN1 has been changed and redistributed to the characteristic Negri-body-like (NBL) structure in the cytoplasm [39].

PFDN2 plays an oncogene role in glioblastoma, breast, pancreatic, and colon cancers [40]. Most breast cancer (BC) shows resistance to taxanes due to changes in tubulin genes, and PFDN2 is one of the neighboring proteins that can interact with sexual tubulin [40]. In two cohort studies of metastatic urothelial carcinoma, an increase in 1q23.3 copy number was found to be associated with low survival, and PFDN2 is one of the genes located in 1q23.3, which is closely related to poor prognosis [41]. A common hallmark of glaucoma is the loss of retinal ganglion cells (RGCs), while γ -synuclein (SNCG) is highly expressed in somatic cells and synapses in RGCs, and PFDN2 can be a candidate upstream regulator to identify SNCG expression [42]. Other studies have shown that the depletion of PFDN2 leads to the formation of ectopic neuroblasts [28].

PFDN3, also known as Von Hippel-Lindau binding protein 1 (VBP1), is a chaperone protein that binds to VHL. VBP1 interacts with the tumor suppressor VHL. VHL acts as a chaperone protein, which changes the intracellular localization of VBP1 from cytoplasm to the nucleus [43]. VBP1 may be a tumor suppressor protein. VBP1 interacts with pVHL (an E3 ubiquitin ligase) in vitro and enhances its stability, which degrades HIF-1 α in an oxygen-dependent manner and inhibits epithelial-mesenchymal transition (EMT) caused by HIF-1 α [44]. Studies have shown that VBP1 and VHL can also interact with p97, a AAA (+) ATPase involved in protein degradation and DNA damage, thereby affecting the polyubiquitination of the human MutS protein family hMSH4 [45]. VBP1 is co-localized with nuclear HDAC1, indicating that the delivery of HDAC1 to the CCT complex occurred in the nucleus [46].

PFDN4, also known as C-1, can function as a transcription factor or cofactor in cell cycle regulation [47]. The expression of PFDN4 may be closely related to the occurrence and development of various tumors (such as breast cancer [48, 49], hepatocellular carcinoma [50], and colorectal cancer [51]) and poor prognosis. In TWIST-depleted gastric cancer cells, PFDN4 expression is up-regulated, and EMT-related morphological and molecular changes promoted by TWIST can be reversed [52]. In addition, accumulation of low-density lipoprotein cholesterol (LDL-c) in the arterial wall is closely related to the initiation and progression of atherosclerosis, and PFDN4 has biological functions related to LDL [19]. A genome-wide association study of Japanese-specific

dermatitis just identified PFDN4 as one of eight new susceptible loci [53].

PFDN5 is differentially expressed in thyroid tumor tissue [54], and abnormal expression of PFDN5 that associated with protein synthesis and processing has been detected in secondary hyperparathyroidism [55]. Uveitis is the most common extra-articular manifestation of ankylosing spondylitis (AS). Compared with AS patients without uveitis, AS patients with uveitis had significantly higher serum PFDN5 levels, and PFDN5 had a protective effect on uveitis cell death, suggesting that PFDN5 can be used as a biomarker for AS uveitis [56]. Knocking down the candidate transcriptional regulator PFDN5 can induce the differentiation of human embryonic stem cells (hESC) [57]. In memory CD4+ T cells activated in asthma [58] and the immature CD4+ T lymphocytes in systemic lupus erythematosus [59], the mRNA levels of differential genes were detected by reverse transcription analysis, and elevated PFDN5 mRNA levels were detected. In analysis of differential gene expression profiles of colon cancer, it was identified that PFDN5 is a possible marker for the clinical prognosis of colorectal cancer [60]. In addition, PFDN5 is closely related to the pathogenesis of neurodegenerative diseases [61].

PFDN6 is a functionally unknown hydrophilic protein (KE2) in a major histocompatibility complex [62]. Response to dexamethasone (DEXA) is one of the key prognostic factors for predicting the outcome of acute lymphocytic leukemia (ALL) [63]. Studies on dexamethasone-resistant leukemia cells have found that PFDN6 may play a potential biomarker role in the prognosis and chemotherapy of ALL [64].

The role of the prefoldin subunits in other species

Studies have shown that PFDN1-deficient mice exhibit phenotypes of cytoskeletal functional defects. For instance, ciliary dyskinesia, B cells, and T cells are significantly damaged in the early stages of maturation, suggesting that PFDN1 is necessary for lymphocyte development and function [27]. Difficult destructuring and saccharification of plant cell walls is one of the main obstacles to the development of lignocellulosic materials, and targeting genes involved in cell wall biosynthesis can reduce recalcitrant. PFDN2 is one of the genes involved in cell wall biosynthesis and can affect the permeability of plant cell walls, but the specific mechanism is not clear [65]. PFDN3/VBP1 has homologs in mice, *Drosophila* and *C. elegans* [66]. Effective chaperone-mediated tubulin biogenesis is crucial in *C. elegans*. In the absence of PFDN3, *C. elegans* displays gonad developmental defects including abnormal distal tip cell migration [66]. DELLA protein is diurnally regulated by gibberellin (GA) plant hormones and interacts with prefoldin subunits,

especially PFDN3 and PFDN5, providing a possible mechanism for cortical microtubule formation [67].

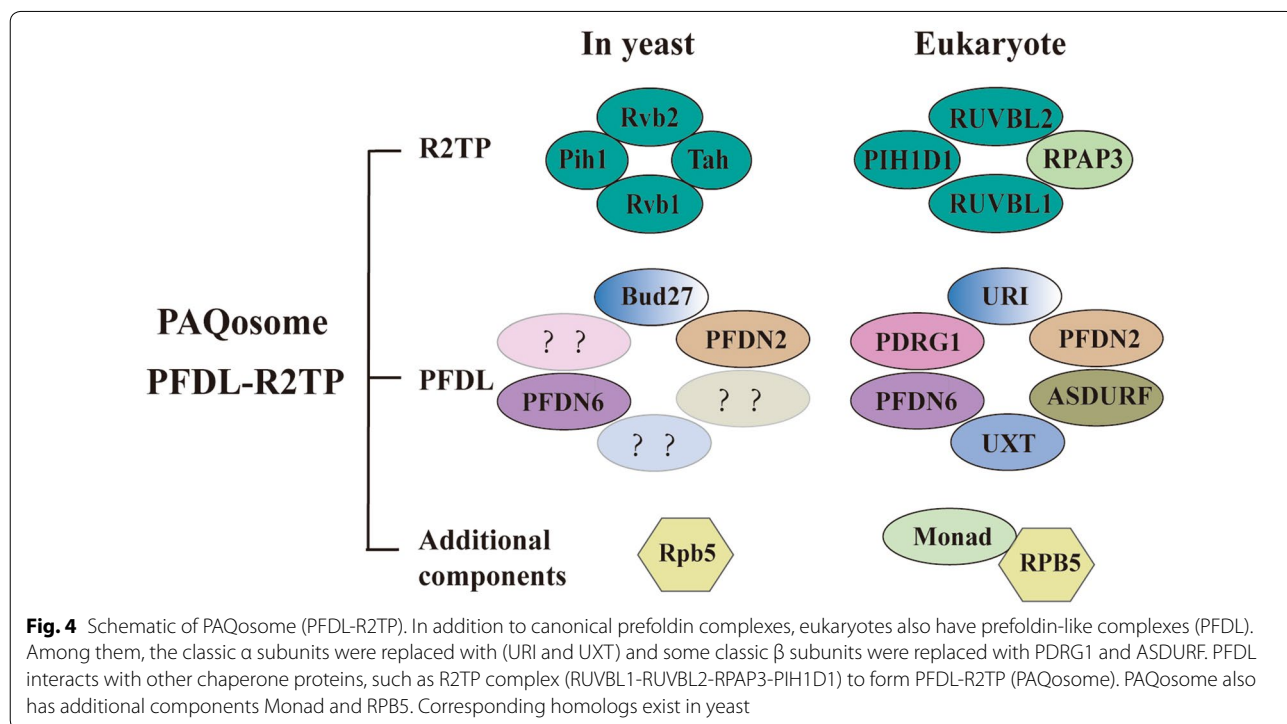
Recent studies have identified a link between hypercholesterolemia and cognitive deficits. Studies have shown that PFDN5 may be an important component of synaptic plasticity in the hippocampus of mice [68] and exposed to hypercholesterolemia in New Zealand white rabbits' prefrontal cortex (PFC), PFDN5 is one of the genes whose expression is down-regulated [69]. Therefore, the study of the PFDN5 gene may help to clarify the mechanism of the link between hypercholesterolemia and cognitive deficits. Like women, breast tumors are the most common tumors in female dogs. Multi-branched DNA (b-DNA) analysis of canine breast tumor frozen specimens revealed that PFDN5 expression was significantly lower in malignant tumors [70, 71]. PFDN5 gene somatic cell deletion is more common in canine breast cancer and it is common and closely related to high Ki-67 scores [72, 73], indicating that down-regulation or deletion of PFDN5 expression has a very important role in the development of canine breast cancer. Also, it was observed that PFDN5nmf5a mutant mice are susceptible to syndromes characterized by photoreceptor degeneration, central nervous system abnormalities, and male infertility, which may be related to the reduction of microtubule and microfilament formation caused by missense mutations in PFDN5 [6]. L110R mice with PFDN5 missense mutations have defective spermatogenesis and reduced

expression of sperm-related genes, which are manifested as male infertility [74]. Bob1 (a homolog of PFDN5) can regulate sex differentiation in yeast by interacting with the MAP kinase BYR1 [75].

In plant-related studies, nuclear accumulation of PFDN5 and PFDN6 occurs in wild-type Arabidopsis in a DELLA-dependent manner, suggesting that accumulation of DELLA protein is necessary for the localization of these two subunits in the nucleus [67]. It is also observed in Arabidopsis that the PFDN6-1 mutant can cause microtubule and cell division defects [76]. In Caenorhabditis elegans, heat shock factor 1 (HSF-1) can increase the expression of PFDN6, promote the binding of PFDN6 to the long-lived gene FOXO, and enhance the transcriptional activity of FOXO, thereby extending the lifespan of C. elegans [77].

Prefoldin subunits are involved in the assemble of prefoldin-like complex

The classic β subunits of prefoldin PFDN2 and PFDN6 can form a heterohexameric complex with URI/RMP, UXT/Art-27, PDRG1 and ASDURF (Fig. 4) [78]. This is a protein complex with weak sequence homology to the prefoldin complex and thus called the prefoldin-like complex (PFDL) [79]. Unlike the prefoldin complex, PFDL is involved in the cytoplasmic assembly of RNA polymerase II [80]. PFDL can interact with another chaperone protein (like R2TP), to form an R2TP/PFDL



complex, also named PAQosome, a 12-subunit chaperone protein [81]. Among them, the subunit compositions of R2TP (RUVBL1-RUVBL2-RPAP3-PIH1D1) is different in yeast and humans [82]. PAQosome also contains two attachments, Monad/WDR92 and RPB5/POLR2E (Fig. 4) [83]. PAQosome can assist in the assembly of HSP90 and is involved many basic cellular functions (e.g., protein synthesis, ribosome biogenesis, transcription, splicing, etc.) [81]; it also helps to stabilize and assemble phosphatidylinositol-3 kinase-related protein kinases [84].

Similarly, each subunit of the prefoldin-like complex also functions independently of the complex. URI is the alpha subunit of PFDL and is also called RNA polymerase II fifth subunit regulatory protein (RMP) [85]. In the cytoplasm, URI acts as a chaperone protein; in the nucleus, URI acts as a transcription regulator and can interact with RPB5 (a subunit common to three eukaryotic RNA polymerases) and RNA polymerase II (pol II) [86, 87]. URI has strong oncogenic activity because it can regulate the functions of many proteins including transcription factors (ER α and AhR) [86]. For example, in a mouse model, excessive expression of URI in hepatocytes can lead to hepatocellular carcinoma (HCC) [85]; decreasing the expression of URI in the intestine will activate the c-Myc expression induced by β -catenin, leading to mouse cell proliferation, DNA damage, and susceptibility to fatal gastrointestinal syndrome (GIS) caused by ionizing radiation (IR) [88]. In addition, URI can induce resistance of cervical cancer [89], colorectal cancer [90], and gastric cancer cells [91], and promote cell survival. Bud27, the URI yeast homolog, participates in the cytoplasmic assembly of three nuclear RNA polymerases in an Rpb5-dependent manner, and therefore plays an important role in transcription extension [92]. Bud27 can also mediate gene expression controlled by TOR, and the TOR pathway is involved in processes involving ribosome biogenesis [93]. Studies have also shown that Bud27 only physically interacts with the PFDN6 component in R2TP/PFDL [94].

Another alpha subunit of PFDL, UXT/Art-27, is a cofactor. Studies have shown that UXT can form a dynamic complex with NF- κ B and is recruited to enhancers of NF- κ B after stimulation, as an important part of NF- κ B transcription enhancer [95]. Studies have shown that this subunit can interact with the N-terminus of the androgen receptor (AR) and can play a role in promoting receptor-induced transcriptional activation [96]. It has been reported that UXT can interact with Als2, a gene that causes mutations in autosomal recessive forms of motor neuron disease, and the interaction of Als2 and UXT has an important role in the activation of the NF- κ B pathway [97]. Also, UXT is a component of centrosome

and is associated with γ -tubulin, which is essential for cell viability [98].

Prefoldin subunit 5 (mm-1) and c-myc

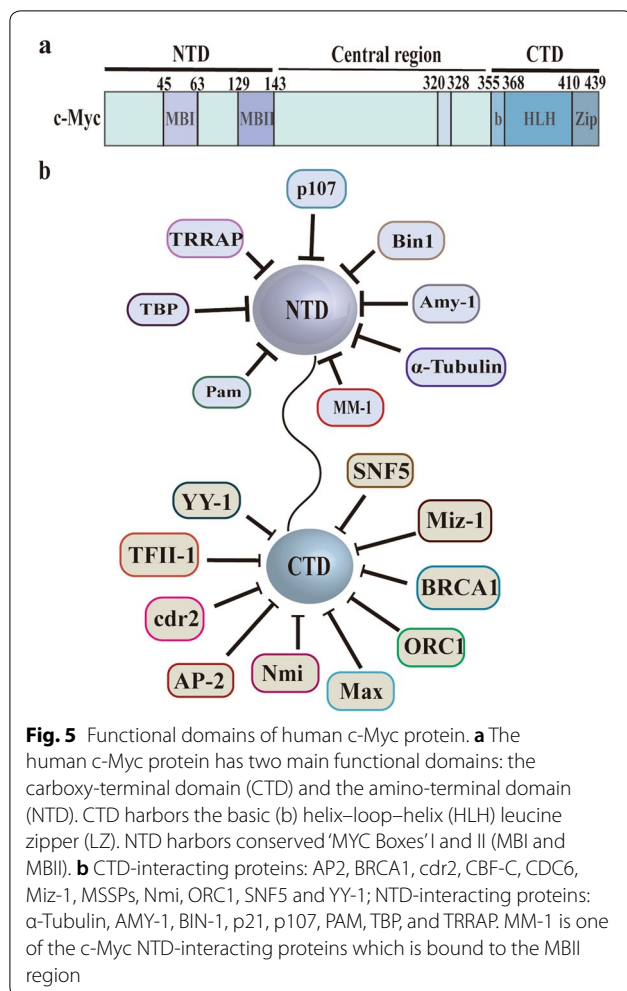
MM-1 Isoforms

The PFDN5 subunit is the most well-known of the six subunits of prefoldin. PFDN5 is also called MM-1 (Myc Modulator-1), a protein that can interact with Myc [99, 100]. MM-1 has four isoforms, namely MM-1 α , MM-1 β , MM-1 γ , and MM-1 δ . The four isoforms of MM-1 have different cellular localizations with c-Myc and have different degrees of inhibitory activity on c-Myc [101]. Isoform MM-1 α is the main expression form of MM-1 in cells. MM-1 β is universally expressed in tissues (except the heart and small intestine), while MM-1 γ and MM-1 δ are strongly expressed in fetal tissues. MM-1 β and MM-1 δ are mainly localized in the cytoplasm, while MM-1 α and MM-1 γ are localized in the nucleus, and MM1 isoforms that bind to c-Myc and TIF1 β are located in the nucleus [101].

MM-1, a c-Myc binding protein

Abnormal expression of the oncogene c-Myc often results in 30–50% of human malignancies. C-Myc not only participates in regulating a variety of cellular metabolic pathways (such as glucose metabolism, glutamine metabolism, and serine metabolism), but also plays a core role as a transcription factor in life activities, such as cell cycle regulation, cell differentiation, and protein synthesis and aging [102]. C-Myc has two main functional domains (Fig. 5a): the carboxy-terminal domain (CTD) and the amino-terminal domain (NTD) [103]. CTD has a basic (b) helix-loop-helix (HLH) leucine zipper (LZ) motif. This region can dimerize with Max and physiologically recognize the DNA target sequence, which is required for all biological behaviors [104]. NTD can participate in transcriptional regulation. It has two short segments of “Myc box” I and II (MBI and MBII) which are conserved in all Myc family proteins and trans-activates the c-Myc target genes [105].

The c-Myc binding proteins can be roughly divided into two groups: the protein that binds b-HLH-Zip at the CTD end and the protein that binds MBI or MBII at the NTD end. c-Myc binding proteins positively or negatively regulate the tumorigenicity and transcriptional activity of c-Myc. The proteins that interact with c-Myc CTD are (Fig. 5b): AP2 [106], BRCA1 [107], cdr2 [108], CBF-C(NF-YC) [109], CDC6 [110], Miz-1 [111], MSSPs [112], Nmi [107], ORC1 [113], SNF5 [114] and YY-1 [115, 116]; NTD-binding proteins are (Fig. 5b): α -Tubulin [117], AMY-1 [118], BIN-1 [119], p21 (cip1/waf1/sdi1) [120], p107 [121, 122], PAM [123], TBP [124] and TRRAP [125]. MM-1 is one of the c-Myc NTD-terminated proteins



which is bound to the MBII region of the NTD and can compete with TRRAP for c-Myc [99].

The regulatory mechanisms of MM-1 on c-Myc

MM1, a nuclear c-Myc binding protein, inhibits c-Myc activity in the nucleus in various ways and is therefore considered a tumor suppressor. As showed in Fig. 5, the regulatory mechanisms of c-Myc mediated by MM-1 are: (a) MM-1 promotes c-Myc degradation by recruiting proteasomes and a novel ubiquitin E3 ligase [126]. For example, MM-1 forms a complex with Rabring7 (a protein containing RING fingers and binding to Rab7) to degrade c-Myc (Fig. 6a) [127]. (b) MM-1 regulates the classic Wnt-β-catenin pathway. MM-1 negatively regulates the expression of wnt4 by binding to Egr-1, thereby indirectly inhibiting c-Myc expression (Fig. 6b) [128]. (c) MM-1 inhibits the E-box-dependent transcriptional activity of c-Myc by recruiting a histone deacetylase (HDAC-mSin3) complex from TIF1β/KAP1/TRIM28 (a transcriptional co-inhibitor) (Fig. 6c) [99]. For example,

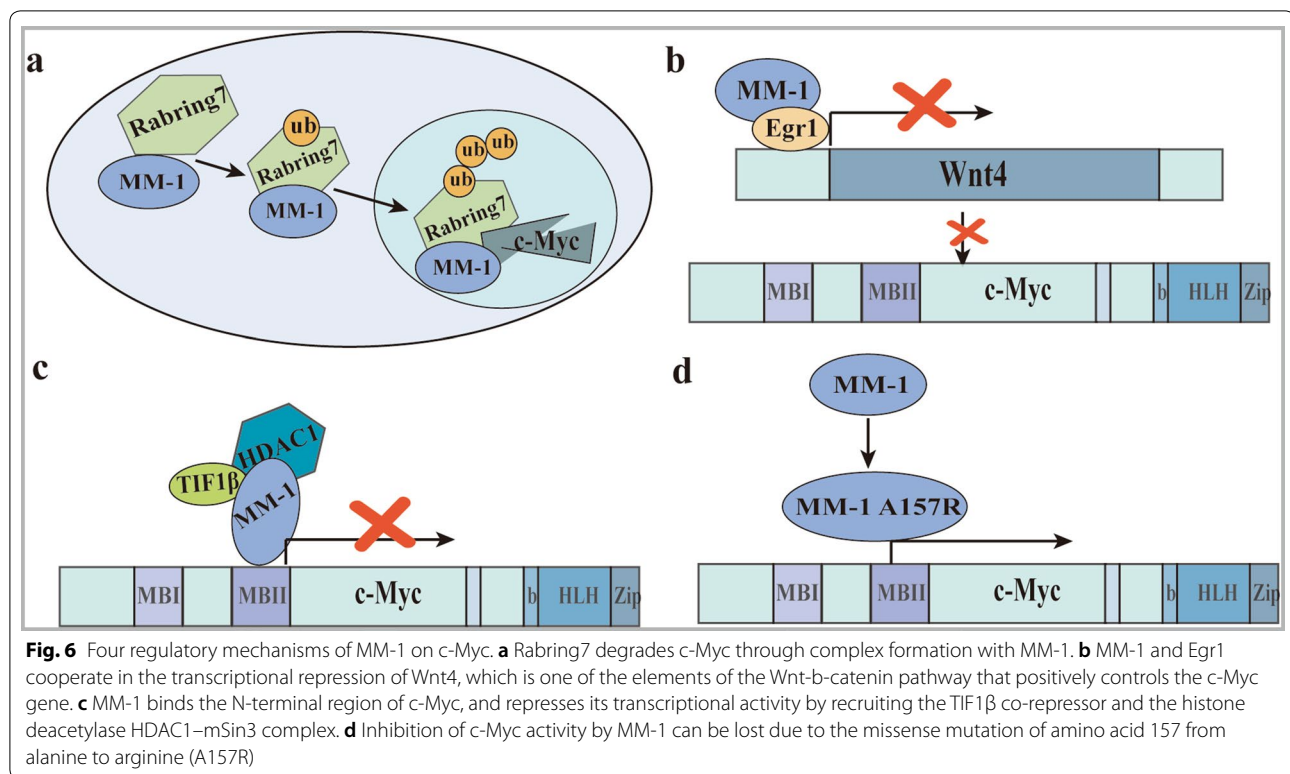
the ARFP/F protein of the hepatitis C virus (HCV) can enhance the transactivation activity of the c-Myc gene by antagonizing the inhibitory effect of MM-1 [129]. Among them, the oncogene c-FMS acts as a target gene involved in the c-Myc-MM-1-TIF1β pathway, and its expression and promoter activity are up-regulated [130]. (d) Inhibition of c-Myc activity by MM-1 can be lost due to the missense mutation of amino acid 157 from alanine to arginine (A157R) (Fig. 6d). A157R mutants are reported to be frequently observed in approximately 50–60% of patients with leukemia or lymphoma [131].

Both p63 and p73 are paralogs with high sequence homology to p53, all three are tumor suppressors, and each has a region in the sequence that is responsible for identifying and binding the target gene sequence, which is called DNA binding domain (DBD). This area is prone to aggregate and form amyloid fibers [132]. It has been reported that MM-1 can interact with p73α rather than p73β, and the expression of MM-1 greatly reduces c-Myc-mediated inhibitory activity on p73α [133]. p63α regulates the activity of c-Myc by directly interacting and regulating the stability of MM-1 protein, which leads to cell cycle progression and tumorigenesis [134]. ΔNp63α mediates the ubiquitination of c-Myc modulator MM-1 through the E3 ligase HERC3 to regulate cell senescence and tumorigenesis [135]. Therefore, to explore the regulatory effect of MM-1 on c-Myc, the key is the upstream molecules of MM-1.

Conclusion

Proper folding of proteins is a key process for a protein to acquire its functional structure and conformation. As an important chaperone protein, prefoldin is involved in the correct folding of proteins, especially the correct folding of tubulin and actin. Prefoldin plays an important role in the development and progression of neurodegenerative diseases. Advanced research on prefoldin may help to develop drugs for treating neurodegenerative diseases. Besides, abnormal expressions of prefoldin subunits occur in different tumors, and play an important role in the occurrence and development of tumors. Prefoldin subunits are expected to serve as molecular targets for tumor prognosis and drug development. Therefore, an advanced understanding of the complex functions of prefoldin can help to analyze the mechanisms of protein misfolding and the pathogenesis of diseases caused by misfolding aggregation.

However, there are still many unresolved problems in prefoldin: 1. The chaperone protein Hsp90 not only has the function of promoting protein folding but also has the function of promoting the release of exosomes. Then, what about prefoldin? 2. Are related changes caused by deletion and mutation of prefoldin in plants and animals



only occurring in specific species? 3. Is there a prominent subunit in the six subunits of prefoldin? 4. Is the prefoldin complex stable? When does the independent function of the Prefoldin subunit appear, before or after the formation of the Prefoldin complex? 5. Is the stability of the complex changed due to some factors? No matter what, the functions of the prefoldin complex and the unique functions of the prefoldin subunit need to be further explored.

Abbreviations

ATP: Adenosine triphosphate; AD: Alzheimer's disease; PD: Parkinson's disease; HD: Huntington's disease; A β : β -Amyloid peptide; hPFD: Human prefoldin; Pins: Infertile partners; INPs: Intermediate neural progenitor cells; AuNPs: Gold nanoparticles; γ PFD: γ -Prefoldin; GC: Gastric cancer; RABV: Rabies virus; NBL: Negri-body-like; BC: Breast cancer; RGCs: Retinal ganglion cells; SNCG: γ -Synuclein; VBP1: Von Hippel-Lindau binding protein 1; EMT: Epithelial–mesenchymal transition; LDL-c: Low-density lipoprotein cholesterol; AS: Ankylosing spondylitis; hESC: Human embryonic stem cells; DEXA: Dexamethasone; ALL: Acute lymphocytic leukemia; GA: Gibberellin; PFC: Prefrontal cortex; b-DNA: Branched DNA; HSF-1: Heat shock factor 1; PFDL: Prefoldin-like complex; pol II: RNA polymerase II; HCC: Hepatocellular carcinoma; GIS: Gastrointestinal syndrome; IR: Ionizing radiation; AR: Androgen receptor; MM-1: Myc modulator-1; HLH: Helix-loop-helix; LZ: Leucine zipper; HCV: Hepatitis C virus; CTD: Carboxy-terminal domain; NTD: Amino-terminal domain; DBD: DNA binding domain.

Author's contributions

JL and LX contributed to drafting and editing of the manuscript, shared the first authorship. QL and YZ designed, revised and finalized the manuscript. JL, YH, LO, and ST participated in the drafting and editing manuscript. PY, YT, SR participated in the revision and coordination. QP, LT, XL, YS contributed to

literature search. MS, DC, HW participated in the conception and coordination. All authors contributed toward data analysis, drafting and revising the paper and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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