

Cyclophilin 40 FACTS & LITERATURE

(necessarily incomplete!)

General:

- Reviews: Smith, 2004; Allan and Ratajczak, 2011
- Note that the official gene name is PPID in mammals; not to be confused with cyclophilin D, which is a mitochondrial protein.
- first discovered as an estrogen receptor associated protein (Ratajczak et al., 1990; Ratajczak et al., 1993) and found to be identical with a CsA-binding protein (Kieffer et al., 1993).
- for more genetic and biochemical interactions of yeast cyclophilins Cpr6 and Cpr7, see <http://www.yeastgenome.org>.
- By global analysis in yeast, the Hsp90 complex can be classified as a stress-inducible chaperone complex as opposed to a chaperone linked to protein synthesis (CLIPs) which also associates with nascent polypeptides; however, Cpr6 and Cpr7 fall into separate classes, Hsp and CLIPs, respectively (Albanèse et al., 2006).
- Evolutionary plasticity of Hsp90 and cochaperones (Johnson and Brown, 2009).

Genetics:

- Budding yeast:
 - o $\Delta cpr7$ has slow growth phenotype (Duina et al., 1996b).
 - o synthetic enhancement of $\Delta cpr7$ by $\Delta hsc82$, $hsp82^{G170D}$ or $\Delta sti1$ (Duina et al., 1996a; see also Flom et al., 2006), or in presence geldanamycin (Dolinski et al., 1998).
 - o $\Delta cpr7$: reduced max. activation of GR and v-src in short term expts (Duina et al., 1996a), and levels of Thi4p (Faou and Tropschug, 2003)
 - o both Cpr6 and Cpr7 dispensable in yeast (Duina et al., 1996b; Dolinski et al., 1997; Warth et al., 1997).
 - o only TPR domain of Cpr7 required to suppress slow growth phenotype and defective GR (Duina et al., 1998b) and pheromone (Lee et al., 2004) signaling of $\Delta cpr7$.
 - o slow growth phenotype (Dolinski et al., 1998; Marsh et al., 1998) and GR (Marsh et al., 1998) signaling can be restored by overexpression of Cns1, but not by overexpression of any other TPR protein (Dolinski et al., 1998). Conversely, Cpr7 overexpression suppresses lethality of temperature-sensitive *cns1* alleles (Tesic et al., 2003). Slow growth phenotype of $\Delta cpr7$ is partially suppressed by thiamine (Faou and Tropschug, 2003).
 - o Cpr6 overexpression suppresses synthetic lethality between $\Delta cpr1$ and mutations in *ZPR1* (Ansari et al., 2002).
 - o Synthetic effects between $\Delta cpr7$ and $\Delta hsc82$ on HSF activity, both required for full negative regulation (Duina et al., 1998a). Double mutant defective for growth on maltose (Bali et al., 2003).

- *Δcpr7* extends chronological life span (Harris et al., 2001).
- *Δcpr7* is defective in pheromone signaling (suppressed by *CNS1* overexpression) and Ste11 kinase activity while *Δcpr6* is only very slightly affected (Lee et al., 2004).
- *Δcpr7* defective in vertebrate AhR signaling (Yao et al., 2004).
- *Δcpr7* improves [*PSI⁺*] propagation in a *SSA1* mutant strain in a probably Hsp90-independent way (Jones et al., 2004), but reduces Hsp104-mediated elimination of prions (Moosavi et al., 2010). No effect of *Δcpr6* and *Δcpr7* by themselves on propagation (Kumar et al., 2015).
- *Δcpr7* but not *Δcpr6* is hypersensitive to drugs that induce protein misfolding (Albanèse et al., 2006). Only the latter is hypersensitive to a Hsp90 inhibitor (Franzosa et al., 2011).
- *CPR7* (and notably the TPR) becomes essential when the charged linker of Hsp90 is deleted; this synthetic lethality can be suppressed by *Cns1* overexpression as well (Zuehlke and Johnson, 2012).
- *Δcpr6* is synthetic sick with *hsp90-A587T* (Zuehlke et al., 2013).
- *Cpr7* (its TPR domain) but not *Cpr6* is a restriction factor for replication of Tomato bushy stunt tobravirus (TBSV) (Lin et al., 2012) and Carnation Italian ringspot tobravirus (Xu et al., 2014).
- *cns1* point mutants are hypersensitive to overexpression of *Cpr6*, but not *Cpr7*, which must be able to bind Hsp90 (Johnson et al., 2014).
- *Δcpr7* are hypersensitive to hygromycin (Tenge et al., 2015).
- *CPR7* required for propagation of {*URE3*} prions; defect can be suppressed by TPR domain alone or by *Cns1* overexpression (Kumar et al., 2015).
- *Cpr6* and *Cpr7* are differentially required for the activity of exogenous clients (Sahasrabudhe et al., 2017).
- *S. pombe* Cyp40 homolog Wis2 suppresses a *cdc25 wee1 win1* triple mutant (Weisman et al., 1996).
- In *C. elegans* it is not clear whether any of the cyclophilins corresponds to cyclophilin 40.
- Mutations in Cyp40 gene (*SQUINT*) of Arabidopsis have effects on vegetative maturation of shoot (Berardini et al., 2001). Can be traced to a reduced Ago1 activity leading to aberrant miRNA activities; no interaction between Cyp40 or Hsp90 and Ago1 could be demonstrated; Hsp90/Squint double mutants have even stronger phenotype (Smith et al., 2009). Hsp90 binding is required (Earley and Poethig, 2011).
- Cyp40 KO in *Leishmania donovani* has no effect on viability but results in ultrastructural defects of promastigotes and prevents parasites from establishing an infection (Yau et al., 2014). Null mutants have increased expression of stress proteins and exosome production (Yau et al., 2016).
- Mouse KO has no obvious phenotype (our unpublished results).
- AAV-mediated overexpression reduces tau amyloid deposits, preserves neurons, and improves cognitive functions in a mouse model, correlating with *in vitro* disaggregase activity (Baker et al., 2017).

Other *in vivo* analyses:

- Overexpression and antibody injections in *Xenopus* oocytes: overexpression delays attenuation of Hsf1; anti-Cyp40 has no effect (Bharadwaj et al., 1999).
- intranuclear localization of Cyp40 changes following heat shock (Mark et al., 2001).
- Cyp40 knock-down reduces AhR (Luu et al., 2008), AR signaling (also inhibited by cyclosporin A) (Periyasamy et al., 2010), replication of Hepatitis C Virus (Goto et al., 2009), and RACK1-mediated reduction of HIF1- α protein (Park et al., 2011).
- Overexpression in mammalian cells does not have much of an effect on steroid receptor function, and cannot compete with inhibition by FKBP51, possibly because of weaker binding (Schülke et al., 2010).
- Knock-down slightly impairs viability of anaplastic large cell lymphoma cells (Pearson et al., 2012). Reduces proliferation of a keratinocyte cell line but also improves resistance to UV-induced apoptosis, ROS production and MTP opening (Jandova et al., 2013).

Biochemistry:

- Use of cyclosporin A and FK506 shows that PPlase activity is not required for GR heterocomplex assembly *in vitro* (Owens-Grillo et al., 1995). In contrast, cyclosporin A blocks assembly with Hsp90-Ago1 complex (Iki et al., 2012).
- yeast Cpr6 (Warth et al., 1997) has PPlase activity. Cpr6 has 100-fold higher activity than Cpr7 (Mayr et al., 2000). Cyp40 PPlase (Pirkl and Buchner, 2001) and *N. crassa* NcCyP41 (Faou and Tropschug, 2003) characteristics.
- Hsp90 - yeast cyclophilin binding constants 14-57 nM (similar to Sti1-Hsp90) (Mayr et al., 2000). Affinity of human Cyp40 for Hsp90 is 226 nM and stoichiometry is 1:1 (Pirkl and Buchner, 2001).
- turnover but not steady-state levels of Cyp40 increases during stress (Mark et al., 2001).
- Cpr7 is monomeric (see e.g. Tesic et al., 2003) as is Cpr6 (Li et al., 2011).
- Cyp40 required to promote AhR-Arnt DNA complexes *in vitro* (Shetty et al., 2004).
- Cyp40 promotes the formation of the AhR/Arnt heterodimer and its DNA binding (Luu et al., 2008).
- Cyp40, in contrast to other TPR co-chaperones, facilitates RISC assembly in an Hsp90-dependent way by promoting or stabilizing the binding of small RNA duplexes to AGO1, but is not present in mature RISC in plants (Iki et al., 2012).
- Binding of MEEVD peptide slightly inhibits PPlase activity in a temperature-dependent way; heat-shock may therefore increase free pool of Cyp40 (Blackburn et al., 2015).
- Yeast Cpr6 is differentially required for assembly of GR vs. MR HBD complexes *in vitro* (Sahasrabudhe et al., 2017).

Structure:

- two alternate structures of full-length bovine cyclophilin-40 (Taylor et al., 2001).
- extensive structure-function comparison of the human cyclophilin family (Davis et al., 2010).
- Structure of Cpr7 shows U-shape (Qiu et al., 2017).

Complexes:

- Cpr6 and Cpr7 bind Rpd3 in a 2-hybrid screen (Duina et al., 1996b); they bind Hsp90 biochemically (Duina et al., 1996a).
- direct binding to Hsp90 (Hoffmann and Handschumacher, 1995; Owens-Grillo et al., 1995). Mutual competition for Hsp90 binding between Cyp40 and FKBP52 (Owens-Grillo et al., 1995; Owens-Grillo et al., 1996; Ratajczak and Carrello, 1996) or Hop (Owens-Grillo et al., 1996) and by a fragment of PP5 containing 4 TPR repeats (Silverstein et al., 1998). Extreme N-terminus of yeast Hsp90 required for high affinity binding of Sti1 but not Cpr6 (Richter et al., 2003). However, mixed Sti/Hop-PPLase-Hsp90 complexes are a favored intermediate and Cpr6-Aha1-Hsp90 ternary complexes exist as well (Li et al., 2011).
- Cpr6, but not Cpr7, promotes association of Aha1, which in turn drives Hsp90 to a partially closed state; together, Cpr6 and Aha1 displace Sti1, and p23 finally the release of Aha1 (Li et al., 2013).
- Hsc70 through TPR domain, no effect on Hsc70 ATPase (Carrello et al., 2004). Also interacts with Hsp70 (Ssa1) *in vivo* in yeast (Zuehlke et al., 2013).
- also in mutant p53 complexes (Whitesell et al., 1998).
- Cpr7 but not Cpr6 is in CsA-sensitive complexes with Cns1 suggesting direct interaction (Dolinski et al., 1998; Marsh et al., 1998). Interaction must be indirect and also does not depend on the MEEVD of Hsp90 (Tescic et al., 2003). MEEVD sufficient for interaction with cyclophilin-40 (Onuoha et al., 2008).
- Cyclophilin-40 is in a cytosolic complex with caveolin, Hsp56, and CypA, and cholesterol (Uittenbogaard et al., 1998). Formation of functional transport complex but not association with cyclophilin-40 is dependent on caveolin palmitoylation (Uittenbogaard and Smart, 2000).
- Cyp40 in complexes with Harc (Scholz et al., 2001).
- Cpr7 binds to Hsp104 in respiring yeast and directly *in vitro*; competed by Hsp90 (Abbas-Terki et al., 2001).
- Binds cytoplasmic dynein through intermediate chain and PPLase domain (Galigniana et al., 2002).
- *N. crassa* NcCYP41 binds Hsp80 (Hsp90) and also directly the Thi4 homolog CyPBP37 (Faou and Tropschug, 2003).
- calcium-binding and chaperone protein S100A1 of the S100 family (Okada et al., 2004). The S100 family proteins S100A1 and S100A2 bind TPR domains in Ca²⁺-dependent fashion competing with Hsp90 (Shimamoto et al., 2010).
- no Hsp90 α /Hsp90 β -isoform specific interactions with a number of cochaperones (p23, immunophilins, Hip, Hop, Hsp70) and substrates detected (Taherian et al., 2008).
- TAP purification of Cyp40 interactors yielded RACK1, Ku70, NF45, and RPS3, which were validated with recombinant proteins (Park et al., 2011).

- Although interaction of Cpr6 and Cpr7 with Hsp90 is normally ATP-dependent, they interact independently of nucleotide with Hsp90 lacking the charged linker domain, and Cpr6 binds even wt Hsp90 in the absence of Cpr7 suggesting that Cpr7 mediates a conformational signal to relay the nucleotide status to the C-terminal TRP-binding domain (Zuehlke and Johnson, 2012).
- Ternary complexes Hsp90-Cpr6-Cpr7 (Zuehlke and Johnson, 2012).
- Interacts with Ura2 independently of Hsp90 (Zuehlke et al., 2013).
- Cpr7 but not Cpr6 binds and inhibits TBSV replication protein p33 via its TPR (Lin et al., 2012).
- Cpr6/7 (and Cns1) interact with the ribosome and there is genetic evidence that this is required for the *in vivo* functions of Cpr6 (Tenge et al., 2015).
- Cyp40 binds the Clostridium toxin components C2I, Ia and CDTa, and cyclosporin A inhibits translocation into the cytoplasm (Ernst et al., 2015).
- Cpr7 directly interacts with Ure2 and promotes fibrillation (Kumar et al., 2015).
- Diphtheria toxin A, required for Hsp90/Hsp70-mediated translocation into cells in PPlase-dependent way (Schuster et al., 2017).
- Binds proline-rich regions of tau and α -synuclein (Baker et al., 2017).

Cyp40 chaperone:

- holds denatured proteins in folding competent state (Freeman et al., 1996).
- Mammalian cyclophilin-40 negatively regulates DNA binding of c-myc but not v-myc (Levenson and Ness, 1998).
- Cpr7 and Cpr6 have PPlase-independent chaperone activity in the citrate synthase aggregation assay and that of Cpr7 is higher than that of Cpr6 (Mayr et al., 2000). Characteristics of Cyp40 (Pirkl and Buchner, 2001).
- Can disaggregate tau and α -synuclein amyloid *in vitro*, both of which are enriched in proline residues (Baker et al., 2017).

Mapping of Cyp40 domains:

- N-terminal domain of 18 kD contains PPlase homology and activity
- C-terminal half contains 3 TPR repeats and a potential calmodulin binding site at extreme C-terminus (see S100A1 above).
- TPR repeats plus some flanking regions required for Hsp90 binding (Hoffmann and Handschumacher, 1995; Duina et al., 1996b; Owens-Grillo et al., 1996; Ratajczak and Carrello, 1996). Detailed mutational analysis reveals importance of MEEVD binding groove (two-carboxylate clamp) and additional residues in TPR domain (Ward et al., 2002).
- Charge-Y motif (-++X Φ YXXMF) immediately past TPR core, discovered in FKBP, may fold back and by analogy also be essential for Hsp90 binding (Cheung-Flynn et al., 2003).
- only TPR domain of Cpr7 required to suppress slow growth phenotype and defective GR signaling of Δ cpr7 (Duina et al., 1998b). Sufficient to maintain viability of Hsp90 mutants lacking charged linker (Zuehlke and Johnson, 2012). A Cpr6 chimera with the last 100 AA of Cpr7 can complement (Zuehlke et al., 2013).

- Suppression of *cns1* lethality by Cpr7 in yeast depends on PPIase and TPR domains, but not catalytic activity (Tescic et al., 2003).
- determinants for binding Hsc70 are similar to those for binding Hsp90 (Carrello et al., 2004).
- Chaperone activity maps to cleft between PPIase and TPR domains (Mok et al., 2006).
- C-terminal basic residues are required for interaction with ribosomes (Tenge et al., 2015).
- PPIase activity required for *in vitro* disaggregase activity (Baker et al., 2017).

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