

Cyclophilin 40 FACTS & LITERATURE

(necessarily incomplete!)

General:

- Reviews: Smith, 2004; Allan and Ratajczak, 2011
- 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 (Tescic 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).
 - o $\Delta cpr7$ 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).
- *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).
- *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).

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 (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).

Biochemistry:

- 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).

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).

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).
- Hsc70 through TPR domain, no effect on Hsc70 ATPase (Carrello et al., 2004).
- 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 Hsc (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).

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 PPIase-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).

Mapping of Cyp40 domains:

- N-terminal domain of 18 kD contains PPIase 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 (-++XΦYXXMF) 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 *Δcpr7* (Duina et al., 1998b).
- 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).

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