

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 tobusvirus (TBSV) (Lin et al., 2012) and Carnation Italian ringspot tobusvirus (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. cerevisiae*: *Cpr7* mitigates protein burden, *Δcpr7* promotes it as well as protein aggregation (Farkas et al., 2018).
- *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 PPIase 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 PPIase activity. Cpr6 has 100-fold higher activity than Cpr7 (Mayr et al., 2000). Cyp40 PPIase (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 PPIase 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-PPIase-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 PPIase 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; reviewed in Shelton 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).

References:

- Abbas-Terki, T., Donzé, O., Briand, P.-A., and Picard, D. (2001). Hsp104 interacts with Hsp90 cochaperones in respiring yeast. *Mol. Cell. Biol.* *21*, 7569–7575.
- Albanèse, V., Yam, A. Y., Baughman, J., Parnot, C., and Frydman, J. (2006). Systems analyses reveal two chaperone networks with distinct functions in eukaryotic cells. *Cell* *124*, 75-88.
- Allan, R. K., and Ratajczak, T. (2011). Versatile TPR domains accommodate different modes of target protein recognition and function. *Cell Stress Chaperones* *16*, 353-367.
- Ansari, H., Greco, G., and Luban, J. (2002). Cyclophilin A peptidyl-prolyl isomerase activity promotes ZPR1 nuclear export. *Mol. Cell. Biol.* *22*, 6993-7003.
- Baker, J. D., Shelton, L. B., Zheng, D., Favretto, F., Nordhues, B. A., Darling, A., Sullivan, L. E., Sun, Z., Solanki, P. K., Martin, M. D. et al. (2017). Human cyclophilin 40 unravels neurotoxic amyloids. *PLoS Biol.* *15*, e2001336.
- Bali, M., Zhang, B., Morano, K. A., and Michels, C. A. (2003). The Hsp90 molecular chaperone complex regulates maltose induction and stability of the *Saccharomyces* MAL gene transcription activator Mal63p. *J. Biol. Chem.* *278*, 47441-47448.
- Berardini, T. Z., Bollman, K., Sun, H., and Poethig, R. S. (2001). Regulation of vegetative phase change in *Arabidopsis thaliana* by cyclophilin 40. *Science* *291*, 2405-2407.
- Bharadwaj, S., Ali, A., and Ovsenek, N. (1999). Multiple components of the HSP90 chaperone complex function in regulation of heat shock factor 1 in vivo. *Mol. Cell. Biol.* *19*, 8033-8041.
- Blackburn, E. A., Wear, M. A., Landré, V., Narayan, V., Ning, J., Erman, B., Ball, K. L., and Walkinshaw, M. D. (2015). Cyclophilin40 isomerase activity is regulated by a temperature-dependent allosteric interaction with Hsp90. *Biosci. Rep.* *35*,
- Carrello, A., Allan, R. K., Morgan, S. L., Owen, B. A., Mok, D., Ward, B. K., Minchin, R. F., Toft, D. O., and Ratajczak, T. (2004). Interaction of the Hsp90 cochaperone cyclophilin 40 with Hsc70. *Cell Stress Chaperones* *9*, 167-181.
- Cheung-Flynn, J., Roberts, P. J., Riggs, D. L., and Smith, D. F. (2003). C-terminal sequences outside the tetratricopeptide repeat domain of FKBP51 and FKBP52 cause differential binding to Hsp90. *J. Biol. Chem.* *278*, 17388-17394.
- Davis, T. L., Walker, J. R., Campagna-Slater, V., Finerty, P. J., Paramanathan, R., Bernstein, G., MacKenzie, F., Tempel, W., Ouyang, H., Lee, W. H. et al. (2010). Structural and biochemical characterization of the human cyclophilin family of peptidyl-prolyl isomerases. *PLoS Biol.* *8*, e1000439.
- Dolinski, K., Muir, S., Cardenas, M., and Heitman, J. (1997). All cyclophilins and FK506 binding proteins are, individually and collectively, dispensable for viability in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* *94*, 13093-13098.
- Dolinski, K. J., Cardenas, M. E., and Heitman, J. (1998). *CNS1* encodes an essential p60/Sti1 homolog in *Saccharomyces cerevisiae* that suppresses cyclophilin 40 mutations and interacts with Hsp90. *Mol. Cell. Biol.* *18*, 7344-7352.

- Duina, A. A., Chang, H.-C. J., Marsh, J. A., Lindquist, S., and Gaber, R. F. (1996a). A cyclophilin function in Hsp90-dependent signal transduction. *Science* *274*, 1713-1715.
- Duina, A. A., Kalton, H. M., and Gaber, R. F. (1998a). Requirement for Hsp90 and a CyP-40-type cyclophilin in negative regulation of the heat shock response. *J. Biol. Chem.* *273*, 18974-18978.
- Duina, A. A., Marsh, J. A., and Gaber, R. F. (1996b). Identification of two CyP-40-like cyclophilins in *Saccharomyces cerevisiae*, one of which is required for normal growth. *Yeast* *12*, 943-952.
- Duina, A. A., Marsh, J. A., Kurtz, R. B., Chang, H. C. J., Lindquist, S., and Gaber, R. F. (1998b). The peptidyl-prolyl isomerase domain of the CyP-40 cyclophilin homolog Cpr7 is not required to support growth or glucocorticoid receptor activity in *Saccharomyces cerevisiae*. *J. Biol. Chem.* *273*, 10819-10822.
- Earley, K. W., and Poethig, R. S. (2011). Binding of the cyclophilin 40 ortholog SQUINT to Hsp90 protein is required for SQUINT function in Arabidopsis. *J. Biol. Chem.* *286*, 38184-38189.
- Ernst, K., Langer, S., Kaiser, E., Osseforth, C., Michaelis, J., Popoff, M. R., Schwan, C., Aktories, K., Kahlert, V., Malesevic, M. et al. (2015). Cyclophilin-facilitated membrane translocation as pharmacological target to prevent intoxication of mammalian cells by binary clostridial actin ADP-ribosylated toxins. *J. Mol. Biol.* *427*, 1224-1238.
- Faou, P., and Tropschug, M. (2003). A novel binding protein for a member of CyP40-type cyclophilins: *N.crassa* CyPBP37, a growth and thiamine regulated protein homolog to yeast Thi4p. *J. Mol. Biol.* *333*, 831-844.
- Farkas, Z., Kalapis, D., Bodí, Z., Szamecz, B., Daraba, A., Almási, K., Kovács, K., Boross, G., Pál, F., Horváth, P. et al. (2018). Hsp70-associated chaperones have a critical role in buffering protein production costs. *eLife in press*,
- Flom, G., Weekes, J., Williams, J. J., and Johnson, J. L. (2006). Effect of mutation of the tetratricopeptide repeat and asparatate-proline 2 domains of Sti1 on Hsp90 signaling and interaction in *Saccharomyces cerevisiae*. *Genetics* *172*, 41-51.
- Franzosa, E. A., Albanese, V., Frydman, J., Xia, Y., and McClellan, A. J. (2011). Heterozygous yeast deletion collection screens reveal essential targets of hsp90. *PLoS ONE* *6*, e28211.
- Freeman, B. C., Toft, D. O., and Morimoto, R. I. (1996). Molecular chaperone machines: chaperone activities of the cylophilin Cyp-40 and the steroid aporeceptor-associated protein p23. *Science* *274*, 1718-1720.
- Galigniana, M. D., Harrell, J. M., Murphy, P. J., Chinkers, M., Radanyi, C., Renoir, J. M., Zhang, M., and Pratt, W. B. (2002). Binding of hsp90-associated immunophilins to cytoplasmic dynein: direct binding and in vivo evidence that the peptidylprolyl isomerase domain is a dynein interaction domain. *Biochem.* *41*, 13602-13610.
- Goto, K., Watashi, K., Inoue, D., Hijikata, M., and Shimotohno, K. (2009). Identification of cellular and viral factors related to anti-hepatitis C virus activity of cyclophilin inhibitor. *Cancer Sci.* *100*, 1943-1950.
- Harris, N., MacLean, M., Hatzianthis, K., Panaretou, B., and Piper, P. W. (2001). Increasing *Saccharomyces cerevisiae* stress resistance, through the overactivation of the heat shock response resulting from defects in the Hsp90

- chaperone, does not extend replicative life span but can be associated with slower chronological ageing of nondividing cells. *Mol. Genet. Genomics* *265*, 258-263.
- Hoffmann, K., and Handschumacher, R. E. (1995). Cyclophilin-40: Evidence for a dimeric complex with hsp90. *Biochem J.* *307*, 5-8.
- Iki, T., Yoshikawa, M., Meshi, T., and Ishikawa, M. (2012). Cyclophilin 40 facilitates HSP90-mediated RISC assembly in plants. *EMBO J.* *31*, 267-278.
- Jandova, J., Janda, J., and Sligh, J. E. (2013). Cyclophilin 40 alters UVA-induced apoptosis and mitochondrial ROS generation in keratinocytes. *Exp. Cell Res.* *319*, 750-760.
- Johnson, J. L., and Brown, C. (2009). Plasticity of the Hsp90 chaperone machine in divergent eukaryotic organisms. *Cell Stress Chaperones* *14*, 83-94.
- Johnson, J. L., Zuehlke, A. D., Tenge, V. R., and Langworthy, J. C. (2014). Mutation of essential Hsp90 co-chaperones SGT1 or CNS1 renders yeast hypersensitive to overexpression of other co-chaperones. *Curr. Genet.* *60*, 265-276.
- Jones, G., Song, Y., Chung, S., and Masison, D. C. (2004). Propagation of *Saccharomyces cerevisiae* [PS⁺] prion is impaired by factors that regulate Hsp70 substrate binding. *Mol. Cell. Biol.* *24*, 3928-3937.
- Kieffer, L. J., Seng, T. W., Li, W., Osterman, D. G., Handschumacher, R. E., and Bayney, R. M. (1993). Cyclophilin-40, a protein with homology to the P59 component of the steroid receptor complex. Cloning of the cDNA and further characterization. *J. Biol. Chem.* *268*, 12303-12310.
- Kumar, N., Gaur, D., Gupta, A., Puri, A., and Sharma, D. (2015). Hsp90-associated immunophilin homolog Cpr7 is required for the mitotic stability of [URE3] prion in *Saccharomyces cerevisiae*. *PLoS Genet.* *11*, e1005567.
- Lee, P., Shabbir, A., Cardozo, C., and Caplan, A. J. (2004). Sti1 and Cdc37 can stabilize Hsp90 in chaperone complexes with a protein kinase. *Mol. Biol. Cell* *15*, 1785-1792.
- Leverson, J. D., and Ness, S. A. (1998). Point mutations in v-Myb disrupt a cyclophilin-catalyzed negative regulatory mechanism. *Mol. Cell* *1*, 203-211.
- Li, J., Richter, K., and Buchner, J. (2011). Mixed Hsp90-cochaperone complexes are important for the progression of the reaction cycle. *Nat. Struct. Mol. Biol.* *18*, 61-66.
- Li, J., Richter, K., Reinstein, J., and Buchner, J. (2013). Integration of the accelerator Aha1 in the Hsp90 co-chaperone cycle. *Nat. Struct. Mol. Biol.* *20*, 326-331.
- Lin, J. Y., Mendu, V., Pogany, J., Qin, J., and Nagy, P. D. (2012). The TPR domain in the host Cyp40-like cyclophilin binds to the viral replication protein and inhibits the assembly of the tombusviral replicase. *PLoS Pathog.* *8*, e1002491.
- Luu, T. C., Bhattacharya, P., and Chan, W. K. (2008). Cyclophilin-40 has a cellular role in the aryl hydrocarbon receptor signaling. *FEBS Lett.* *582*, 3167-3173.
- Mark, P. J., Ward, B. K., Kumar, P., Lahooti, H., Minchin, R. F., and Ratajczak, T. (2001). Human cyclophilin 40 is a heat shock protein that exhibits altered intracellular localization following heat shock. *Cell Stress Chaperones* *6*, 59-70.
- Marsh, J. A., Kalton, H. M., and Gaber, R. F. (1998). Cns1 is an essential protein associated with the hsp90 chaperone complex in *Saccharomyces cerevisiae*

- that can restore cyclophilin 40-dependent functions in *cpr7Δ* cells. *Mol. Cell Biol.* **18**, 7353-7359.
- Mayr, C., Richter, K., Lilie, H., and Buchner, J. (2000). Cpr6 and Cpr7, two closely related Hsp90-associated immunophilins from *Saccharomyces cerevisiae*, differ in their functional properties. *J. Biol. Chem.* **275**, 34140-34146.
- Mok, D., Allan, R. K., Carrello, A., Wangoo, K., Walkinshaw, M. D., and Ratajczak, T. (2006). The chaperone function of cyclophilin 40 maps to a cleft between the prolyl isomerase and tetratricopeptide repeat domains. *FEBS Lett.* **580**, 2761-2768.
- Moosavi, B., Wongwigkarn, J., and Tuite, M. F. (2010). Hsp70/Hsp90 co-chaperones are required for efficient Hsp104-mediated elimination of the yeast [PSI(+)] prion but not for prion propagation. *Yeast* **27**, 167-179.
- Okada, M., Hatakeyama, T., Itoh, H., Tokuta, N., Tokumitsu, H., and Kobayashi, R. (2004). S100A1 is a novel molecular chaperone and a member of the Hsp70/Hsp90 multichaperone complex. *J. Biol. Chem.* **279**, 4221-4233.
- Onuoha, S. C., Coulstock, E. T., Grossmann, J. G., and Jackson, S. E. (2008). Structural studies on the co-chaperone Hop and its complexes with Hsp90. *J. Mol. Biol.* **379**, 732-744.
- Owens-Grillo, J. K., Czar, M. J., Hutchison, K. A., Hoffman, K., Perdew, G. H., and Pratt, W. B. (1996). A model of protein targeting mediated by immunophilins and other proteins that bind to hsp90 via tetratricopeptide repeat domains. *J. Biol. Chem.* **271**, 13468-13475.
- Owens-Grillo, J. K., Hoffmann, K., Hutchison, K. A., Yem, A. W., Deibel, M. R., Handschumacher, R. E., and Pratt, W. B. (1995). The cyclosporin A-binding immunophilin CyP-40 and the FK506-binding immunophilin Hsp56 bind to a common site on Hsp90 and exist in independent cytosolic heterocomplexes with the untransformed glucocorticoid receptor. *J. Biol. Chem.* **270**, 20479-20484.
- Park, M. S., Chu, F., Xie, J., Wang, Y., Bhattacharya, P., and Chan, W. K. (2011). Identification of cyclophilin-40-interacting proteins reveals potential cellular function of cyclophilin-40. *Anal. Biochem.* **410**, 257-265.
- Pearson, J. D., Mohammed, Z., Bacani, J. T., Lai, R., and Ingham, R. J. (2012). The heat shock protein-90 co-chaperone, Cyclophilin 40, promotes ALK-positive, anaplastic large cell lymphoma viability and its expression is regulated by the NPM-ALK oncoprotein. *BMC Cancer* **12**, 229.
- Periyasamy, S., Hinds, T., Jr., Shemshedini, L., Shou, W., and Sanchez, E. R. (2010). FKBP51 and Cyp40 are positive regulators of androgen-dependent prostate cancer cell growth and the targets of FK506 and cyclosporin A. *Oncogene* **29**, 1691-1701.
- PirkI, F., and Buchner, J. (2001). Functional analysis of the Hsp90-associated human peptidyl prolyl *cis/trans* isomerases FKBP51, FKBP52 and Cyp40. *J. Mol. Biol.* **308**, 795-806.
- Qiu, Y., Ge, Q., Wang, M., Lv, H., Ebrahimi, M., Niu, L., Teng, M., and Li, X. (2017). The crystal structure of the Hsp90 co-chaperone Cpr7 from *Saccharomyces cerevisiae*. *J. Struct. Biol.* **197**, 379-387.
- Ratajczak, T., and Carrello, A. (1996). Cyclophilin 40 (CyP-40), mapping of its hsp90 binding domain and evidence that FKBP52 competes with CyP-40 for hsp90 binding. *J. Biol. Chem.* **271**, 2961-2965.

- Ratajczak, T., Carrello, A., Mark, P. J., Warner, B. J., Simpson, R. J., Moritz, R. L., and House, A. K. (1993). The cyclophilin component of the unactivated estrogen receptor contains a tetratricopeptide repeat domain and shares identity with p59 (FKBP59). *J. Biol. Chem.* *268*, 13187-13192.
- Ratajczak, T., Hlaing, J., Brockway, M. J., and Hahnel, R. (1990). Isolation of untransformed bovine estrogen receptor without molybdate stabilization. *J. Steroid Biochem.* *35*, 543-553.
- Richter, K., Muschler, P., Hainzl, O., Reinstein, J., and Buchner, J. (2003). Sti1 is a non-competitive inhibitor of the Hsp90 ATPase. Binding prevents the N-terminal dimerization reaction during the ATPase cycle. *J. Biol. Chem.* *278*, 10328-10333.
- Sahasrabudhe, P., Rohrberg, J., Biebl, M. M., Rutz, D. A., and Buchner, J. (2017). The plasticity of the Hsp90 co-chaperone system. *Mol. Cell* *67*, 947-961 e945.
- Scholz, G. M., Cartledge, K., and Hall, N. E. (2001). Identification and characterization of Harc: A novel Hsp90 associating relative of Cdc37. *J. Biol. Chem.* *18*, 18.
- Schülke, J. P., Wochnik, G. M., Lang-Rollin, I., Gassen, N. C., Knapp, R. T., Berning, B., Yassouridis, A., and Rein, T. (2010). Differential impact of tetratricopeptide repeat proteins on the steroid hormone receptors. *PLoS ONE* *5*, e11717.
- Schuster, M., Schnell, L., Feigl, P., Birkhofer, C., Mohr, K., Roeder, M., Carle, S., Langer, S., Tippel, F., Buchner, J. et al. (2017). The Hsp90 machinery facilitates the transport of diphtheria toxin into human cells. *Sci. Rep.* *7*, 613.
- Shelton, L. B., Koren, J., 3rd, and Blair, L. J. (2017). Imbalances in the Hsp90 chaperone machinery: implications for tauopathies. *Front. Neurosci.* *11*, 724.
- Shetty, P. V., Wang, X., and Chan, W. K. (2004). CyP40, but not Hsp70, in rabbit reticulocyte lysate causes the aryl hydrocarbon receptor-DNA complex formation. *Arch. Biochem. Biophys.* *429*, 42-49.
- Shimamoto, S., Kubota, Y., Tokumitsu, H., and Kobayashi, R. (2010). S100 proteins regulate the interaction of Hsp90 with Cyclophilin 40 and FKBP52 through their tetratricopeptide repeats. *FEBS Lett.* *584*, 1119-1125.
- Silverstein, A. M., Grammatikakis, N., Cochran, B. H., Chinkers, M., and Pratt, W. B. (1998). p50(cdc37) binds directly to the catalytic domain of Raf as well as to a site on hsp90 that is topologically adjacent to the tetratricopeptide repeat binding site. *J. Biol. Chem.* *273*, 20090-20095.
- Smith, D. F. (2004). Tetratricopeptide repeat cochaperones in steroid receptor complexes. *Cell Stress Chaperones* *9*, 109-121.
- Smith, M. R., Willmann, M. R., Wu, G., Berardini, T. Z., Möller, B., Weijers, D., and Poethig, R. S. (2009). Cyclophilin 40 is required for microRNA activity in Arabidopsis. *Proc. Natl. Acad. Sci. USA* *106*, 5424-5429.
- Taherian, A., Krone, P. H., and Ovsenek, N. (2008). A comparison of Hsp90 α and Hsp90 β interactions with cochaperones and substrates. *Biochem. Cell Biol.* *86*, 37-45.
- Taylor, P., Dornan, J., Carrello, A., Minchin, R. F., Ratajczak, T., and Walkinshaw, M. D. (2001). Two structures of cyclophilin 40. Folding and fidelity in the TPR domains. *Structure* *9*, 431-438.
- Tenge, V. R., Zuehlke, A. D., Shrestha, N., and Johnson, J. L. (2015). The Hsp90 cochaperones Cpr6, Cpr7, and Cns1 interact with the intact ribosome. *Eukaryot. Cell* *14*, 55-63.

- Tesic, M., Marsh, J. A., Cullinan, S. B., and Gaber, R. F. (2003). Functional interactions between Hsp90 and the co-chaperones Cns1 and Cpr7 in *Saccharomyces cerevisiae*. *J. Biol. Chem.* *278*, 32692-32701.
- Uittenbogaard, A., and Smart, E. J. (2000). Palmitoylation of caveolin-1 is required for cholesterol binding, chaperone complex formation, and rapid transport of cholesterol to caveolae. *J. Biol. Chem.* *275*, 25595-25599.
- Uittenbogaard, A., Ying, Y., and Smart, E. J. (1998). Characterization of a cytosolic heat-shock protein-caveolin chaperone complex. Involvement in cholesterol trafficking. *J. Biol. Chem.* *273*, 6525-6532.
- Ward, B. K., Allan, R. K., Mok, D., Temple, S. E., Taylor, P., Dornan, J., Mark, P. J., Shaw, D. J., Kumar, P., Walkinshaw, M. D. et al. (2002). A structure-based mutational analysis of cyclophilin 40 identifies key residues in the core tetratricopeptide repeat domain that mediate binding to Hsp90. *J. Biol. Chem.* *277*, 40799-40809.
- Warth, R., Briand, P.-A., and Picard, D. (1997). Functional analysis of the yeast 40 kDa cyclophilin Cyp40 and its role for viability and steroid receptor regulation. *Biol. Chem.* *378*, 381-391.
- Weisman, R., Creanor, J., and Fantes, P. (1996). A multicopy suppressor of a cell cycle defect in *S. pombe* encodes a heat shock-inducible 40 kDa cyclophilin-like protein. *EMBO J.* *15*, 447-456.
- Whitesell, L., Sutphin, P. D., Pulcini, E. J., Martinez, J. D., and Cook, P. H. (1998). The physical association of multiple molecular chaperone proteins with mutant p53 is altered by geldanamycin, an hsp90-binding agent. *Mol. Cell. Biol.* *18*, 1517-1524.
- Xu, K., Lin, J. Y., and Nagy, P. D. (2014). The hop-like stress-induced protein 1 cochaperone is a novel cell-intrinsic restriction factor for mitochondrial tombusvirus replication. *J. Virol.* *88*, 9361-9378.
- Yao, G., Craven, M., Drinkwater, N., and Bradfield, C. A. (2004). Interaction networks in yeast define and enumerate the signaling steps of the vertebrate aryl hydrocarbon receptor. *PLoS Biol.* *2*, E65.
- Yau, W. L., Lambertz, U., Colineau, L., Pescher, P., MacDonald, A., Zander, D., Retzlaff, S., Eick, J., Reiner, N. E., Clos, J. et al. (2016). Phenotypic characterization of a *Leishmania donovani* cyclophilin 40 null mutant. *J. Eukaryot. Microbiol.* *63*, 823-833.
- Yau, W. L., Pescher, P., MacDonald, A., Hem, S., Zander, D., Retzlaff, S., Blisnick, T., Rotureau, B., Rosenqvist, H., Wiese, M. et al. (2014). The *Leishmania donovani* chaperone cyclophilin 40 is essential for intracellular infection independent of its stage-specific phosphorylation status. *Mol. Microbiol.* *93*, 80-97.
- Zuehlke, A. D., and Johnson, J. L. (2012). Chaperoning the chaperone: a role for the co-chaperone Cpr7 in modulating Hsp90 function in *Saccharomyces cerevisiae*. *Genetics* *191*, 805-814.
- Zuehlke, A. D., Wren, N., Tenge, V., and Johnson, J. L. (2013). Interaction of heat shock protein 90 and the co-chaperone Cpr6 with Ura2, a bifunctional enzyme required for pyrimidine biosynthesis. *J. Biol. Chem.* *288*, 27406-27414.