Hop/Sti1 FACTS & LITERATURE

(necessarily incomplete!)

Hop = p60 = Sti1 = Stip1 = Stress-inducible protein 1

General:

- Reviews:
  - General: Frydman and Höhfeld, 1997; Odunuga et al., 2004; Smith, 2004; da Fonseca et al., 2021; Schwarz et al., 2023
  - In neurodegeneration: Bohush et al., 2019.
  - For stress response, notably in plants: Toribio et al., 2020
  - Hsp90 complex in malaria (Shonhai et al., 2021).
  - Sti1/Hop as proteostatic switch (Bhattacharya and Picard, 2021).
  - Small molecules to disrupt Hop-Hsp90 interaction (Wang et al., 2021).
  - Hop in disease (Altinok et al., 2021).
- yeast Sti1 and mammalian Hop are 42% identical.
- upregulated by viral transformation (Honoré et al., 1992), in colon cancer (Kubota et al., 2010), HCC (Chen et al., 2017; Su et al., 2018), and pancreatic cancer (Jing et al., 2019).
- Localization: primarily cytoplasmic by IF (Lässle et al., 1997), but also in Golgi and vesicles (Honoré et al., 1992), and about 6% even on the cell surface (Martins et al., 1997; Zanata et al., 2002) or in the membrane fraction (Sakudo et al., 2005). Certain treatments including G1/S arrest (Longshaw et al., 2004) and heat-shock or treatment with leptomycin B promote more nuclear localization (Daniel et al., 2008). Recruited to stress granules along with Hsp90 and several other co-chaperones (Pare et al., 2009). Accumulates in the nucleus upon overexpression of PIAS1 and partially in PML bodies, and increased PIAS1 expression in glioblastoma cells correlates with that too (Soares et al., 2013). More nuclear HOP in *Arabidopsis* exposed to heat stress (Fernández-Bautista et al., 2018); salt stress induces more nuclear accumulation of HOP1/2 (and Hsp90 in a HOP1/2-dependent way) (Zhang et al., 2022).
- Plants have Hop, too (Zhang et al., 2003).
- By global analysis in yeast, the Hsp90 complex including Sti1 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 (Albanèse et al., 2006). Part of chaperone supercomplex with Hsp90 and Hsp70, based on integrated analysis of genetic and physical interactions (Rizzolo et al., 2017).
- differential presence of different domains across evolution (see Flom et al., 2007).
- Evolutionary plasticity of Hsp90 and cochaperones (Johnson and Brown, 2009).
- Present in exosomes (Cruz et al., 2017).

Genetics in budding yeast (*S. cerevisiae*):

- Discovery with ts and cs phenotype of Δ*sti1* (Nicolet and Craig, 1989).
- Synthetic lethality and allele-specific complementation between *HSP90* and *STI1* (Chang et al., 1997), and synthetic lethality with Δ*cpr7* (Duina et al., 1996), *mps1-*

1 (Jones et al., 1999), Δ*sse1* (Liu et al., 1999b), *cdc37-34* (Abbas-Terki et al., 2002) and *cdc37*^{S14A} (Caplan et al., 2007). GR hormonal response and v-Src activity impaired in Δ*sti1* (Chang et al., 1997; Carrigan et al., 2004). Synthetic growth defects at 18°C and 37°C in Δ*sti1* Δ*sba1* (Fang et al., 1998). Δ*sti1* strain is hypersensitive to Hsp90 inhibitors (Liu et al., 1999b; Piper et al., 2003; Zhao et al., 2005; Parsons et al., 2006). Synthetic lethal screen yields *HSC82*, *CPR7*, *YDJ1*, *SSL2*, and *UTP21* (Flom et al., 2005). Synthetic interaction with mutations in *TOM20* and *MIM1* (Hoseini et al., 2016). Altered mitochondrial morphology at 37°C (Hoseini et al., 2016). Series of temperature-sensitive mutations in M domain of Hsp82, which are defective for interaction with Hsp70, are synthetic lethal with Δ*sti1* (Kravats et al., 2018). Δ*sti1* synthetically sick with Δ*emc2* and *STI1* overexpression fails to suppress sensitivity to Hsp90 inhibitor in Δ*emc2* background (Kudze et al., 2018). Δ*sti1* causes large decrease in Hsp90 "availability" and activates HSR (Alford and Brandman, 2018). Extensive analysis of genetic interactions between Δ*sti1* and deletions of other co-chaperones genes and their effects on model clients (Biebl et al., 2020).

- Sti1 overexpression cannot suppress lethality of Δ*cns1* (Dolinski et al., 1998; Marsh et al., 1998) and Cns1 cannot suppress synthetic lethality of Δ*sti1 hsp82* (Dolinski et al., 1998) in budding yeast.
- Sti1 overexpression weakly suppresses *{PSI*$^{+}$*}* (prion) phenotype in yeast, notably with a particular *ssa1* allele (Kryndushkin et al., 2002; Jones et al., 2004). Deletion improves it; effects are through Hsp70 (Jones et al., 2004). Deletion impairs Hsp104-mediated elimination of prions (Moosavi et al., 2010; Reidy and Masison, 2010; Gorkovskiy et al., 2017), and both TPR domains and Hsp90 interaction are required for curing (Reidy and Masison, 2010); Sti1 is also required for allowing overexpression of ubiquitin to promote the curing. Overexpression suppresses Htt103Q- and Rnq1-induced toxicity and growth defects by promoting formation of larger foci; loss of Sti1 has the opposite effect (Wolfe et al., 2013). Required for suppression of Htt103Q toxicity by Cbk1 and Pop2 (Wolfe et al., 2014). Δ*sti1* normal for the propagation of *{PSI*$^{+}$*}* and *{URE3}* prions (Kumar et al., 2015).
- A Δ*sti1* budding yeast strain is defective in pheromone signaling, Ste11 kinase activity, and Hsp90 and Cdc37 loading onto Ste11; these defects (but not v-Src function) can all be suppressed by Cdc37 overexpression (Lee et al., 2004). Also defective in vertebrate AhR signaling (Yao et al., 2004).
- A *tpk2* ts allele is synthetically lethal with Δ*sti1*, but can be partially rescued by a dominant *CDC37* mutation (Ren et al., 2007).
- Hop, and other TRP-containing proteins, fished out in a 2-hybrid with the Hsc70 substrate binding domain (Liu et al., 1999a).
- A Δ*sti1* yeast strain is defective for for glucocorticoid receptor signaling and this can be complemented with human Hop (Carrigan et al., 2004; Nelson et al., 2004; Röhl et al., 2015a).
- Sti1 not required for folding of VHL but for degradation of misfolded VHL in yeast (McClellan et al., 2005).
- Sti1 domain requirements for Hsp70-mediated functions (prion suppression), Hsp90-mediated ones (drug sensitivity), and ones that depend on both (substrate maturation) are different (Song and Masison, 2005).
- Complementation of Δ*ydj1* Δ*sti1* synthetic lethality with Sti1 mutants correlates with resistance to radicicol and support of GR function (Flom et al., 2006). TPR1 and DP1 domains not required for viability but for GR function (Flom et al., 2007).

- Hsc82 G309S mutant particularly dependent on Sti1 to mediate interaction with Hsp70 (Flom et al., 2007).
- Sti1 is required for rapid galactose induction, possibly for removal of nucleosomes at target promoters (Floer et al., 2008).
- Sti1 required for maturation and activation of the maltose-inducible transcription factor Mal63 (Ran et al., 2008).
- Partitioning of misfolded proteins between JUNQ and IPOD depends on Sti1; misfolded VHL is directed to IPOD in Δ*sti1* (Kaganovich et al., 2008).
- Δ*sti1* strains are hypersensitive to molybdate (Millson et al., 2009).
- Δ*sti1* are defective for mitochondrial import of some precursor proteins, notably at elevated temperature (Hoseini et al., 2016).
- Sti1 is differentially required for the activity of exogenous clients in budding yeast (Sahasrabudhe et al., 2017).
- Two clusters of Hsp82 point mutants lead to restrictive Sti1-dependence; inverse correlation between Hsp70-binding and Sti1-dependence; these results are consistent with Sti1 promoting recruitment of client-loaded Hsp70 and client transfer through a conformational change of Hsp90 favoring N-terminal closure (Reidy et al., 2018).
- Sti1 mitigates protein burden, Δ*sti1* promotes it as well as protein aggregation (Farkas et al., 2018).
- *STI1* is required for K48-ubiquitination-mediated degradation of cytoplasmic proteins, but not K11-ubiquitination-mediated degradation of nuclear proteins (Samant et al., 2018).
- Comprehensive analysis of co-chaperone double mutants in budding yeast for growth and specific clients (Biebl et al., 2020). Sti1 forms an epistatic module with Cns1 and Cpr7; reduced Cdc37 is particularly deleterious for v-Src in Δ*sti1* strain; for some kinases Sti1 may be able to partially replace Cdc37; Δ*sti1* further increases aggregation of Hsp90 client eEF2 in Δ*cpr7* strain (Biebl et al., 2020).
- Required for the formation of "Hsp70/90/104 and proteasome-dependent heat-induced inclusions" (HAPIs), linking protein folding and degradation (Eisele et al., 2021).
- Synthetic lethality between Δ*sti1* and *ssa1* point mutants in NBD (Ssa1 as sole Hsp70), potentially because these mutants interact with Ydj1 more strongly at the expense of Hsp90, resulting in issues for Hsp90 clients (Gaur et al., 2022).
- Deletions of *HSP82* or *HSC82* exacerbate toxicity of mammalian Nrf2 (Ngo et al., 2022).
- Deletion of *STI1* strongly affects loading and closing mutants of Hsp90 (Mercier et al., 2023).

Genetics in other organisms:

- Sti1 overexpression suppresses *cut4* mutants in *S. pombe* (Cut4 is a component of the cyclosome) (Yamashita et al., 1996).
- <u>*C. elegans*</u>: knock-down in an *hsf1* mutant leads to sterility (defects in gonadal development) (Gaiser et al., 2009), and a *sti1* null mutant has decreased fertility, a shortened lifespan and an impaired heat stress response (Song et al., 2009). Knock-down aggravates protein aggregation toxicity of Aβ42, but has no effect on lifespan (Brehme et al., 2014). Hsp90 and its co-chaperones Aha1, Hop, and p23 are required for muscle integrity and motility in a unc45 mutant background

(Frumkin et al., 2014). Mutations of *sti-1* (or *hsp-90* or other co-chaperone genes suppress the neurite growth defect of mutations of *mec-15*, which encodes an F-box protein targeting the Hsp90 client DLK-1; *pph-5* mutations have the same effect, probably because PP5 removes inhibitory phosphates from several serines (S240, 254 and 289) on Sti-1 (Zheng et al., 2020). Overexpression of STI1 protects it against toxicity of Aβ peptide (Lackie et al., 2020a).

- Maternal Hop is important for canalization in *Drosophila* by preventing transposon expression through a complex with Piwi and Hsp90 (Gangaraju et al., 2011). Loss of function of Hop is viable and enhances tau toxicity in fly model (Ambegaokar and Jackson, 2011). Required in germ line nurse cells to allow piRNA biogenesis and transposon silencing (Karam et al., 2017; see also Cappucci et al., 2019). KD in *Drosophila* reduces polyQ protein aggregation and toxicity (Xu et al., 2019).
- Mouse: *stip1*-KO is embryonically lethal at day 10; Hsp90 clients are reduced by 50%, and even MEFs cannot be maintained in culture; heterozygotes display increased cellular stress and are more sensitive to cerebral ischemia (Beraldo et al., 2013). Heterozygote astrocytes are hypersensitive to irradiation (Soares et al., 2013), hyperactive and show signs of attention deficits (Beraldo et al., 2015). In contrast, overexpression does not lead to a behavioral phenotype (Beraldo et al., 2015). A hypomorph (ΔTPR1), which poorly accumulates, has high mortality after birth, reduced GR and GRK2 levels, and age-dependent hippocampal neurodegeneration (Lackie et al., 2020b). Overexpression worsens Aβ accumulation and AD plaque formation (Lackie et al., 2020a). Hypomorphic mutant has less α-synuclein inclusions and phenotypic effects in α-synuclein-overexpressing strain (Lackie et al., 2022). Vicious cycle where α-synuclein induces Hop expression, which in turn promotes the formation of toxic α-synuclein conformers (Lackie et al., 2022).
- Essential in *Leishmania donovani*; overexpression of radicicol-resistant point mutant allows the demonstration that Hsp90 is required at multiple life stages and that growth is improved by mutation to canonical MEEVD and Sti1 interaction is important (Hombach et al., 2013).
- KD in *Trypanosoma brucei* or KO of one allele in *T. cruzi* does not affect growth, but the latter impairs differentiation (Schmidt et al., 2018).
- *hop3* loss-of-function mutant of *Arabidopsis thaliana* shows reduced pollen germination, hypersensitivity to ER stress (Fernández-Bautista et al., 2017), and to pathogens because of impact on jasmonic acid receptor COI1 (Muñoz et al., 2021).
- *Arabidopsis hop1 hop2 hop3* triple mutant is defective for long-term thermotolerance (Fernández-Bautista et al., 2018) and auxin signaling (Muñoz et al., 2022). *hop1 hop2* double mutant is hypersensitive to salt stress by affecting nuclear accumulation of Hsp90 and brassinosteroid signaling (Zhang et al., 2022). Triple *hop* mutant has defects in GA signaling with predominant function of HOP2 and HOP3 (Mangano et al., 2023).

Other *in vivo* analyses:

- Overexpression and antibody injections in Xenopus oocytes: anti-Hop delays attenuation of Hsf1 activity; attenuation accelerated by Hop overexpression (Bharadwaj et al., 1999).
- Drug sensitivity: Δ*sti1* and even more so Δ*sse1* Δ*sti1* yeast strains are hypersensitive to Hsp90 drugs (Liu et al., 1999b; Piper et al., 2003; see also Song

and Masison, 2005). Δ*sti1* strains are hypersensitive to the induction of aneuploidy by Hsp90 inhibitors and *STI1* overexpression increases resistance (Chen et al., 2012).

- Antibodies inhibit import into lysosomes *in vitro* (Agarraberes and Dice, 2001).
- Overexpression of Hop partially inhibits glucocorticoid receptor function (Brychzy et al., 2003).
- Promotes sequential triage of ricin catalytic A chain from Hsc70 system to Hsp90-CHIP thereby protecting cells (Spooner et al., 2008).
- Hop knock-down in mouse ES cells reduces Stat3 and impairs embryoid body formation (Longshaw et al., 2009).
- see below for use of novel inhibitors of interaction with Hsp90.
- Nitrosylation or knock-down improves CFTR ΔF508 maturation (Marozkina et al., 2010). Hop is part of a quality control system for misfolded membrane proteins (Okiyoneda et al., 2010).
- Overexpression promotes expression of USP2 in transgenic silk worms (Hong et al., 2010).
- Knock-down reduces expression of MMP-2 and several other Hsp90 client protein and invasion of pancreatic cancer cells (Walsh et al., 2011). Also reduces polarization and migration of endothelial cells (Li et al., 2012).
- Knock-down of Hop leads to decrease in RhoC GTPase, cell migration (Willmer et al., 2013), and to increased nuclear actin and reduced F-actin (Beckley et al., 2020).
- Knock-down reduces and overexpression augments levels of the KCNQ4 potassium channel (Gao et al., 2013).
- Upregulated in ischemic brains, possibly because it promotes proliferation, migration and recruitment of bone marrow derived cells (Lee et al., 2013).
- Sti1p through its TPR1 domain acts as restriction factor for the replication of Carnation Italian ringspot tombusvirus in yeast and plants (Xu et al., 2014).
- Overexpression in tomato protoplasts reduces cytosolic accumulation of some chloroplast precursor proteins (Tillmann et al., 2015).
- KD impairs superoxide production by Nox5 (Chen et al., 2015).
- KD impairs maturation of CLC-1 (Peng et al., 2016).
- Knock-down in tomato stabilizes HsfB1 (Röth et al., 2017).
- Overexpressed and secreted in hepatocellular carcinoma patients (Chen et al., 2017; Su et al., 2018); higher levels in serum of patients with ovarian cancer (Tsai et al., 2012) and gastric cancer (Zhai et al., 2018a).
- Knock-down in tobacco displays mild growth retardation and selectively affects some PAMPs (e.g. CERK1 but not FLS2); renders tobacco tolerant to potato virus Y; Hop associates with viral replication complexes (Lamm et al., 2017).
- Overexpression promotes and KD prevents expression of mesenchymal markers upon heat-shock, through effects on Snail1 nuclear localization; KD also reduces metastatic potential of HCC in xenograft experiments (Su et al., 2018).
- Hop KD blocks Hsp90-promoted release of exosomes, possibly by failing to maintain Hsp90 in open conformation and to maintain its membrane deformation activity (Lauwers et al., 2018).
- KD in honeybee reduces mRNA levels of antioxidation-related genes (Zhai et al., 2018b).
- KD reduces emerin protein levels, which is associated with a deformation and size reduction of the nucleus (Kituyi and Edkins, 2018).

- Overexpression of honeybee *STIP1* in *E. coli* confers some protection against oxidative stress and STIP1 protein *in vitro* protects DNA from hydroxyl radicals (Zhai et al., 2018b).
- For CTA1 ER-cytosol translocation, Hsc70 and Hsp90 independently play complementary roles, independently of Hop (Burress et al., 2019).
- KD reduces migration and invasion of pancreatic cancer cell lines (Jing et al., 2019).
- Overexpressed in glioma, and knock-down in glioma cell lines reduces proliferation and invasion, and increases apoptosis (Yin et al., 2019).
- Preference for Hsp70-like protein (HSPA1L) over Hsp70 does not explain opposing effects of these Hsp70 proteins on some substrates (Serlidaki et al., 2020).
- Overexpression of *Triticum aestivum TaSTI-2A* in rice improves stress tolerance and in yield and stress tolerance in *Arabidopsis* (Meena et al., 2020).
- Knock-down reduces levels of Hsf1 (Ruckova et al., 2012; Chakraborty and Edkins, 2020) and activity at multiple levels, and reduces viability under basal and heat-stressed conditions (Chakraborty and Edkins, 2020).
- Overexpression in mammalian neurons protects against toxicity of Aβ peptide, mainly through action of extracellular Hop (Lackie et al., 2020a).
- Hop KO in human cell lines reveals that Hop promotes shift of proteostasis from folding to degradation; KOs more resistant to heat and other stresses, but more sensitive to Hsp90 inhibitors; folding and anti-aggregation activities work even better, dependent on direct interaction of Hsc70/Hsp70 with Hsp90; vast majority of clients not affected with GR, v-Src, and proteasome as notable exceptions; proteasome activity reduced, but not levels of components, possibly because docking of lid is impaired (Bhattacharya et al., 2020).
- In concert with Hsp90, Hop/Sti1 modulates TDP-43 misfolding, aggregation, and toxicity in yeast, mammalian cells and embryos (Lin et al., 2021).
- Hop KD reduces accumulation of C/EBPβ in HL-60 cells (Qi et al., 2021).
- Upon heat shock, induced Hsp70 in *Drosophila* ovaries/testes interacts with Hsp90 complex, which displaces Ago3, Hop, Hsp90 to lysosomes and results in the disruption of piRNA loading and increased steady-state levels of RNA from transposable elements (Cappucci et al., 2019).
- Y134 and Y152 mutants are destabilized, promote JAK2 activity less well, are less secreted, reduce cell viability and resistance; also phenocopied with the use of cell-penetrating wt peptides (Chao et al., 2022).
- Mutations of Y354 reduce accumulation of GR and v-Src, and v-Src activity in mammalian cells (Castelli et al., 2023).
- Overexpression in rat cardiocytes promotes transition of connexin Cx43 from Hsp70 to Hsp90 and inhibits ubiquitination, and this is offset by Hsp90 KD (An et al., 2023).
- Overexpression or KD of Hop in wheat promotes and reduces, respectively, tolerance to drought, salt, and heat stress (Wang et al., 2023).

Biochemistry:

- Methodological reviews: Buchner et al., 1998
- dimeric (Bose et al., 1996; Prodromou et al., 1999; Hildenbrand et al., 2011) or rather monomeric (Yi et al., 2010; Li et al., 2011). Monomeric, dimer being very weak (Southworth and Agard, 2011). Hop monomer can bind Hsp90 dimer

whereas FKBP52 can also bind Hsp90 monomer (Ebong et al., 2011). Hop from *Plasmodium* may form dimers (Zininga et al., 2015; Silva et al., 2020), or only monomers under carefully controlled conditions and by biophysical analyses (Makumire et al., 2020).

- heat-shock -> changes in isoform composition (Lässle et al., 1997).
- casein kinase II, pp90^{rsk} , and cell cycle kinases phosphorylate mouse Hop *in vitro* (Lässle et al., 1997; Longshaw et al., 2000). Phosphorylation sites modulate nuclear localization (Longshaw et al., 2004). Further study on *in vivo* phosphorylation (Daniel et al., 2008). Sites identified by phosphoproteome analysis in *Leishmania*, some of which are essential for viability (Morales et al., 2010). Hyperphosporylated by a PIKK kinase in response to DNA damage (Quanz et al., 2012).
- Tyrosine 134 and 152 are phosphorylated by JAK2; mutants are destabilized, promote JAK2 activity less well, are less secreted, reduce cell viability and resistance; also phenocopied with the use of cell-penetrating wt peptides (Chao et al., 2022).
- Phosphorylation of tyrosine 354 between TPR2A and TPR2B may control open and closed states; analyses by molecular dynamics and co-IPs show that phosphorylation or mutation favor a closed state, which reduces Hsp70/Hsp90 binding; mutations reduce accumulation of GR and v-Src, and v-Src activity in mammalian cells (Castelli et al., 2023).
- all of Hop in reticulocyte lysates is immunoadsorbed with Hsp90 (Silverstein et al., 1999).
- Crystal structure of N-terminal and central TPR domains with bound EEVD-containing peptides (Scheufler et al., 2000). Central grooves form a "two-carboxylate clamp" structure that contacts the C-terminal Asp. Structure of TPR2A with non-cognate Hsp70 ligand (Kajander et al., 2009). Structure of TPR2A-TPR2B with Hsp90 peptide (Schmid et al., 2012). Solution structure of TPR2A and with a small molecule inhibitor (Darby et al., 2020).
- Cryo-EM structure of GR loading complex shows that Hop wraps around, makes extensive contacts with Hsp90 and also interacts directly with GR (Wang et al., 2022).
- Cleaved by granzyme B, but this does not contribute to apoptosis while sensitizing cells to irradiation (Bredemeyer et al., 2006).
- enhances reconstitution of functional Chk1 with Hsp90, Hsp70, Hsp40, Cdc37 and CK2 (Arlander et al., 2006; Felts et al., 2007).
- *C. elegans* Hop lacks TPR1 domain, but interacts both with Hsp70 and Hsp90 competitively (Gaiser et al., 2009; Song et al., 2009).
- Hsp90 required for maintenance under heat stress and for refolding in collaboration with Hop-Hsp70 (Walerych et al., 2009).
- Hop can be nitrosylated (Marozkina et al., 2010).
- Screen with protein arrays reveals Sti1 as a potential RNA binding protein that binds mRNAs encoding proteins enriched in GO terms suggesting they act in telomere maintenance and DNA recombination (Scherrer et al., 2010).
- NMR structure of DP domains (Schmid et al., 2012).
- Phosphorylation of serine just N-terminal of MEEVD of Hsp90 reduces and favors binding to CHIP and HOP, respectively, tilting the balance between degradation and chaperoning; mimicked by point mutations (Muller et al., 2013).

- Binds and hydrolyzes ATP through TPR1-DP1-TPR2A portion (Yamamoto et al., 2014).
- Phosphorylation of Hop or yeast Sti1 reduces binding to Hsp70 and GR activity *in vivo* in yeast (Röhl et al., 2015a).
- Homology modelling of *Plasmodium* Hop shows that the convex surface of TPR2 is considerably less conserved (Hatherley et al., 2015).
- Hsp70 may initially bind to TPR1 in an open conformation before transferring to TPR2B upon Sti1 binding to Hsp90, thereby promoting client transfer (Röhl et al., 2015b).
- In a purified fly system, the chaperone complex consisting of Hsp83, Hsc70, Hop, p23 and Droj2 promotes RNA loading into Ago2 by increasing the dwell time of the Dicer-R2D2-siRNA complex on Ago2; this depends on the 5'-phosphate of the guide strand and on the ATPase of both Hsc70 and Hsp83 (Iwasaki et al., 2015). Also required for the Dicer-independent loading of duplex RNA in the human system (Naruse et al., 2018).
- Relatively poorly conserved Hop of *Leishmania braziliensis* also binds Hsp90 and inhibits its ATPase (Batista et al., 2016).
- Binding to Hsp70, but not Hsc70, is stimulated upon stress by ADR1-mediated acetylation of Hsp70 on K77 (Seo et al., 2016).
- Yeast Sti1 is differentially required for assembly of GR vs. MR HBD complexes *in vitro* (Sahasrabudhe et al., 2017).
- Luciferase refolding with yeast proteins requires Sti1 and is defective for Hsp70-binding mutants of Hsp82 (Kravats et al., 2018).
- Refolding of luciferase *in vitro* and *in vivo*, both in yeast and human cells, works better without Hop/Sti1, dependent on direct interaction of Hsp90 and Hsp70 (Bhattacharya et al., 2020).
- Overexpression of honeybee *STIP1* in *E. coli* confers some protection against oxidative stress and STIP1 protein *in vitro* protects DNA from hydroxyl radicals (Zhai et al., 2018b).
- Biophysical and structural characterization of *Sorghum* Hop (Adão et al., 2019).
- Handover of p53 from Hsp70 and folding to native state requires Hop *in vitro* (Dahiya et al., 2019).

Complexes:

- Mutual competition for Hsp90 binding with Cyp40 and FKBP52 (Owens-Grillo et al., 1996; see also Chang et al., 1997). But there is evidence for Hsp90-FKBP52-Hop and Hsp90-FKBP52-p23-Hop complexes (Hildenbrand et al., 2011). Moreover, mixed Sti/Hop-PPIase-Hsp90 complexes are a favored intermediate and Sti/Hop displacement requires ATP and p23 (Li et al., 2011). Despite mixed complexes, FKBPs clearly compete with Hop (Ebong et al., 2016).
- Hop holds Hsp70 and Hsp90 together in a tripartite complex (Chen et al., 1996).
- Hop may be ADP/ATP exchange factor for Hsc70 (Gross and Hessefort, 1996), but others see only binding to ADP-bound Hsp70 (Johnson et al., 1998); Hsp40 stimulates Hsp70 binding to Hop by stimulating conversion to Hsp70•ADP (Hernández et al., 2002).
- Hop unable to bind Hsp70 in the presence of misfolded substrates unless Hip is present ; dominant-negative Hip blocks this (Prapapanich et al., 1998).
- Hop binds ADP-bound form of Hsp90 and blocks its ATP-dependent conversion to p23-binding form (Johnson et al., 1998), except if Hop is also bound to Hsp70 (Hernández et al., 2002). Hop can bind both open and closed states of Hsp90β; its interaction with the C-terminal domain induces a conformational change between the Hsp90β monomers (Lott et al., 2020).
- Stoichiometry: Hop dimer binds two molecules of Hsp70 in the absence of Hsp90, but only one in the ternary complex (Hernández et al., 2002). One molecule of Hop binds Hsp90β dimer (Lott et al., 2020).
- Hop binds C-terminal domain of Hsp70s that is distinct from substrate binding site -> can form ternary complexes with substrate; binding of Hop to Hsc70 inhibited by Hap46 even though the latter binds the ATPase domain of Hsc70 -> steric hindrance between the two even though they bind separate sites (Gebauer et al., 1998b).
- Two molecules of Hop can bind Hsp90 dimer independently, but asymmetric trimer may be the favored form *in vivo* (Southworth and Agard, 2011). Cryo-EM structure of GR-Hsp90-Hsp70-Hop (Kirschke et al., 2014). Several structures indicating substrate (GR LBD) transfer from Hsp70 to Hsp90 machinery, highlighting notably that GR binds Hsp90 dimer opposite of Hop (Alvira et al., 2014).
- Yeast Sti1 specifically stimulates ATPase activity of yeast Ssa1 (yeast Hsp70) 200-fold (Wegele et al., 2003).
- Hop binds CCT and stimulates its nucleotide exchange but blocks its refolding activity (Gebauer et al., 1998a).
- Sti1 (yeast Hop) binds N-terminal domain of Hsp82 and blocks access to ATP; antagonized by Cpr6 (Prodromou et al., 1999). Hop does not affect rate of ATPase of human Hsp90, but inhibits the substrate-stimulated rate (McLaughlin et al., 2002). Sti1 blocks ATPase of yeast Hsp90 but not nucleotide binding, probably by blocking N-terminal dimerization of Hsp90 (Richter et al., 2003). Blocks earliest conformational changes after ATP binding and involving ATPase lid (Hessling et al., 2009). Also blocks C-terminal opening of Hsp90 (Ratzke et al., 2010). EM analysis shows that the TPR1 domain of a single Hop molecule can sterically block Hsp90 N-terminal dimerization by being situated between the Hsp90 monomers and interacting with the adjacent N-terminal/middle domains; nevertheless, the TPR1 domain remains available for Hsp70 (Southworth and Agard, 2011).
- Full-length Sti1 blocks interaction of Hsp90 with Aha1 (Lotz et al., 2003).

- Sti1 binds to Hsp82 dimer as dimer and induces a large conformational change (Prodromou et al., 1999).
- There are multiple distinct binding determinants on Hsp90 for PP5 and FKBP52 versus Hop, but C-terminal MEEVD necessary under most conditions (Chen et al., 1998; Carrello et al., 1999; Ramsey et al., 2000). Determinants of EEVD containing ligands of Hsp70 and Hsp90 characterized in detail: MEEVD necessary and sufficient to bind TPR2A; additional contacts help in the case of Hsp70; differential requirements for individual amino acid positions (Brinker et al., 2002). Affinity of for entire Hsp90 considerably higher than for MEEVD alone (Hernández et al., 2002). Extreme N-terminus required for high affinity binding of Sti1 but not Cpr6 (Richter et al., 2003). Additional contacts in C-terminal and middle domains of Hsp90 (Onuoha et al., 2008).
- Hsp90 - yeast cyclophilin or Sti1 binding constants 14-57 nM; measured with Hsp90 on BiaCore chip (Mayr et al., 2000). Affinity of Sti1 for Ssa1 (yeast Hsp70) is 7.5 and 3 µM without and with ATP, respectively (Wegele et al., 2003).
- Binding constants for Hsp90 and Hsp70 are 90 nM and 1.3 µM, respectively, but the latter affinity increases to 250 nM in the ternary complex (Hernández et al., 2002).
- in complexes with Harc (Scholz et al., 2001) through Hsp90 or Hsp70 (Cartledge et al., 2007).
- Binds Hsp104 in respiring yeast and directly *in vitro* (Abbas-Terki et al., 2001). This interaction is strongly inhibited by Ssd1, which is required for Hsp104 oligomerization and function (Mir et al., 2009).
- binds and recruits PrP^c on the cell surface; interaction maps to short peptide (Zanata et al., 2002). PrP^c in stimulating SOD activity (Sakudo et al., 2005).
- part of a multichaperone complex with Tom70-directed mitochondrial precursors (Young et al., 2003; Bhangoo et al., 2007), also in budding yeast (Hoseini et al., 2016). Yeast Sti1 interacts with Tom20 and Tom70 (Hoseini et al., 2016).
- in OCA-S coactivator complex with GAPDH (Zheng et al., 2003).
- Direct interaction of yeast Sti1 with Cdc37 (Abbas-Terki et al., 2002), and 2-hybrid interaction with *C. albicans* Cdc37 (Ni et al., 2004). Direct interaction of Hop with Cdc37 (Harst et al., 2005).
- Two-hybrid interaction with Crk1 of *Candida albicans* (Ni et al., 2004).
- Interleukin-1 receptor-associated kinase 1 (De Nardo et al., 2005).
- Competes with Aha1 (Harst et al., 2005; Sun et al., 2012), p23 and Cdc37 for binding to Hsp90 (Harst et al., 2005), and yet, complexes with Hsp90-FKBP52-p23-Hop seem to form (Hildenbrand et al., 2011).
- Potassium channel HERG, possibly during trafficking (Walker et al., 2007).
- no Hsp90α/Hsp90β-isoform specific interactions with a number of cochaperones (p23, immunophilins, Hip, Hop, Hsp70) and substrates detected (Taherian et al., 2008). None either *in vitro* (Chadli et al., 2008).
- in mature complex of Mal63 with Hsp70 and Hsp90 (Ran et al., 2008).
- The S100 family proteins S100A2 and S100A6 bind TPR domains in Ca^{2+}-dependent fashion competing with Hsp90 and Hsp70 (Shimamoto et al., 2008).
- Coimmunoprecipitates (along with Hsp90) with Stat3 (Longshaw et al., 2009).
- Inhibitor screens to block interaction with Hsp90 (Yi et al., 2009). Small molecules (Yi and Regan, 2008) and modified TPR modules (Cortajarena et al., 2008) block it *in vitro* and *in vivo*. Cell-permeable hybrid TPR peptide specifically inhibits interaction with Hop and affects Hsp90 clients and cell growth (Horibe et al., 2011).

Compound that blocks interaction between Hop and Hsp90 but does not induce Hsp70 (Pimienta et al., 2011). NMR-directed design of small molecule inhibitor (Darby et al., 2020). Peptides that inhibit TPR2A-Hsp90 interaction *in vitro* (Vaaltyn et al., 2022).

- PAMP receptor OsCERK1 in rice along with Hsp90; interact at endoplasmic reticulum and required for transport to membrane upon interaction with OsRac1 (Chen et al., 2010).
- Sse1 and Sse2 as part of an early quality control step with Hsp70 (Mandal et al., 2010).
- Piwi in *Drosophila* (Gangaraju et al., 2011).
- Co-IPs with MMP-2 from conditioned medium (Walsh et al., 2011).
- PP5 pulls out Hop in TPR-dependent fashion, possibly indirect (Skarra et al., 2011).
- Blocks methylation of Hsp90 by SMYD2 (Abu-Farha et al., 2011).
- Toc64-dependent chloroplast precursor proteins (Fellerer et al., 2011), and Tom34-containing Hsp90 complex for mitochondrial Tom70 pathway (Faou and Hoogenraad, 2012).
- Interacts with tubulin in TPR2a-independent way (Li et al., 2012).
- In Hsp90-Hsp70 complexes with KCNQ4 (Gao et al., 2013).
- Colocalizes with purinosomes (French et al., 2013).
- thiazide-sensitive NaCl cotransporter NCC (SLC12A3) (Donnelly et al., 2013).
- Interacts with E3 SUMO ligase PIAS1 and gets sumoylated by it (Soares et al., 2013).
- Direct interaction with Rho GTPase Rnd1 affects Rnd1 functions in cytoskeleton retraction and neurite outgrowth (de Souza et al., 2014).
- Replication proteins of Carnation Italian ringspot tombusvirus (Xu et al., 2014).
- L protein of human respiratory syncytial virus along with Hsp90 (Munday et al., 2015).
- PKM2 complex with Hsp90-Hop-p23 stabilizes mutant EGFR (Yang et al., 2015).
- In complexes with CLC-1 with Hsp90β (Peng et al., 2016).
- Associates with JAK2 through N-terminus and links it to Hsp90 (Tsai et al., 2016).
- Interacts along with Hsp90 with Cdk1 and EZH2 to stabilize complex (Göllner et al., 2017).
- HOP3 of *Arabidopsis thaliana* interacts with HSP90.1, HSP70 and unexpectedly also with BiP through its ATPase domain (Fernández-Bautista et al., 2017).
- Binds the activin A receptor type II-like kinase 2 (ALK2) and promotes SMAD signaling in ovarian cancer cells (Tsai et al., 2012).
- Acts as scaffold for GSK3β and LSD1 (perhaps with Hsp90), and promotes the phosphorylation of the latter by the former (Tsai et al., 2018). According to another study, only p23 and Aha1, but not Hop interact with GSK3β (Tang et al., 2022).
- *S. cerevisiae:* protein burden affects Sti1 interactome (Farkas et al., 2018).
- Emerin, possibly not simultaneously with Hsp90 (Kituyi and Edkins, 2018).
- TAP purification of Sti1 interactors from *C. albicans* (O'Meara et al., 2019).
- Mouse Stip1 directly interacts with actin (Beckley et al., 2020).
- Hop interactions with cellular proteins, including many proteasomal proteins, largely dependent on interaction with Hsp90-Hsp70, i.e. formation of ternary complex (Bhattacharya et al., 2020).
- Co-IPs with C/EBPβ (Qi et al., 2021).

- Hop is an integral part of the Hsp90 "epichaperome" (integrated Hsp90-centered proteome hubs) of certain types of cancer (Rodina et al., 2016). Alzheimer's disease-related stressors switch chaperome into epichaperome, also containing Hop (Inda et al., 2020).
- HOP3 interacts with jasmonic acid receptor "coronatine insensitive 1" (COI1) protein (Muñoz et al., 2021), and with TIR1 in a complex that also contains Hsp90 and SGT1b (Muñoz et al., 2022).
- Interacts directly with α-synuclein through TRP2A, and *in vivo* colocalizes with phosphorylated α-synuclein filaments (Lackie et al., 2022).
- HOP2 and HOP3 interact the the E3 ligase in plants (Mangano et al., 2023).
- Wheat Hsp TaHSP17.4 interacts with Hop (Wang et al., 2023).

Hop chaperone?

- no activity *in vitro* (Bose et al., 1996; Freeman et al., 1996).
- absolutely required for assembly of GR-Hsp90 complexes *in vitro* (Dittmar et al., 1996).
- Hop stimulates refolding by Hsp70+Ydj1 (Johnson et al., 1998). Hop has no effect on ATP and substrate binding of Hsc70, but interferes with protein refolding (Gebauer et al., 1998b).
- Hop functions as an adaptor that directs Hsp90 to preexisting Hsp70-PR complexes (Chen and Smith, 1998).
- a combination of Hsp90, Hsc70, and co-chaperones is required for DNA binding ability of EcR/USP heterodimer *in vitro* (not for hormone binding) (Arbeitman and Hogness, 2000.
- Hop may (Morishima et al., 2000) or may not (Rajapandi et al., 2000) accelerate rate of formation of GR-Hsp90 complexes.
- Promotes an Hsp90 NM domain rotation and thus an interaction of Hsp70 and Hsp90 ATPase domains, and subsequent recovery of Hsp70-mediated block of ligand binding of GR (Kirschke et al., 2014).
- Hsp90 inhibitor GA arrests GR-Hsp90 assembly at intermediate state with Hop (see Whitesell and Cook, 1996; Kirschke et al., 2014).
- Assembly of GR HBD complexes with *C. elegans* and human proteins, including Hop, reveals cooperativity, and unexpected disruptive effects of p23 and Hop (Kaziales et al., 2020).
- Hop remodels Hsp70-Hsp40-GR LBD complex for client transfer to Hsp90: Interaction of Hop TPR2B with middle domain of Hsp90 may stall client loading complex by inhibiting Hsp90 ATPase, and the shift of Hsp70 binding to TPR2B may release it to support further client processing; release of Hsp70 dependent on TPR1, possibly as exit site after client transfer and arrival of p23; when p23 enters the complex, which still contains Hop, the interplay between Hop DP2, p23 (including direct contacts between DP2 and p23), and the client releases TPR2B from the Hsp90 middle domain, enabling Hsp90 closure (Dahiya et al., 2022).

Mapping of Hop domains:

- N-terminal TPR region (TPR1) binds Hsp70 (Chen et al., 1996; Lässle et al., 1997; Chen and Smith, 1998; van Der Spuy et al., 2000) and Hsp104 (Abbas-Terki et al., 2001); central TPR-containing region (TPR2A) binds Hsp90 (Chen et al., 1996;

Chen and Smith, 1998). The former binds C-terminal heptapeptide with EEVD of Hsp70, the latter the pentapeptide MEEVD of Hsp90 (Scheufler et al., 2000).

- Mutations in C-terminal DP (DP2) motif disrupt interaction with Hsp70 perhaps by perturbing some interdomain interaction (Chen and Smith, 1998) or structural integrity (Nelson et al., 2003) (see also Carrigan et al., 2004). Not seen by others (Flom et al., 2007).
- Ligand of TPR2B cluster remains unknown (Scheufler et al., 2000; Brinker et al., 2002), but mutations in carboxylate clamp diminish Hsp70 binding without affecting steroid receptor-related functions (Carrigan et al., 2004).
- Complementation of Δ*sti1* yeast strain for glucocorticoid receptor function: TPR1 and TPR2A point mutations are partial, DP2 mutation is defective (Carrigan et al., 2004), and DP2 of *Drosophila* Hop cannot complement for this function (Carrigan et al., 2005). DP domains and especially DP2 are important for Hsp90 client processing (Schmid et al., 2012). TPR1-DP1 domain partially dispensable (Röhl et al., 2015a). L508 in Hop DP2 is important for full viability, for contact with client, and for GR and v-Src functions (Wang et al., 2022).
- Somewhat different results from independent *in vivo* complementation experiments in yeast, e.g. DP2 not required for Hsp70-mediated function, and TPR2B mutants are defective in Hsp90-mediated functions (Song and Masison, 2005).
- Mutational analysis of Hsc70 binding to mSti1 shows that hydrophobic contacts contribute and that Hsc70 binding to TPR1 is more specific than binding of Hsp90 to TPR2A; AA substitutions in TPR1 can confer Hsp90 binding, but a similar specificity switch of TPR2A is not possible (Odunuga et al., 2003).
- Complementation of Δ*ydj1* Δ*sti1* synthetic lethality with Sti1 mutants for viability, radicicol resistance, and GR function does *not* correlate with Hsp90 interaction, but points out importance of DP2, and either TPR1 or TPR2B (Flom et al., 2006).
- Dimerization contained in TRP2A domain of Sti1 (Flom et al., 2007; Onuoha et al., 2008). A TPR2B point mutant can be both monomeric and dimeric (Goncalves et al., 2010).
- Sti1 interaction domains: both TPR1 and TPR2B contribute to Hsp70 binding with TPR1 being the primary site; TRP2A insufficient to bind Hsp90 without TPR2B (Flom et al., 2007), but both can bind peptides albeit with different affinities (Schmid et al., 2012). TRP2A-TPR2B are core domains for Hsp90 inhibition (Lee et al., 2012; Schmid et al., 2012) and TPR2A and B can bind the middle domain of Hsp90, or also simultaneously Hsp90 and Hsp70, respectively (Schmid et al., 2012). Interaction data consistent with model where TPR2A binds the MEEVD and then TPR2B the middle domain of Hsp90 (Lee et al., 2012; Schmid et al., 2012). Hsp70 binding to TPR2B is important to release it from the middle domain of Hsp90 and reverse stalling the cycle (Dahiya et al., 2022).
- Analysis of coevolution with Hsp90 and Hsp70 suggest additional functional domains (Travers and Fares, 2007).
- Bipartite NLS overlaps TPR2a (Daniel et al., 2008).
- PrPc binding motif maps to AA 230-245 in TPR2A (Ostapchenko et al., 2013) or rather multiple domains of Stip1 (Maciejewski et al., 2016).
- Various pieces of N-terminal domain can interact with PIAS1 (Soares et al., 2013).
- Binds and hydrolyzes ATP through TPR1-DP1-TPR2A portion (Yamamoto et al., 2014).
- Linker between DP1 and TPR2A is important for regulating the interactions of Sti1 with Hsp70 and client activation (Röhl et al., 2015b).

- All three TPR domains can bind S100A1 dimers with distinct affinities (Maciejewski et al., 2017).
- TPR point mutants analyzed by luminescence resonance energy transfer (LRET) (Bhattacharya et al., 2018).
- Interaction with actin is through TPR2AB-DP2 (Beckley et al., 2020).
- Binds α-synuclein through TPR2A (Lackie et al., 2022).

Extracellular:

- Evidence for Hop secretion by tissue culture cells (Eustace and Jay, 2004; Lima et al., 2007; see also Baker-Williams et al., 2019) and ovarian cancer (Wang et al., 2010).
- Mouse Sti1 or the PrP^c interacting peptide of Sti1 confer neuroprotection (Zanata et al., 2002). Elicits neuritogenesis and neuroprotection dependent on interaction and activation of kinases (Lopes et al., 2005). Extracellular Hop stimulates activation of MAPK, possibly in endocytosis-dependent way (Americo et al., 2007). Sti1 secreted by astrocytes may be involved in neuroprotection (Lima et al., 2007). Stimulation of glioma but not normal glia cells by secreted Sti1 may involve PrP^c (Erlich et al., 2007). There are both PrP^c-dependent and independent pathways for neuroprotection and control of proliferation in the developing retina (Arruda-Carvalho et al., 2007) and astrocytes (Arantes et al., 2009; Beraldo et al., 2013; Hartmann et al., 2013). Intra-hippocampal infusion of antibodies to Hop/Sti1 impairs both short- and longterm memory (Coitinho et al., 2007). PrP^c-dependent stimulation of translation by Sti1 is mediated by mTOR signaling and gets corrupted by PrP^{Sc} (Roffé et al., 2010). Sti1 modulates activity of α7 nicotinic acetylcholine receptor (α7nAChR) for which PrP^c may act as receptor or co-receptor (Beraldo et al., 2010). STI1-PrP^c plays a role for neural stemness as assessed by neurosphere formation (Santos et al., 2011). Promotes axonogenesis through PrPc/α7nAChR pathway and involving extracellular Ca^{2+} (Santos et al., 2013). Protects neurons against Aβ0-induced cytotoxicity by preventing its binding to PrPc; involves α7nAChR and upregulation in AD model suggests a protective role there, too (Ostapchenko et al., 2013). Both PrP^c and Hop are highly expressed in glioblastoma cells and stimulated proliferation can be blocked with a Hop peptide corresponding to the interaction domain (Lopes et al., 2015).
- Hsp90 complex with secreted co-chaperones p23, Hop, Hsp70 and Hsp40 increases activation of MMP-2 (ATP-independent!) (Sims et al., 2011).
- Extracellular STI1 is not sufficient to maintain viability of *sti1*-KO MEFs (Beraldo et al., 2013).
- STIP1 promotes growth and survival of hepatocellular carcinoma cells through a PI3K/Akt-dependent autocrine loop; blocked by neutralizing antibodies (Chen et al., 2017). Recombinant Hop increases ovarian cancer cell proliferation (Tsai et al., 2012) and osteolytic metastasis of renal cancer cells (Wang et al., 2017); promotes proliferation and inhibits apoptosis of gastric cancer cells; autocrine loop through ERK and othet signaling molecules can be inhibited with anti-Hop antibodies added to the medium (Zhai et al., 2018a).
- Overexpression in mammalian neurons protects against toxicity of Aβ peptide, mainly through action of extracellular Hop (Lackie et al., 2020a).
- Y134A and Y152A mutants reduce secretion (Chao et al., 2022).

Hop relatives:

- Yeast Cns1 is a distant relative with 13-20 % identity.
- N-terminus of yeast Sgt1 has homology (27% identity) to portions of human Hop (Stemmann et al., 2002).
- Ubiquilin-2 (UBQLN2) and Hip and other proteins contains stretches of homology with Sti1/Hop, which correspond to DP2, and have been coined Sti1-domains (Höhfeld et al., 1995; Kaye et al., 2000).

Unusual stuff:

- Patients with neuro-Behcet's disease have higher levels of Hop autoantibodies in serum and cerebrospinal fluid (Vural et al., 2011).
- Mothers of children with autism have increased levels of Hop autoantibodies (Braunschweig et al., 2013).

References:

Abbas-Terki, T., Briand, P.-A., Donzé, O., and Picard, D. (2002). The Hsp90 co-chaperones Cdc37 and Sti1 interact physically and genetically. Biol. Chem. *383*, 1335-1342.

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.

Abu-Farha, M., Lanouette, S., Elisma, F., Tremblay, V., Butson, J., Figeys, D., and Couture, J. F. (2011). Proteomic analyses of the SMYD family interactomes identify HSP90 as a novel target for SMYD2. J. Mol. Cell. Biol. *3*, 301-308.

Adão, R., Zanphorlin, L. M., Lima, T. B., Sriranganadane, D., Dahlström, K. M., Pinheiro, G. M. S., Gozzo, F. C., Barbosa, L. R. S., and Ramos, C. H. I. (2019). Revealing the interaction mode of the highly flexible *Sorghum bicolor* Hsp70/Hsp90 organizing protein (Hop): A conserved carboxylate clamp confers high affinity binding to Hsp90. J. Proteomics *191*, 191-201.

Agarraberes, F. A., and Dice, J. F. (2001). A molecular chaperone complex at the lysosomal membrane is required for protein translocation. J. Cell Sci. *114*, 2491-2499.

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.

Alford, B. D., and Brandman, O. (2018). Quantification of Hsp90 availability reveals differential coupling to the heat shock response. J. Cell Biol. *217*, 3809-3816.

Altinok, S., Sanchez-Hodge, R., Stewart, M., Smith, K., and Schisler, J. C. (2021). With or without you: co-chaperones mediate health and disease by modifying chaperone function and protein triage. Cells *10*, 3121.

Alvira, S., Cuellar, J., Rohl, A., Yamamoto, S., Itoh, H., Alfonso, C., Rivas, G., Buchner, J., and Valpuesta, J. M. (2014). Structural characterization of the substrate transfer mechanism in Hsp70/Hsp90 folding machinery mediated by Hop. Nat. Commun. *5*, 5484.

Ambegaokar, S. S., and Jackson, G. R. (2011). Functional genomic screen and network analysis reveal novel modifiers of tauopathy dissociated from tau phosphorylation. Hum. Mol. Genet. *20*, 4947-4977.

Americo, T. A., Chiarini, L. B., and Linden, R. (2007). Signaling induced by hop/STI-1 depends on endocytosis. Biochem. Biophys. Res. Commun. *358*, 620-625.

An, L., Gao, H., Zhong, Y., Liu, Y., Cao, Y., Yi, J., Huang, X., Wen, C., Tong, R., Pan, Z., Yan, X., Liu, M., Wang, S., Bai, X., Wu, H., and Hu, T. (2023). Molecular chaperones HSP40, HSP70, STIP1, and HSP90 are involved in stabilization of Cx43. Cytotechnology *75*, 207-217.

Arantes, C., Nomizo, R., Lopes, M. H., Hajj, G. N., Lima, F. R., and Martins, V. R. (2009). Prion protein and its ligand stress inducible protein 1 regulate astrocyte development. Glia *57*, 1439-1449.

Arbeitman, M. N., and Hogness, D. S. (2000). Molecular chaperones activate the Drosophila ecdysone receptor, an RXR heterodimer. Cell *101*, 67-77.

Arlander, S. J., Felts, S. J., Wagner, J. M., Stensgard, B., Toft, D. O., and Karnitz, L. M. (2006). Chaperoning checkpoint kinase 1 (Chk1), an Hsp90 client, with purified chaperones. J. Biol. Chem. *281*, 2989-2998.

Arruda-Carvalho, M., Njaine, B., Silveira, M. S., Linden, R., and Chiarini, L. B. (2007). Hop/STI1 modulates retinal proliferation and cell death independent of PrP^{C}. Biochem. Biophys. Res. Commun. *361*, 474-480.

Baker-Williams, A. J., Hashmi, F., Budzynski, M. A., Woodford, M. R., Gleicher, S., Himanen, S. V., Makedon, A. M., Friedman, D., Cortes, S., Namek, S., Stetler-Stevenson, W. G., Bratslavsky, G., Bah, A., Mollapour, M., Sistonen, L., and Bourboulia, D. (2019). Co-chaperones TIMP2 and AHA1 competitively regulate extracellular HSP90:client MMP2 activity and matrix proteolysis. Cell Rep. *28*, 1894-1906 e1896.

Batista, F. A., Seraphim, T. V., Santos, C. A., Gonzaga, M. R., Barbosa, L. R., Ramos, C. H., and Borges, J. C. (2016). Low sequence identity but high structural and functional conservation: The case of Hsp70/Hsp90 organizing protein (Hop/Sti1) of *Leishmania braziliensis*. Arch. Biochem. Biophys. *600*, 12-22.

Beckley, S. J., Hunter, M. C., Kituyi, S. N., Wingate, I., Chakraborty, A., Schwarz, K., Makhubu, M. P., Rousseau, R. P., Ruck, D. K., de la Mare, J. A., Blatch, G. L., and Edkins, A. L. (2020). STIP1/HOP regulates the actin cytoskeleton through interactions with actin and changes in actin-binding proteins cofilin and profilin. Int. J. Mol. Sci. *21*, 3152.

Beraldo, F. H., Arantes, C. P., Santos, T. G., Queiroz, N. G. T., Young, K., Rylett, R. J., Markus, R. P., Prado, M. A. M., and Martins, V. R. (2010). Role of α7 nicotinic acetylcholine receptor in

calcium signaling induced by prion protein interaction with stress-inducible protein 1. J. Biol. Chem. *285*, 36542-36550.

Beraldo, F. H., Soares, I. N., Goncalves, D. F., Fan, J., Thomas, A. A., Santos, T. G., Mohammad, A. H., Roffe, M., Calder, M. D., Nikolova, S., Hajj, G. N., Guimaraes, A. L., Massensini, A. R., Welch, I., Betts, D. H., Gros, R., Drangova, M., Watson, A. J., Bartha, R., Prado, V. F. et al. (2013). Stress-inducible phosphoprotein 1 has unique cochaperone activity during development and regulates cellular response to ischemia via the prion protein. FASEB J. *27*, 3594-3607.

Beraldo, F. H., Thomas, A., Kolisnyk, B., Hirata, P. H., De Jaeger, X., Martyn, A. C., Fan, J., Goncalves, D. F., Cowan, M. F., Masood, T., Martins, V. R., Gros, R., Prado, V. F., and Prado, M. A. (2015). Hyperactivity and attention deficits in mice with decreased levels of stress-inducible phosphoprotein 1 (STIP1). Dis. Model Mech. *8*, 1457-1466.

Bhangoo, M. K., Tzankov, S., Fan, A. C., Dejgaard, K., Thomas, D. Y., and Young, J. C. (2007). Multiple 40-kDa heat-shock protein chaperones function in Tom70-dependent mitochondrial import. Mol. Biol. Cell *18*, 3414-3428.

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.

Bhattacharya, K., Bernasconi, L., and Picard, D. (2018). Luminescence resonance energy transfer between genetically encoded donor and acceptor for protein-protein interaction studies in the molecular chaperone HSP70/HSP90 complexes. Sci. Rep. *8*, 2801.

Bhattacharya, K., and Picard, D. (2021). The Hsp70-Hsp90 go-between Hop/Stip1/Sti1 is a proteostatic switch and may be a drug target in cancer and neurodegeneration. Cell. Mol. Life Sci. *78*, 7257-7273.

Bhattacharya, K., Weidenauer, L., Morán Luengo, T., Pieters, E. C., Echeverría, P. C., Bernasconi, L., Wider, D., Sadian, Y., Koopman, M. B., Villemin, M., Bauer, C., Rüdiger, S. G. D., Quadroni, M., and Picard, D. (2020). The Hsp70-Hsp90 co-chaperone Hop/Stip1 shifts the proteostatic balance from folding towards degradation. Nat. Commun. *11*, 5975.

Biebl, M. M., Riedl, M., and Buchner, J. (2020). Hsp90 co-chaperones form plastic genetic networks adapted to client maturation. Cell Rep. *32*, 108063.

Bohush, A., Bieganowski, P., and Filipek, A. (2019). Hsp90 and its co-chaperones in neurodegenerative diseases. Int. J. Mol. Sci. *20*, 4976.

Bose, S., Weikl, T., Bügl, H., and Buchner, J. (1996). Chaperone function of Hsp90-associated proteins. Science *274*, 1715-1717.

Braunschweig, D., Krakowiak, P., Duncanson, P., Boyce, R., Hansen, R. L., Ashwood, P., Hertz-Picciotto, I., Pessah, I. N., and Van de Water, J. (2013). Autism-specific maternal autoantibodies recognize critical proteins in developing brain. Transl. Psychiatry *3*, e277.

Bredemeyer, A. J., Carrigan, P. E., Fehniger, T. A., Smith, D. F., and Ley, T. J. (2006). Hop cleavage and function in granzyme B-induced apoptosis. J. Biol. Chem. *281*, 37130-37141.

Brehme, M., Voisine, C., Rolland, T., Wachi, S., Soper, J. H., Zhu, Y., Orton, K., Villella, A., Garza, D., Vidal, M., Ge, H., and Morimoto, R. I. (2014). A chaperome subnetwork safeguards proteostasis in aging and neurodegenerative disease. Cell Rep. *9*, 1135-1150.

Brinker, A., Scheufler, C., von der Mülbe, F., Fleckenstein, B., Herrmann, C., Jung, G., Moarefi, I., and Hartl, F. U. (2002). Ligand discrimination by TPR domains. Relevance and selectivity of EEVD- recognition in Hsp70÷Hop÷Hsp90 complexes. J. Biol. Chem. *277*, 19265-19275.

Brychzy, A., Rein, T., Winklhofer, K. F., Hartl, F. U., Young, J. C., and Obermann, W. M. (2003). Cofactor Tpr2 combines two TPR domains and a J domain to regulate the Hsp70/Hsp90 chaperone system. EMBO J. *22*, 3613-3623.

Buchner, J., Weikl, T., Bugl, H., Pirkl, F., and Bose, S. (1998). Purification of Hsp90 partner proteins Hop/p60, p23, and FKBP52. Methods Enzymol. *290*, 418-429.

Burress, H., Kellner, A., Guyette, J., Tatulian, S. A., and Teter, K. (2019). HSC70 and HSP90 chaperones perform complementary roles in translocation of the cholera toxin A1 subunit from the endoplasmic reticulum to the cytosol. J. Biol. Chem. *294*, 12122-12131.

Caplan, A. J., Ma'ayan, A., and Willis, I. M. (2007). Multiple kinases and system robustness: a link between Cdc37 and genome integrity. Cell Cycle *6*, 3145-3147.

Cappucci, U., Noro, F., Casale, A. M., Fanti, L., Berloco, M., Alagia, A. A., Grassi, L., Le Pera, L., Piacentini, L., and Pimpinelli, S. (2019). The Hsp70 chaperone is a major player in stress-induced transposable element activation. Proc. Natl. Acad. Sci. USA *116*, 17943-17950.

Carrello, A., Ingley, E., Minchin, R. F., Tsai, S., and Ratajczak, T. (1999). The common tetratricopeptide repeat acceptor site for steroid receptor- associated immunophilins and Hop is located in the dimerization domain of Hsp90. J. Biol. Chem. *274*, 2682-2689.

Carrigan, P. E., Nelson, G. M., Roberts, P. J., Stoffer, J., Riggs, D. L., and Smith, D. F. (2004). Multiple domains of the co-chaperone Hop are important for Hsp70 binding. J. Biol. Chem. *279*, 16185-16193.

Carrigan, P. E., Riggs, D. L., Chinkers, M., and Smith, D. F. (2005). Functional comparison of human and Drosophila Hop reveals novel role in steroid receptor maturation. J. Biol. Chem. *280*, 8906-8911.

Cartledge, K., Elsegood, C., Roiniotis, J., Hamilton, J. A., and Scholz, G. M. (2007). Importance of the C-terminal domain of Harc for binding to Hsp70 and Hop as well as its response to heat shock. Biochem. *46*, 15144-15152.

Castelli, M., Bhattacharya, K., Abboud, E., Serapian, S. A., Picard, D., and Colombo, G. (2023). Phosphorylation of the Hsp90 co-chaperone Hop changes its conformational dynamics and biological function. J. Mol. Biol. *435*, 167931.

Chadli, A., Felts, S. J., and Toft, D. O. (2008). GCUNC45 is the first Hsp90 co-chaperone to show α/β isoform specificity. J. Biol. Chem. *283*, 9509-9512.

Chakraborty, A., and Edkins, A. L. (2020). Hop depletion reduces HSF1 levels and activity and coincides with reduced stress resilience. Biochem. Biophys. Res. Commun. *527*, 440-446.

Chang, H.-C. J., Nathan, D. F., and Lindquist, S. (1997). In vivo analysis of the Hsp90 cochaperone Sti1 (p60). Mol. Cell. Biol. *17*, 318-325.

Chao, A., Liao, M. J., Chen, S. H., Lee, Y. S., Tsai, C. N., Lin, C. Y., and Tsai, C. L. (2022). JAK2-mediated phosphorylation of stress-induced phosphoprotein-1 (STIP1) in human cells. Int. J. Mol. Sci. *23*, 2420.

Chen, F., Haigh, S., Yu, Y., Benson, T., Wang, Y., Li, X., Dou, H., Bagi, Z., Verin, A. D., Stepp, D. W., Csanyi, G., Chadli, A., Weintraub, N. L., Smith, S. M., and Fulton, D. J. (2015). Nox5 stability and superoxide production is regulated by C-terminal binding of Hsp90 and CO-chaperones. Free Radic. Biol. Med. *89*, 793-805.

Chen, G., Bradford, W. D., Seidel, C. W., and Li, R. (2012). Hsp90 stress potentiates rapid cellular adaptation through induction of aneuploidy. Nature *482*, 246-250.

Chen, L., Hamada, S., Fujiwara, M., Zhu, T., Thao, N. P., Wong, H. L., Krishna, P., Ueda, T., Kaku, H., Shibuya, N., Kawasaki, T., and Shimamoto, K. (2010). The Hop/Sti1-Hsp90 chaperone complex facilitates the maturation and transport of a PAMP receptor in rice innate immunity. Cell Host Microbe *7*, 185-196.

Chen, S., Prapapanich, V., Rimerman, R. A., Honoré, B., and Smith, D. F. (1996). Interactions of p60, a mediator of progesterone receptor assembly, with heat shock proteins Hsp90 and Hsp70. Mol. Endocrinol. *10*, 682-693.

Chen, S., and Smith, D. F. (1998). Hop as an adaptor in the heat shock protein 70 (Hsp70) and hsp90 chaperone machinery. J. Biol. Chem. *273*, 35194-35200.

Chen, S., Sullivan, W. P., Toft, D. O., and Smith, D. F. (1998). Differential interactions of p23 and the TPR-containing proteins Hop, Cyp40, FKBP52 and FKBP51 with Hsp90 mutants. Cell Stress Chaperones *3*, 118-129.

Chen, Z., Xu, L., Su, T., Ke, Z., Peng, Z., Zhang, N., Peng, S., Zhang, Q., Liu, G., Wei, G., Guo, Y., He, M., and Kuang, M. (2017). Autocrine STIP1 signaling promotes tumor growth and is associated with disease outcome in hepatocellular carcinoma. Biochem. Biophys. Res. Commun. *493*, 365-372.

Coitinho, A. S., Lopes, M. H., Hajj, G. N., Rossato, J. I., Freitas, A. R., Castro, C. C., Cammarota, M., Brentani, R. R., Izquierdo, I., and Martins, V. R. (2007). Short-term memory formation and long-term memory consolidation are enhanced by cellular prion association to stress-inducible protein 1. Neurobiol. Dis. *26*, 282-290.

Cortajarena, A. L., Yi, F., and Regan, L. (2008). Designed TPR modules as novel anticancer agents. ACS Chem. Biol. *3*, 161-166.

Cruz, L., Arevalo Romero, J. A., Brandao Prado, M., Santos, T. G., and Hohmuth Lopes, M. (2017). Evidence of extracellular vesicles biogenesis and release in mouse embryonic stem cells. Stem Cell Rev. *14*, 262-276.

da Fonseca, A. C. C., Matias, D., Geraldo, L. H. M., Leser, F. S., Pagnoncelli, I., Garcia, C., do Amaral, R. F., da Rosa, B. G., Grimaldi, I., de Camargo Magalhaes, E. S., Coppola-Segovia, V., de Azevedo, E. M., Zanata, S. M., and Lima, F. R. S. (2021). The multiple functions of the co-chaperone stress inducible protein 1. Cytokine Growth Factor Rev. *57*, 73-84.

Dahiya, V., Agam, G., Lawatscheck, J., Rutz, D. A., Lamb, D. C., and Buchner, J. (2019). Coordinated conformational processing of the tumor suppressor protein p53 by the Hsp70 and Hsp90 chaperone machineries. Mol. Cell *74*, 1-15.

Dahiya, V., Rutz, D. A., Moessmer, P., Mühlhofer, M., Lawatscheck, J., Rief, M., and Buchner, J. (2022). The switch from client holding to folding in the Hsp70/Hsp90 chaperone machineries is regulated by a direct interplay between co-chaperones. Mol. Cell *82*, 1543-1556.

Daniel, S., Bradley, G., Longshaw, V. M., Soti, C., Csermely, P., and Blatch, G. L. (2008). Nuclear translocation of the phosphoprotein Hop (Hsp70/Hsp90 organizing protein) occurs under heat shock, and its proposed nuclear localization signal is involved in Hsp90 binding. Biochim. Biophys. Acta *1783*, 1003-1014.

Darby, J. F., Vidler, L. R., Simpson, P. J., Al-Lazikani, B., Matthews, S. J., Sharp, S. Y., Pearl, L. H., Hoelder, S., and Workman, P. (2020). Solution structure of the Hop TPR2A domain and investigation of target druggability by NMR, biochemical and in silico approaches. Sci. Rep. *10*, 16000.

De Nardo, D., Masendycz, P., Ho, S., Cross, M., Fleetwood, A. J., Reynolds, E. C., Hamilton, J. A., and Scholz, G. M. (2005). A central role for the Hsp90.Cdc37 molecular chaperone module in interleukin-1 receptor-associated-kinase-dependent signaling by toll-like receptors. J. Biol. Chem. *280*, 9813-9822.

de Souza, L. E., Moura Costa, M. D., Bilek, E. S., Lopes, M. H., Martins, V. R., Puschel, A. W., Mercadante, A. F., Nakao, L. S., and Zanata, S. M. (2014). STI1 antagonizes cytoskeleton collapse mediated by small GTPase Rnd1 and regulates neurite growth. Exp. Cell Res. *324*, 84-91.

Dittmar, K. D., Hutchison, K. A., Owens-Grillo, J. K., and Pratt, W. B. (1996). Reconstitution of the steroid receptor•hsp90 heterocomplex assembly system of rabbit reticulocyte lysate. J. Biol. Chem. *271*, 12833-12839.

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.

Donnelly, B. F., Needham, P. G., Snyder, A. C., Roy, A., Khadem, S., Brodsky, J. L., and Subramanya, A. R. (2013). Hsp70 and Hsp90 multichaperone complexes sequentially regulate thiazide-sensitive cotransporter endoplasmic reticulum-associated degradation and biogenesis. J. Biol. Chem. *288*, 13124-13135.

Duina, A. A., Chang, H.-C. J., Marsh, J. A., Lindquist, S., and Gaber, R. F. (1996). A cyclophilin function in Hsp90-dependent signal transduction. Science *274*, 1713-1715.

Ebong, I. O., Beilsten-Edmands, V., Patel, N. A., Morgner, N., and Robinson, C. V. (2016). The interchange of immunophilins leads to parallel pathways and different intermediates in the assembly of Hsp90 glucocorticoid receptor complexes. Cell Discov. *2*, 16002.

Ebong, I. O., Morgner, N., Zhou, M., Saraiva, M. A., Daturpalli, S., Jackson, S. E., and Robinson, C. V. (2011). Heterogeneity and dynamics in the assembly of the heat shock protein 90 chaperone complexes. Proc. Natl. Acad. Sci. USA *108*, 17939-17944.

Eisele, F., Eisele-Bürger, A. M., Hao, X., Berglund, L. L., Höög, J. L., Liu, B., and Nyström, T. (2021). An Hsp90 co-chaperone links protein folding and degradation and is part of a conserved protein quality control. Cell Rep. *35*, 109328.

Erlich, R. B., Kahn, S. A., Lima, F. R., Muras, A. G., Martins, R. A., Linden, R., Chiarini, L. B., Martins, V. R., and Moura Neto, V. (2007). STI1 promotes glioma proliferation through MAPK and PI3K pathways. Glia *55*, 1690-1698.

Eustace, B. K., and Jay, D. G. (2004). Extracellular roles for the molecular chaperone, hsp90. Cell Cycle *3*, 1098-1100.

Fang, Y., Fliss, A. E., Rao, J., and Caplan, A. J. (1998). SBA1 encodes a yeast hsp90 cochaperone that is homologous to vertebrate p23. Mol. Cell. Biol. *18*, 3727-3734.

Faou, P., and Hoogenraad, N. J. (2012). Tom34: A cytosolic cochaperone of the Hsp90/Hsp70 protein complex involved in mitochondrial protein import. Biochim. Biophys. Acta *1823*, 348-357.

Farkas, Z., Kalapis, D., Bodi, Z., Szamecz, B., Daraba, A., Almási, K., Kovács, K., Boross, G., Pál, F., Horváth, P., Balassa, T., Molnár, C., Pettkó-Szandtner, A., Klement, E., Rutkai, E., Szvetnik, A., Papp, B., and Pál, C. (2018). Hsp70-associated chaperones have a critical role in buffering protein production costs. eLife *7*, e29845.

Fellerer, C., Schweiger, R., Schongruber, K., Soll, J., and Schwenkert, S. (2011). Cytosolic HSP90 cochaperones HOP and FKBP interact with freshly synthesized chloroplast preproteins of Arabidopsis. Mol. Plant *4*, 1133-1145.

Felts, S. J., Karnitz, L. M., and Toft, D. O. (2007). Functioning of the Hsp90 machine in chaperoning checkpoint kinase 1 (Chk1) and the progesterone receptor (PR). Cell Stress Chaperones *12*, 353-363.

Fernández-Bautista, N., Fernández-Calvino, L., Muñoz, A., and Castellano, M. M. (2017). HOP3, a member of the HOP family in Arabidopsis, interacts with BiP and plays a major role in the ER stress response. Plant Cell Environ. *40*, 1341-1355.

Fernández-Bautista, N., Fernández-Calvino, L., Muñoz, A., Toribio, R., Mock, H. P., and Castellano, M. M. (2018). HOP family plays a major role in long-term acquired thermotolerance in Arabidopsis. Plant Cell Environ. *41*, 1852-1869.

Floer, M., Bryant, G. O., and Ptashne, M. (2008). HSP90/70 chaperones are required for rapid nucleosome removal upon induction of the GAL genes of yeast. Proc. Natl. Acad. Sci. USA *105*, 2975-2980.

Flom, G., Behal, R. H., Rosen, L., Cole, D. G., and Johnson, J. L. (2007). Definition of the minimal fragments of Sti1 required for dimerization, interaction with Hsp70 and Hsp90 and in vivo functions. Biochem. J. *404*, 159-167.

Flom, G., Weekes, J., and Johnson, J. L. (2005). Novel interaction of the Hsp90 chaperone machine with Ssl2, an essential DNA helicase in Saccharomyces cerevisiae. Curr. Genet. *47*, 368-380.

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.

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.

French, J. B., Zhao, H., An, S., Niessen, S., Deng, Y., Cravatt, B. F., and Benkovic, S. J. (2013). Hsp70/Hsp90 chaperone machinery is involved in the assembly of the purinosome. Proc. Natl. Acad. Sci. USA *110*, 2528-2533.

Frumkin, A., Dror, S., Pokrzywa, W., Bar-Lavan, Y., Karady, I., Hoppe, T., and Ben-Zvi, A. (2014). Challenging muscle homeostasis uncovers novel chaperone interactions in *Caenorhabditis elegans*. Front. Mol. Biosci. *1*, 21.

Frydman, J., and Höhfeld, J. (1997). Chaperones get in touch: the Hip-Hop connection. Trends Biochem. Sci. *22*, 87-92.

Gaiser, A. M., Brandt, F., and Richter, K. (2009). The non-canonical hop protein from Caenorhabditis elegans exerts essential functions and forms binary complexes with either Hsc70 or Hsp90. J. Mol. Biol. *391*, 621-634.

Gangaraju, V. K., Yin, H., Weiner, M. M., Wang, J., Huang, X. A., and Lin, H. (2011). Drosophila Piwi functions in Hsp90-mediated suppression of phenotypic variation. Nat. Genet. *43*, 153-158.

Gao, Y., Yechikov, S., Vazquez, A. E., Chen, D., and Nie, L. (2013). Distinct roles of molecular chaperones HSP90α and HSP90β in the biogenesis of KCNQ4 channels. PLoS ONE *8*, e57282.

Gaur, D., Kumar, N., Ghosh, A., Singh, P., Kumar, P., Guleria, J., Kaur, S., Malik, N., Saha, S., Nystrom, T., and Sharma, D. (2022). Ydj1 interaction at nucleotide-binding-domain of yeast Ssa1 impacts Hsp90 collaboration and client maturation. PLoS Genet. *18*, e1010442.

Gebauer, M., Melki, R., and Gehring, U. (1998a). The chaperone cofactor Hop/p60 interacts with the cytosolic chaperonin- containing TCP-1 and affects its nucleotide exchange and protein folding activities. J. Biol. Chem. *273*, 29475-29480.

Gebauer, M., Zeiner, M., and Gehring, U. (1998b). Interference between proteins hap46 and Hop/p60, which bind to different domains of the molecular chaperone hsp70/hsc70. Mol. Cell. Biol. *18*, 6238-6244.

Göllner, S., Oellerich, T., Agrawal-Singh, S., Schenk, T., Klein, H. U., Rohde, C., Pabst, C., Sauer, T., Lerdrup, M., Tavor, S., Stölzel, F., Herold, S., Ehninger, G., Köhler, G., Pan, K. T., Urlaub, H., Serve, H., Dugas, M., Spiekermann, K., Vick, B. et al. (2017). Loss of the histone methyltransferase EZH2 induces resistance to multiple drugs in acute myeloid leukemia. Nat. Med. *23*, 69-78.

Goncalves, D. C., Gava, L. M., and Ramos, C. H. (2010). Human Hsp70/Hsp90 organizing protein (Hop) D456G is a mixture of monomeric and dimeric species. Protein Pept. Lett. *17*, 492-498.

Gorkovskiy, A., Reidy, M., Masison, D. C., and Wickner, R. B. (2017). Hsp104 disaggregase at normal levels cures many [*PSI+]* prion variants in a process promoted by Sti1p, Hsp90, and Sis1p. Proc. Natl. Acad. Sci. USA *114*, E4193-E4202.

Gross, M., and Hessefort, S. (1996). Purification and characterization of a 66-kDa protein from rabbit reticulocyte lysate which promotes the recycling of Hsp. J. Biol. Chem. *271*, 16833-16841.

Harst, A., Lin, H., and Obermann, W. M. (2005). Aha1 competes with Hop, p50 and p23 for binding to the molecular chaperone Hsp90 and contributes to kinase and hormone receptor activation. Biochem. J. *387*, 789-796.

Hartmann, C. A., Martins, V. R., and Lima, F. R. (2013). High levels of cellular prion protein improve astrocyte development. FEBS Lett. *587*, 238-244.

Hatherley, R., Clitheroe, C. L., Faya, N., and Tastan Bishop, Ö. (2015). Plasmodium falciparum Hop: detailed analysis on complex formation with Hsp70 and Hsp90. Biochem. Biophys. Res. Commun. *456*, 440-445.

Hernández, M. P., Sullivan, W. P., and Toft, D. O. (2002). The assembly and intermolecular properties of the hsp70-Hop-hsp90 molecular chaperone complex. J. Biol. Chem. *277*, 38294-38304.

Hessling, M., Richter, K., and Buchner, J. (2009). Dissection of the ATP-induced conformational cycle of the molecular chaperone Hsp90. Nat. Struct. Mol. Biol. *16*, 287-293.

Hildenbrand, Z. L., Molugu, S. K., Herrera, N., Ramirez, C., Xiao, C., and Bernal, R. A. (2011). Hsp90 can accommodate the simultaneous binding of the FKBP52 and HOP proteins. Oncotarget *2*, 45-58.

Höhfeld, J., Minami, Y., and Hartl, F.-U. (1995). Hip, a novel cochaperone involved in the eukaryotic Hsc70/Hsp40 reaction cycle. Cell *83*, 589-598.

Hombach, A., Ommen, G., Chrobak, M., and Clos, J. (2013). The Hsp90-Sti1 interaction is critical for *Leishmania donovani* proliferation in both life cycle stages. Cell. Microbiol. *15*, 585-600.

Hong, S. M., Yamashita, J., Mitsunobu, H., Uchino, K., Kobayashi, I., Sezutsu, H., Tamura, T., Nakajima, H., Miyagawa, Y., Lee, J. M., Mon, H., Miyata, Y., Kawaguchi, Y., and Kusakabe, T. (2010). Efficient soluble protein production on transgenic silkworms expressing cytoplasmic chaperones. Appl. Microbiol. Biotechnol. *87*, 2147-2156.

Honoré, B., Leffers, H., Madsen, P., Rasmussen, H. H., Vandekerckhove, J., and Celis, J. E. (1992). Molecular cloning and expression of a transforming-sensitive human protein containing the TPR motif and sharing identity to the stress-inducible yeast protein STI1. J. Biol. Chem. *267*, 8485-8491.

Horibe, T., Kohno, M., Haramoto, M., Ohara, K., and Kawakami, K. (2011). Designed hybrid TPR peptide targeting Hsp90 as a novel anticancer agent. J. Transl. Med. *9*, 8.

Hoseini, H., Pandey, S., Jores, T., Schmitt, A., Franz-Wachtel, M., Macek, B., Buchner, J., Dimmer, K. S., and Rapaport, D. (2016). The cytosolic cochaperone Sti1 is relevant for mitochondrial biogenesis and morphology. FEBS J. *283*, 3338-3352.

Inda, M. C., Joshi, S., Wang, T., Bolaender, A., Gandu, S., Koren Iii, J., Che, A. Y., Taldone, T., Yan, P., Sun, W., Uddin, M., Panchal, P., Riolo, M., Shah, S., Barlas, A., Xu, K., Chan, L. Y. L., Gruzinova, A., Kishinevsky, S., Studer, L. et al. (2020). The epichaperome is a mediator of toxic hippocampal stress and leads to protein connectivity-based dysfunction. Nat. Commun. *11*, 319.

Iwasaki, S., Sasaki, H. M., Sakaguchi, Y., Suzuki, T., Tadakuma, H., and Tomari, Y. (2015). Defining fundamental steps in the assembly of the Drosophila RNAi enzyme complex. Nature *521*, 533-536.

Jing, Y., Liang, W., Liu, J., Zhang, L., Wei, J., Zhu, Y., Yang, J., Ji, K., Zhang, Y., and Huang, Z. (2019). Stress-induced phosphoprotein 1 promotes pancreatic cancer progression through activation of the FAK/AKT/MMP signaling axis. Pathol. Res. Pract. *215*, 152564.

Johnson, B. D., Schumacher, R. J., Ross, E. D., and Toft, D. O. (1998). Hop modulates hsp70/hsp90 interactions in protein folding. J. Biol. Chem. *273*, 3679-3686.

Johnson, J. L., and Brown, C. (2009). Plasticity of the Hsp90 chaperone machine in divergent eukaryotic organisms. Cell Stress Chaperones *14*, 83-94.

Jones, G., Song, Y., Chung, S., and Masison, D. C. (2004). Propagation of *Saccharomyces cerevisiae* [*PSI*$^+$] prion is impaired by factors that regulate Hsp70 substrate binding. Mol. Cell. Biol. *24*, 3928-3937.

Jones, M. H., Bachant, J. B., Castillo, A. R., Giddings, T. H. J., and Winey, M. (1999). Yeast Dam1p is required to maintain spindle integrity during mitosis and interacts with the Mps1p kinase. Mol. Biol. Cell *10*, 2377-2391.

Kaganovich, D., Kopito, R., and Frydman, J. (2008). Misfolded proteins partition between two distinct quality control compartments. Nature *454*, 1088-1095.

Kajander, T., Sachs, J. N., Goldman, A., and Regan, L. (2009). Electrostatic interactions of Hsp-organizing protein tetratricopeptide domains with Hsp70 and Hsp90: computational analysis and protein engineering. J. Biol. Chem. *284*, 25364-25374.

Karam, J. A., Parikh, R. Y., Nayak, D., Rosenkranz, D., and Gangaraju, V. K. (2017). Co-chaperone Hsp70/Hsp90-organizing protein (Hop) is required for transposon silencing and Piwi-interacting RNA (piRNA) biogenesis. J. Biol. Chem. *292*, 6039-6046.

Kaye, F. J., Modi, S., Ivanovska, I., Koonin, E. V., Thress, K., Kubo, A., Kornbluth, S., and Rose, M. D. (2000). A family of ubiquitin-like proteins binds the ATPase domain of Hsp70-like Stch. FEBS Lett. *467*, 348-355.

Kaziales, A., Barkovits, K., Marcus, K., and Richter, K. (2020). Glucocorticoid receptor complexes form cooperatively with the Hsp90 co-chaperones Pp5 and FKBPs. Sci. Rep. *10*, 10733.

Kirschke, E., Goswami, D., Southworth, D., Griffin, P. R., and Agard, D. A. (2014). Glucocorticoid receptor function regulated by coordinated action of the hsp90 and hsp70 chaperone cycles. Cell *157*, 1685-1697.

Kituyi, S. N., and Edkins, A. L. (2018). Hop/STIP1 depletion alters nuclear structure via depletion of nuclear structural protein emerin. Biochem. Biophys. Res. Commun. *507*, 503-509.

Kravats, A. N., Hoskins, J. R., Reidy, M., Johnson, J. L., Doyle, S. M., Genest, O., Masison, D. C., and Wickner, S. (2018). Functional and physical interaction between yeast Hsp90 and Hsp70. Proc. Natl. Acad. Sci. USA *115*, E2210-E2219.

Kryndushkin, D. S., Smirnov, V. N., Ter-Avanesyan, M. D., and Kushnirov, V. V. (2002). Increased expression of Hsp40 chaperones, transcriptional factors, and ribosomal protein Rpp0 can cure yeast prions. J. Biol. Chem. *277*, 23702-23708.

Kubota, H., Yamamoto, S., Itoh, E., Abe, Y., Nakamura, A., Izumi, Y., Okada, H., Iida, M., Nanjo, H., Itoh, H., and Yamamoto, Y. (2010). Increased expression of co-chaperone HOP with HSP90 and HSC70 and complex formation in human colonic carcinoma. Cell Stress Chaperones *15*, 1003-1011.

Kudze, T., Mendez-Dorantes, C., Jalloh, C. S., and McClellan, A. J. (2018). Evidence for interaction between Hsp90 and the ER membrane complex. Cell Stress Chaperones *23*, 1101-1115.

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.

Lackie, R. E., de Miranda, A. S., Lim, M. P., Novikov, V., Madrer, N., Karunatilleke, N. C., Rutledge, B. S., Tullo, S., Brickenden, A., Maitland, M. E. R., Greenberg, D., Gallino, D., Luo, W., Attaran, A., Shlaifer, I., Del Cid Pellitero, E., Schild-Poulter, C., Durcan, T. M., Fon, E. A., Duennwald, M. et al. (2022). Stress-inducible phosphoprotein 1 (HOP/STI1/STIP1) regulates the accumulation and toxicity of α-synuclein in vivo. Acta Neuropathol. *144*, 881-910.

Lackie, R. E., Marques-Lopes, J., Ostapchenko, V. G., Good, S., Choy, W. Y., van Oosten-Hawle, P., Pasternak, S. H., Prado, V. F., and Prado, M. A. M. (2020a). Increased levels of Stress-inducible phosphoprotein-1 accelerates amyloid-β deposition in a mouse model of Alzheimer's disease. Acta Neuropathol. Commun. *8*, 143.

Lackie, R. E., Razzaq, A. R., Farhan, S. M. K., Qiu, L. R., Moshitzky, G., Beraldo, F. H., Lopes, M. H., Maciejewski, A., Gros, R., Fan, J., Choy, W. Y., Greenberg, D. S., Martins, V. R., Duennwald, M. L., Lerch, J. P., Soreq, H., Prado, V. F., and Prado, M. A. M. (2020b). Modulation of hippocampal neuronal resilience during aging by the Hsp70/Hsp90 co-chaperone STI1. J. Neurochem. *153*, 727-758.

Lamm, C. E., Kraner, M. E., Hofmann, J., Bornke, F., Mock, H. P., and Sonnewald, U. (2017). Hop/Sti1 - a two-faced cochaperone involved in pattern recognition receptor maturation and viral infection. Front. Plant Sci. *8*, 1754.

Lässle, M., Blatch, G. L., Kundra, V., Takatori, T., and Zetter, B. R. (1997). Stress-inducible, murine protein mSTI1. J. Biol. Chem. *272*, 1876-1884.

Lauwers, E., Wang, Y. C., Gallardo, R., Van der Kant, R., Michiels, E., Swerts, J., Baatsen, P., Zaiter, S. S., McAlpine, S. R., Gounko, N. V., Rousseau, F., Schymkowitz, J., and Verstreken, P. (2018). Hsp90 mediates membrane deformation and exosome release. Mol. Cell *71*, 689-702.

Lee, C. T., Graf, C., Mayer, F. J., Richter, S. M., and Mayer, M. P. (2012). Dynamics of the regulation of Hsp90 by the co-chaperone Sti1. European Molecular Biology Organization Journal *31*, 1518-1528.

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.

Lee, S. D., Lai, T. W., Lin, S. Z., Lin, C. H., Hsu, Y. H., Li, C. Y., Wang, H. J., Lee, W., Su, C. Y., Yu, Y. L., and Shyu, W. C. (2013). Role of stress-inducible protein-1 in recruitment of bone marrow derived cells into the ischemic brains. EMBO Mol. Med. *5*, 1227-1246.

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., Sun, X., Wang, Z., Chen, L., Li, D., Zhou, J., and Liu, M. (2012). Regulation of vascular endothelial cell polarization and migration by Hsp70/Hsp90-organizing protein. PLoS ONE *7*, e36389.

Lima, F. R., Arantes, C. P., Muras, A. G., Nomizo, R., Brentani, R. R., and Martins, V. R. (2007). Cellular prion protein expression in astrocytes modulates neuronal survival and differentiation. J. Neurochem. *103*, 2164-2176.

Lin, L. T., Razzaq, A., Di Gregorio, S. E., Hong, S., Charles, B., Lopes, M. H., Beraldo, F., Prado, V. F., Prado, M. A. M., and Duennwald, M. L. (2021). Hsp90 and its co-chaperone Sti1 control TDP-43 misfolding and toxicity. FASEB J. *35*, e21594.

Liu, F. H., Wu, S. J., Hu, S. M., Hsiao, C. D., and Wang, C. (1999a). Specific interaction of the 70-kDa heat shock cognate protein with the tetratricopeptide repeats. J. Biol. Chem. *274*, 34425-34432.

Liu, X. D., Morano, K. A., and Thiele, D. J. (1999b). The yeast Hsp110 family member, Sse1, is an Hsp90 cochaperone. J. Biol. Chem. *274*, 26654-26660.

Longshaw, V. M., Baxter, M., Prewitz, M., and Blatch, G. L. (2009). Knockdown of the co-chaperone Hop promotes extranuclear accumulation of Stat3 in mouse embryonic stem cells. Eur. J. Cell Biol. *88*, 153-166.

Longshaw, V. M., Chapple, J. P., Balda, M. S., Cheetham, M. E., and Blatch, G. L. (2004). Nuclear translocation of the Hsp70/Hsp90 organizing protein mSTI1 is regulated by cell cycle kinases. J. Cell Sci. *117*, 701-710.

Longshaw, V. M., Dirr, H. W., Blatch, G. L., and Lässle, M. (2000). The in vitro phosphorylation of the co-chaperone mSTI1 by cell cycle kinases substantiates a predicted casein kinase II-p34cdc2-NLS (CcN) motif. Biol. Chem. *381*, 1133–1138.

Lopes, M. H., Hajj, G. N., Muras, A. G., Mancini, G. L., Castro, R. M., Ribeiro, K. C., Brentani, R. R., Linden, R., and Martins, V. R. (2005). Interaction of cellular prion and stress-inducible protein 1 promotes neuritogenesis and neuroprotection by distinct signaling pathways. J. Neurosci. *25*, 11330-11339.

Lopes, M. H., Santos, T. G., Rodrigues, B. R., Queiroz-Hazarbassanov, N., Cunha, I. W., Wasilewska-Sampaio, A. P., Costa-Silva, B., Marchi, F. A., Bleggi-Torres, L. F., Sanematsu, P. I., Suzuki, S. H., Oba-Shinjo, S. M., Marie, S. K., Toulmin, E., Hill, A. F., and Martins, V. R. (2015). Disruption of prion protein-HOP engagement impairs glioblastoma growth and cognitive decline and improves overall survival. Oncogene *34*, 3305-3314.

Lott, A., Oroz, J., and Zweckstetter, M. (2020). Molecular basis of the interaction of Hsp90 with its co-chaperone Hop. Protein Sci. *29*, 2422-2432.

Lotz, G. P., Lin, H., Harst, A., and Obermann, W. M. (2003). Aha1 binds to the middle domain of Hsp90, contributes to client protein activation, and stimulates the ATPase activity of the molecular chaperone. J. Biol. Chem. *278*, 17228-17235.

Maciejewski, A., Ostapchenko, V. G., Beraldo, F. H., Prado, V. F., Prado, M. A., and Choy, W. Y. (2016). Domains of STIP1 responsible for regulating PrPC-dependent amyloid-β oligomer toxicity. Biochem. J. *473*, 2119-2130.

Maciejewski, A., Prado, V. F., Prado, M. A. M., and Choy, W. Y. (2017). Molecular basis for the interaction between stress-inducible phosphoprotein 1 (STIP1) and S100A1. Biochem. J. *474*, 1853-1866.

Makumire, S., Zininga, T., Vahokoski, J., Kursula, I., and Shonhai, A. (2020). Biophysical analysis of *Plasmodium falciparum* Hsp70-Hsp90 organising protein (PfHop) reveals a monomer that is characterised by folded segments connected by flexible linkers. PLoS ONE *15*, e0226657.

Mandal, A. K., Gibney, P. A., Nillegoda, N. B., Theodoraki, M. A., Caplan, A. J., and Morano, K. A. (2010). Hsp110 chaperones control client fate determination in the hsp70-Hsp90 chaperone system. Mol. Biol. Cell *21*, 1439-1448.

Mangano, S., Muñoz, A., Fernández-Calvino, L., and Castellano, M. M. (2023). HOP co-chaperones contribute to GA signaling by promoting the accumulation of the F-box protein SNE in *Arabidopsis*. Plant Commun. *4*, 100517.

Marozkina, N. V., Yemen, S., Borowitz, M., Liu, L., Plapp, M., Sun, F., Islam, R., Erdmann-Gilmore, P., Townsend, R. R., Lichti, C. F., Mantri, S., Clapp, P. W., Randell, S. H., Gaston, B., and Zaman, K. (2010). Hsp 70/Hsp 90 organizing protein as a nitrosylation target in cystic fibrosis therapy. Proc. Natl. Acad. Sci. USA *107*, 11393-11398.

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 *cpr7*∆ cells. Mol. Cell. Biol. *18*, 7353-7359.

Martins, V. R., Graner, E., Garcia-Abreu, J., de Souza, S. J., Mercadante, A. F., Veiga, S. S., Zanata, S. M., Neto, V. M., and Brentani, R. R. (1997). Complementary hydropathy identifies a cellular prion protein receptor. Nat. Med. *3*, 1376-1382.

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.

McClellan, A. J., Scott, M. D., and Frydman, J. (2005). Folding and quality control of the VHL tumor suppressor proceed through distinct chaperone pathways. Cell *121*, 739-748.

McLaughlin, S. H., Smith, H. W., and Jackson, S. E. (2002). Stimulation of the weak ATPase activity of human Hsp90 by a client protein. J. Mol. Biol. *315*, 787-798.

Meena, S., Deb, S., Samtani, H., and Khurana, P. (2020). Dissecting the molecular function of triticum aestivum *STI* family members under heat stress. Front. Genet. *11*, 873.

Mercier, R., Yama, D., LaPointe, P., and Johnson, J. L. (2023). Hsp90 mutants with distinct defects provide novel insights into cochaperone regulation of the folding cycle. PLoS Genet. *19*, e1010772.

Millson, S. H., Nuttall, J. M., Mollapour, M., and Piper, P. W. (2009). The Hsp90/Cdc37p chaperone system is a determinant of molybdate resistance in *Saccharomyces cerevisiae*. Yeast *26*, 339-347.

Mir, S. S., Fiedler, D., and Cashikar, A. G. (2009). Ssd1 is required for thermotolerance and Hsp104-mediated protein disaggregation in Saccharomyces cerevisiae. Mol. Cell. Biol. *29*, 187-200.

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.

Morales, M. A., Watanabe, R., Dacher, M., Chafey, P., Osorio y Fortea, J., Scott, D. A., Beverley, S. M., Ommen, G., Clos, J., Hem, S., Lenormand, P., Rousselle, J. C., Namane, A., and Spath, G. F. (2010). Phosphoproteome dynamics reveal heat-shock protein complexes specific to the *Leishmania donovani* infectious stage. Proc. Natl. Acad. Sci. USA *107*, 8381-8386.

Morishima, Y., Kanelakis, K. C., Silverstein, A. M., Dittmar, K. D., Estrada, L., and Pratt, W. B. (2000). The hsp organizer protein hop enhances the rate of but is not essential for glucocorticoid receptor folding by the multiprotein Hsp90-based chaperone system. J. Biol. Chem. *275*, 6894-6900.

Muller, P., Ruckova, E., Halada, P., Coates, P. J., Hrstka, R., Lane, D. P., and Vojtesek, B. (2013). C-terminal phosphorylation of Hsp70 and Hsp90 regulates alternate binding to co-chaperones CHIP and HOP to determine cellular protein folding/degradation balances. Oncogene *32*, 3101-3110.

Munday, D. C., Wu, W., Smith, N., Fix, J., Noton, S. L., Galloux, M., Touzelet, O., Armstrong, S. D., Dawson, J. M., Aljabr, W., Easton, A. J., Rameix-Welti, M. A., de Oliveira, A. P., Simabuco, F. M., Ventura, A. M., Hughes, D. J., Barr, J. N., Fearns, R., Digard, P., Eléouët, J. F., and Hiscox, J. A. (2015). Interactome analysis of the human respiratory syncytial virus RNA polymerase complex identifies protein chaperones as important cofactors that promote L-protein stability and RNA synthesis. J. Virol. *89*, 917-930.

Muñoz, A., Mangano, S., Toribio, R., Fernández-Calvino, L., Del Pozo, J. C., and Castellano, M. M. (2022). The co-chaperone HOP participates in TIR1 stabilisation and in auxin response in plants. Plant Cell Environ. *45*, 2508-2519.

Muñoz, A., Santamaria, M. E., Fernández-Bautista, N., Mangano, S., Toribio, R., Martínez, M., Berrocal-Lobo, M., Diaz, I., and Castellano, M. M. (2021). The co-chaperone HOP3 participates in jasmonic acid signaling by regulating CORONATINE-INSENSITIVE 1 activity. Plant Physiol. *187*, 1679-1689.

Naruse, K., Matsuura-Suzuki, E., Watanabe, M., Iwasaki, S., and Tomari, Y. (2018). In vitro reconstitution of chaperone-mediated human RISC assembly. RNA *24*, 6-11.

Nelson, G. M., Huffman, H., and Smith, D. F. (2003). Comparison of the carboxy-terminal DP-repeat region in the co-chaperones Hop and Hip. Cell Stress Chaperones *8*, 125-133.

Nelson, G. M., Prapapanich, V., Carrigan, P. E., Roberts, P. J., Riggs, D. L., and Smith, D. F. (2004). The heat shock protein 70 cochaperone Hip enhances functional maturation of glucocorticoid receptor. Mol. Endocrinol. *18*, 1620-1630.

Ngo, V., Brickenden, A., Liu, H., Yeung, C., Choy, W. Y., and Duennwald, M. L. (2022). A novel yeast model detects Nrf2 and Keap1 interactions with Hsp90. Dis. Model Mech. *15*, dmm049258.

Ni, J., Gao, Y., Liu, H., and Chen, J. (2004). Candida albicans Cdc37 interacts with the Crk1 kinase and is required for Crk1 production. FEBS Lett. *561*, 223-230.

Nicolet, C. M., and Craig, E. A. (1989). Isolation and characterization of STI1, a stress-inducible gene from *Saccharomyces cerevisiae*. Mol. Cell. Biol. *9*, 3638-3646.

O'Meara, T. R., O'Meara, M. J., Polvi, E. J., Pourhaghighi, M. R., Liston, S. D., Lin, Z. Y., Veri, A. O., Emili, A., Gingras, A. C., and Cowen, L. E. (2019). Global proteomic analyses define an

environmentally contingent Hsp90 interactome and reveal chaperone-dependent regulation of stress granule proteins and the R2TP complex in a fungal pathogen. PLoS Biol. *17*, e3000358.

Odunuga, O. O., Hornby, J. A., Bies, C., Zimmermann, R., Pugh, D. J., and Blatch, G. L. (2003). Tetratricopeptide repeat motif-mediated Hsc70-mSTI1 interaction: Molecular characterization of the critical contacts for successful binding and specificity. J. Biol. Chem. *278*, 6896-6904.

Odunuga, O. O., Longshaw, V. M., and Blatch, G. L. (2004). Hop: more than an Hsp70/Hsp90 adaptor protein. Bioessays *26*, 1058-1068.

Okiyoneda, T., Barriere, H., Bagdany, M., Rabeh, W. M., Du, K., Hohfeld, J., Young, J. C., and Lukacs, G. L. (2010). Peripheral protein quality control removes unfolded CFTR from the plasma membrane. Science *329*, 805-810.

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.

Ostapchenko, V. G., Beraldo, F. H., Mohammad, A. H., Xie, Y. F., Hirata, P. H., Magalhaes, A. C., Lamour, G., Li, H., Maciejewski, A., Belrose, J. C., Teixeira, B. L., Fahnestock, M., Ferreira, S. T., Cashman, N. R., Hajj, G. N., Jackson, M. F., Choy, W. Y., Macdonald, J. F., Martins, V. R., Prado, V. F., and Prado, M. A. (2013). The prion protein ligand, stress-inducible phosphoprotein 1, regulates amyloid-β oligomer toxicity. J. Neurosci. *33*, 16552-16564.

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.

Pare, J. M., Tahbaz, N., Lopez-Orozco, J., LaPointe, P., Lasko, P., and Hobman, T. C. (2009). Hsp90 regulates the function of argonaute 2 and its recruitment to stress granules and P-bodies. Mol. Biol. Cell *20*, 3273-3284.

Parsons, A. B., Lopez, A., Givoni, I. E., Williams, D. E., Gray, C. A., Porter, J., Chua, G., Sopko, R., Brost, R. L., Ho, C. H., Wang, J., Ketela, T., Brenner, C., Brill, J. A., Fernandez, G. E., Lorenz, T. C., Payne, G. S., Ishihara, S., Ohya, Y., Andrews, B. et al. (2006). Exploring the mode-of-action of bioactive compounds by chemical-genetic profiling in yeast. Cell *126*, 611-625.

Peng, Y. J., Huang, J. J., Wu, H. H., Hsieh, H. Y., Wu, C. Y., Chen, S. C., Chen, T. Y., and Tang, C. Y. (2016). Regulation of CLC-1 chloride channel biosynthesis by FKBP8 and Hsp90β. Sci. Rep. *6*, 32444.

Pimienta, G., Herbert, K. M., and Regan, L. (2011). A compound that inhibits the HOP-Hsp90 complex formation and has unique killing effects in breast cancer cell lines. Mol. Pharmaceutics *8*, 2252-2261.

Piper, P. W., Millson, S. H., Mollapour, M., Panaretou, B., Siligardi, G., Pearl, L. H., and Prodromou, C. (2003). Sensitivity to Hsp90-targeting drugs can arise with mutation to the Hsp90 chaperone, cochaperones and plasma membrane ATP binding cassette transporters of yeast. Eur. J. Biochem. *270*, 4689-4695.

Prapapanich, V., Chen, S., and Smith, D. F. (1998). Mutation of Hip's carboxy-terminal region inhibits a transitional stage of progesterone receptor assembly. Mol. Cell. Biol. *18*, 944-952.

Prodromou, C., Siligardi, G., O'Brien, R., Woolfson, D. N., Regan, L., Panaretou, B., Ladbury, J. E., Piper, P. W., and Pearl, L. H. (1999). Regulation of Hsp90 ATPase activity by tetratricopeptide repeat (TPR)- domain co-chaperones. EMBO J. *18*, 754-762.

Qi, X., Zhang, X., Liu, X., Tang, W., Dai, J., Chen, A., Lin, Q., Zhu, T., and Li, J. (2021). HDN-1 induces cell differentiation toward apoptosis in promyelocytic leukemia cells depending on its selective effect on client proteins of Hsp90. Toxicol. Appl. Pharmacol. *417*, 115459.

Quanz, M., Herbette, A., Sayarath, M., de Koning, L., Dubois, T., Sun, J. S., and Dutreix, M. (2012). Heat shock protein 90α (Hsp90α) is phosphorylated in response to DNA damage and accumulates in repair foci. J. Biol. Chem. *287*, 8803-8815.

Rajapandi, T., Greene, L. E., and Eisenberg, E. (2000). The molecular chaperones hsp90 and hsc70 are both necessary and sufficient to activate hormone binding by glucocorticoid receptor. J. Biol. Chem. *275*, 22597-22604.

Ramsey, A. J., Russell, L. C., Whitt, S. R., and Chinkers, M. (2000). Overlapping sites of tetratricopeptide repeat protein binding and chaperone activity in heat shock protein 90. J. Biol. Chem. *275*, 17857-17862.

Ran, F., Bali, M., and Michels, C. A. (2008). Hsp90/Hsp70 chaperone machine regulation of the Saccharomyces MAL-activator as determined in vivo using noninducible and constitutive mutant alleles. Genetics *179*, 331-343.

Ratzke, C., Mickler, M., Hellenkamp, B., Buchner, J., and Hugel, T. (2010). Dynamics of heat shock protein 90 C-terminal dimerization is an important part of its conformational cycle. Proc. Natl. Acad. Sci. USA *107*, 16101-16106.

Reidy, M., Kumar, S., Anderson, D. E., and Masison, D. C. (2018). Dual roles for yeast Sti1/Hop in regulating the Hsp90 chaperone cycle. Genetics *209*, 1139-1154.

Reidy, M., and Masison, D. C. (2010). Sti1 regulation of Hsp70 and Hsp90 is critical for curing of *Saccharomyces cerevisiae [PSI+]* prions by Hsp104. Mol. Cell. Biol. *30*, 3542-3552.

Ren, M., Santhanam, A., Lee, P., Caplan, A., and Garrett, S. (2007). Alteration of the protein kinase binding domain enhances function of the Saccharomyces cerevisiae molecular chaperone Cdc37. Eukaryot. Cell *6*, 1363-1372.

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.

Rizzolo, K., Huen, J., Kumar, A., Phanse, S., Vlasblom, J., Kakihara, Y., Zeineddine, H. A., Minic, Z., Snider, J., Wang, W., Pons, C., Seraphim, T. V., Boczek, E. E., Alberti, S., Costanzo, M., Myers, C. L., Stagljar, I., Boone, C., Babu, M., and Houry, W. A. (2017). Features of the chaperone cellular network revealed through systematic interaction mapping. Cell Rep. *20*, 2735-2748.

Rodina, A., Wang, T., Yan, P., Gomes, E. D., Dunphy, M. P., Pillarsetty, N., Koren, J., Gerecitano, J. F., Taldone, T., Zong, H., Caldas-Lopes, E., Alpaugh, M., Corben, A., Riolo, M., Beattie, B., Pressl, C., Peter, R. I., Xu, C., Trondl, R., Patel, H. J. et al. (2016). The epichaperome is an integrated chaperome network that facilitates tumour survival. Nature *538*, 397-401.

Roffé, M., Beraldo, F. H., Bester, R., Nunziante, M., Bach, C., Mancini, G., Gilch, S., Vorberg, I., Castilho, B. A., Martins, V. R., and Hajj, G. N. M. (2010). Prion protein interaction with stress-inducible protein 1 enhances neuronal protein synthesis via mTOR. Proc. Natl. Acad. Sci. USA *107*, 13147-13152.

Röhl, A., Tippel, F., Bender, E., Schmid, A. B., Richter, K., Madl, T., and Buchner, J. (2015a). Hop/Sti1 phosphorylation inhibits its co-chaperone function. EMBO Rep. *16*, 240-249.

Röhl, A., Wengler, D., Madl, T., Lagleder, S., Tippel, F., Herrmann, M., Hendrix, J., Richter, K., Hack, G., Schmid, A. B., Kessler, H., Lamb, D. C., and Buchner, J. (2015b). Hsp90 regulates the dynamics of its cochaperone Sti1 and the transfer of Hsp70 between modules. Nat. Commun. *6*, 6655.

Röth, S., Mirus, O., Bublak, D., Scharf, K. D., and Schleiff, E. (2017). DNA-binding and repressor function are prerequisites for the turnover of the tomato heat stress transcription factor HsfB1. Plant J. *89*, 31-44.

Ruckova, E., Muller, P., Nenutil, R., and Vojtesek, B. (2012). Alterations of the Hsp70/Hsp90 chaperone and the HOP/CHIP co-chaperone system in cancer. Cell. Mol. Biol. Lett. *17*, 446-458.

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.

Sakudo, A., Lee, D. C., Li, S., Nakamura, T., Matsumoto, Y., Saeki, K., Itohara, S., Ikuta, K., and Onodera, T. (2005). PrP^c cooperates with STI1 to regulate SOD activity in PrP^c-deficient neuronal cell line. Biochem. Biophys. Res. Commun. *328*, 14-19.

Samant, R. S., Livingston, C. M., Sontag, E. M., and Frydman, J. (2018). Distinct proteostasis circuits cooperate in nuclear and cytoplasmic protein quality control. Nature *563*, 407-411.

Santos, T. G., Beraldo, F. H., Hajj, G. N., Lopes, M. H., Roffe, M., Lupinacci, F. C., Ostapchenko, V. G., Prado, V. F., Prado, M. A., and Martins, V. R. (2013). Laminin-γ1 chain and stress inducible protein 1 synergistically mediate PrPC-dependent axonal growth via Ca2+ mobilization in dorsal root ganglia neurons. J. Neurochem. *124*, 210-223.

Santos, T. G., Silva, I. R., Costa-Silva, B., Lepique, A. P., Martins, V. R., and Lopes, M. H. (2011). Enhanced neural progenitor/stem cells self-renewal via the interaction of stress-inducible protein 1 with the prion protein. Stem Cells *29*, 1126-1136.

Scherrer, T., Mittal, N., Janga, S. C., and Gerber, A. P. (2010). A screen for RNA-binding proteins in yeast indicates dual functions for many enzymes. PLoS ONE *5*, e15499.

Scheufler, C., Brinker, A., Bourenkov, G., Pegoraro, S., Moroder, L., Bartunik, H., Hartl, F. U., and Moarefi, I. (2000). Structure of TPR domain-peptide complexes: critical elements in the assembly of the Hsp70-Hsp90 multichaperone machine. Cell *101*, 199-210.

Schmid, A. B., Lagleder, S., Grawert, M. A., Rohl, A., Hagn, F., Wandinger, S. K., Cox, M. B., Demmer, O., Richter, K., Groll, M., Kessler, H., and Buchner, J. (2012). The architecture of functional modules in the Hsp90 co-chaperone Sti1/Hop. EMBO J. *31*, 1506-1517.

Schmidt, J. C., Manhaes, L., Fragoso, S. P., Pavoni, D. P., and Krieger, M. A. (2018). Involvement of STI1 protein in the differentiation process of *Trypanosoma cruzi*. Parasitol. Int. *67*, 131-139.

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.

Schwarz, K., Baindur-Hudson, S., Blatch, G. L., and Edkins, A. L. (2023). Hsp70/Hsp90 Organising Protein (Hop): Coordinating much more than chaperones. Subcell. Biochem. *101*, 81-125.

Seo, J. H., Park, J. H., Lee, E. J., Vo, T. T., Choi, H., Kim, J. Y., Jang, J. K., Wee, H. J., Lee, H. S., Jang, S. H., Park, Z. Y., Jeong, J., Lee, K. J., Seok, S. H., Park, J. Y., Lee, B. J., Lee, M. N., Oh, G. T., and Kim, K. W. (2016). ARD1-mediated Hsp70 acetylation balances stress-induced protein refolding and degradation. Nat. Commun. *7*, 12882.

Serlidaki, D., van Waarde, M., Rohland, L., Wentink, A. S., Dekker, S. L., Kamphuis, M. J., Boertien, J. M., Brunsting, J. F., Nillegoda, N. B., Bukau, B., Mayer, M. P., Kampinga, H. H., and Bergink, S. (2020). Functional diversity between HSP70 paralogs caused by variable interactions with specific co-chaperones. J. Biol. Chem. *295*, 7301-7316.

Shimamoto, S., Takata, M., Tokuda, M., Oohira, F., Tokumitsu, H., and Kobayashi, R. (2008). Interactions of S100A2 and S100A6 with the tetratricopeptide repeat proteins, Hsp90/Hsp70-organizing protein and kinesin light chain. J. Biol. Chem. *283*, 28246-28258.

Shonhai, A., Picard, D., and Blatch, G. L. (2021). Heat shock proteins of malaria. Adv. Exp. Med. Biol. *1340*,

Silva, N. S. M., Bertolino-Reis, D. E., Dores-Silva, P. R., Anneta, F. B., Seraphim, T. V., Barbosa, L. R. S., and Borges, J. C. (2020). Structural studies of the Hsp70/Hsp90 organizing protein of *Plasmodium falciparum* and its modulation of Hsp70 and Hsp90 ATPase activities. Biochim. Biophys. Acta Proteins Proteom. *1868*, 140282.

Silverstein, A. M., Galigniana, M. D., Kanelakis, K. C., Radanyi, C., Renoir, J. M., and Pratt, W. B. (1999). Different regions of the immunophilin FKBP52 determine its association with the glucocorticoid receptor, hsp90, and cytoplasmic dynein. J. Biol. Chem. *274*, 36980-36986.

Sims, J. D., McCready, J., and Jay, D. G. (2011). Extracellular heat shock protein (Hsp)70 and Hsp90α assist in matrix metalloproteinase-2 activation and breast cancer cell migration and invasion. PLoS ONE *6*, e18848.

Skarra, D. V., Goudreault, M., Choi, H., Mullin, M., Nesvizhskii, A. I., Gingras, A. C., and Honkanen, R. E. (2011). Label-free quantitative proteomics and SAINT analysis enable interactome mapping for the human Ser/Thr protein phosphatase 5. Proteomics *11*, 1508-1516.

Smith, D. F. (2004). Tetratricopeptide repeat cochaperones in steroid receptor complexes. Cell Stress Chaperones *9*, 109-121.

Soares, I. N., Caetano, F. A., Pinder, J., Rodrigues, B. R., Beraldo, F. H., Ostapchenko, V. G., Durette, C., Pereira, G. S., Lopes, M. H., Queiroz-Hazarbassanov, N., Cunha, I. W., Sanematsu, P. I., Suzuki, S., Bleggi-Torres, L. F., Schild-Poulter, C., Thibault, P., Dellaire, G., Martins, V. R., Prado, V. F., and Prado, M. A. (2013). Regulation of Stress-Inducible Phosphoprotein 1 nuclear retention by Protein Inhibitor of Activated STAT PIAS1. Mol. Cell. Proteomics *12*, 3253-3270.

Song, H. O., Lee, W., An, K., Lee, H. S., Cho, J. H., Park, Z. Y., and Ahnn, J. (2009). C. elegans STI-1, the homolog of Sti1/Hop, is involved in aging and stress response. J. Mol. Biol. *390*, 604-617.

Song, Y., and Masison, D. C. (2005). Independent regulation of Hsp70 and Hsp90 chaperones by Hsp70/Hsp90-organizing protein Sti1 (Hop1). J. Biol. Chem. *280*, 34178-34185.

Southworth, D. R., and Agard, D. A. (2011). Client-loading conformation of the Hsp90 molecular chaperone revealed in the cryo-EM structure of the human Hsp90:Hop complex. Mol. Cell *42*, 771-781.

Spooner, R. A., Hart, P. J., Cook, J. P., Pietroni, P., Rogon, C., Höhfeld, J., Roberts, L. M., and Lord, J. M. (2008). Cytosolic chaperones influence the fate of a toxin dislocated from the endoplasmic reticulum. Proc. Natl. Acad. Sci. USA *105*, 17408-17413.

Stemmann, O., Neidig, A., Köcher, T., Wilm, M., and Lechner, J. (2002). Hsp90 enables Ctf13p/Skp1p to nucleate the budding yeast kinetochore. Proc. Natl. Acad. Sci. USA *99*, 8585-8590.

Su, T., Liao, J., Dai, Z., Xu, L., Chen, S., Wang, Y., Peng, Z., Zhang, Q., Peng, S., and Kuang, M. (2018). Stress-induced phosphoprotein 1 mediates hepatocellular carcinoma metastasis after insufficient radiofrequency ablation. Oncogene *37*, 3514-3527.

Sun, L., Prince, T., Manjarrez, J. R., Scroggins, B. T., and Matts, R. L. (2012). Characterization of the interaction of Aha1 with components of the Hsp90 chaperone machine and client proteins. Biochim. Biophys. Acta *1823*, 1092-1101.

Taherian, A., Krone, P. H., and Ovsenek, N. (2008). A comparison of Hsp90α and Hsp90β interactions with cochaperones and substrates. Biochem. Cell Biol. *86*, 37-45.

Tang, W., Wu, Y., Qi, X., Yu, R., Lu, Z., Chen, A., Fan, X., and Li, J. (2022). PGK1-coupled HSP90 stabilizes GSK3β expression to regulate the stemness of breast cancer stem cells. Cancer Biol. Med. *19*, 486-503.

Tillmann, B., Roth, S., Bublak, D., Sommer, M., Stelzer, E. H., Scharf, K. D., and Schleiff, E. (2015). Hsp90 is involved in the regulation of cytosolic precursor protein abundance in tomato. Mol. Plant *8*, 228-241.

Toribio, R., Mangano, S., Fernández-Bautista, N., Muñoz, A., and Castellano, M. M. (2020). HOP, a co-chaperone involved in response to stress in plants. Front. Plant Sci. *11*, 591940.

Travers, S. A., and Fares, M. A. (2007). Functional coevolutionary networks of the Hsp70-Hop-Hsp90 system revealed through computational analyses. Mol. Biol. Evol. *24*, 1032-1044.

Tsai, C. L., Chao, A., Jung, S. M., Tsai, C. N., Lin, C. Y., Chen, S. H., Sue, S. C., Wang, T. H., Wang, H. S., and Lai, C. H. (2016). Stress-induced phosphoprotein-1 maintains the stability of JAK2 in cancer cells. Oncotarget *7*, 50548-50563.

Tsai, C. L., Chao, A. S., Jung, S. M., Lin, C. Y., Chao, A., and Wang, T. H. (2018). Stress-induced phosphoprotein 1 acts as a scaffold protein for glycogen synthase kinase-3 β-mediated phosphorylation of lysine-specific demethylase 1. Oncogenesis *7*, 31.

Tsai, C. L., Tsai, C. N., Lin, C. Y., Chen, H. W., Lee, Y. S., Chao, A., Wang, T. H., Wang, H. S., and Lai, C. H. (2012). Secreted stress-induced phosphoprotein 1 activates the ALK2-SMAD signaling pathways and promotes cell proliferation of ovarian cancer cells. Cell Rep. *2*, 283-293.

Vaaltyn, M. C., Mateos-Jimenez, M., Muller, R., Mackay, C. L., Edkins, A. L., Clarke, D. J., and Veale, C. G. L. (2022). Native mass spectrometry-guided screening identifies hit fragments for HOP-HSP90 PPI inhibition. Chembiochem. *23*, e202200322.

van Der Spuy, J., Kana, B. D., Dirr, H. W., and Blatch, G. L. (2000). Heat shock cognate protein 70 chaperone-binding site in the co- chaperone murine stress-inducible protein 1 maps to within threeconsecutive tetratricopeptide repeat motifs. Biochem. J. *345*, 645-651.

Vural, B., Ugurel, E., Tuzun, E., Kurtuncu, M., Zuliani, L., Cavus, F., Icoz, S., Erdag, E., Gul, A., Gure, A. O., Vincent, A., Ozbek, U., Eraksoy, M., and Akman-Demir, G. (2011). Anti-neuronal and stress-induced-phosphoprotein 1 antibodies in neuro-Behcet's disease. J. Neuroimmunol. *239*, 91-97.

Walerych, D., Olszewski, M. B., Gutkowska, M., Helwak, A., Zylicz, M., and Zylicz, A. (2009). Hsp70 molecular chaperones are required to support p53 tumor suppressor activity under stress conditions. Oncogene *28*, 4284-4294.

Walker, V. E., Atanasiu, R., Lam, H., and Shrier, A. (2007). Co-chaperone FKBP38 Promotes HERG Trafficking. J. Biol. Chem. *282*, 23509-23516.

Walsh, N., Larkin, A., Swan, N., Conlon, K., Dowling, P., McDermott, R., and Clynes, M. (2011). RNAi knockdown of Hop (Hsp70/Hsp90 organising protein) decreases invasion via MMP-2 down regulation. Cancer Lett. *306*, 180-189.

Wang, J., You, H., Qi, J., Yang, C., Ren, Y., and Cheng, H. (2017). Autocrine and paracrine STIP1 signaling promote osteolytic bone metastasis in renal cell carcinoma. Oncotarget *8*, 17012-17026.

Wang, L., Bergkvist, L., Kumar, R., Winblad, B., and Pavlov, P. F. (2021). Targeting chaperone/co-chaperone interactions with small molecules: a novel approach to tackle neurodegenerative diseases. Cells *10*, 2596.

Wang, R. Y., Noddings, C. M., Kirschke, E., Myasnikov, A. G., Johnson, J. L., and Agard, D. A. (2022). Structure of Hsp90-Hsp70-Hop-GR reveals the Hsp90 client-loading mechanism. Nature *601*, 460-464.

Wang, T. H., Chao, A., Tsai, C. L., Chang, C. L., Chen, S. H., Lee, Y. S., Chen, J. K., Lin, Y. J., Chang, P. Y., Wang, C. J., Chao, A. S., Chang, S. D., Chang, T. C., Lai, C. H., and Wang, H. S. (2010). Stress-induced phosphoprotein 1 as a secreted biomarker for human ovarian cancer promotes cancer cell proliferation. Mol. Cell. Proteomics *9*, 1873-1884.

Wang, Y. X., Yu, T. F., Wang, C. X., Wei, J. T., Zhang, S. X., Liu, Y. W., Chen, J., Zhou, Y. B., Chen, M., Ma, Y. Z., Lan, J. H., Zheng, J. C., Li, F., and Xu, Z. S. (2023). Heat shock protein TaHSP17.4, a TaHOP interactor in wheat, improves plant stress tolerance. Int. J. Biol. Macromol. *246*, 125694.

Wegele, H., Haslbeck, M., Reinstein, J., and Buchner, J. (2003). Sti1 is a novel activator of the Ssa proteins. J. Biol. Chem. *278*, 25970-25976.

Whitesell, L., and Cook, P. (1996). Stable and specific binding of heat shock protein 90 by geldanamycin disrupts glucocorticoid receptor function in intact cells. Mol. Endocrinol. *10*, 705-712.

Willmer, T., Contu, L., Blatch, G. L., and Edkins, A. L. (2013). Knockdown of Hop downregulates RhoC expression, and decreases pseudopodia formation and migration in cancer cell lines. Cancer Lett. *328*, 252-260.

Wolfe, K. J., Ren, H. Y., Trepte, P., and Cyr, D. M. (2013). The Hsp70/90 cochaperone, Sti1, suppresses proteotoxicity by regulating spatial quality control of amyloid-like proteins. Mol. Biol. Cell *24*, 3588-3602.

Wolfe, K. J., Ren, H. Y., Trepte, P., and Cyr, D. M. (2014). Polyglutamine-rich suppressors of huntingtin toxicity act upstream of Hsp70 and Sti1 in spatial quality control of amyloid-like proteins. PLoS ONE *9*, e95914.

Xu, F., Kula-Eversole, E., Iwanaszko, M., Hutchison, A. L., Dinner, A., and Allada, R. (2019). Circadian clocks function in concert with heat shock organizing protein to modulate mutant huntingtin aggregation and toxicity. Cell Rep. *27*, 59-70 e54.

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.

Yamamoto, S., Subedi, G. P., Hanashima, S., Satoh, T., Otaka, M., Wakui, H., Sawada, K., Yokota, S., Yamaguchi, Y., Kubota, H., and Itoh, H. (2014). ATPase activity and ATP-dependent conformational change in the co-chaperone Hsp70/Hsp90-organizing protein (HOP). J. Biol. Chem. *289*, 9880-9886.

Yamashita, Y. M., Nakaseko, Y., Samejima, I., Kumada, K., Yamada, H., Michaelson, D., and Yanagida, M. (1996). 20S cyclosome complex formation and proteolytic activity inhibited by the cAMP/PKA pathway. Nature *384*, 276-279.

Yang, Y. C., Cheng, T. Y., Huang, S. M., Su, C. Y., Yang, P. W., Lee, J. M., Chen, C. K., Hsiao, M., Hua, K. T., and Kuo, M. L. (2015). Cytosolic PKM2 stabilizes mutant EGFR protein expression through regulating HSP90-EGFR association. Oncogene *35*, 3387-3398.

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.

Yi, F., Doudevski, I., and Regan, L. (2010). HOP is a monomer: investigation of the oligomeric state of the co-chaperone HOP. Protein Sci. *19*, 19-25.

Yi, F., and Regan, L. (2008). A novel class of small molecule inhibitors of Hsp90. ACS Chem. Biol. *3*, 645-654.

Yi, F., Zhu, P., Southall, N., Inglese, J., Austin, C. P., Zheng, W., and Regan, L. (2009). An AlphaScreen-based high-throughput screen to identify inhibitors of Hsp90-cochaperone interaction. J. Biomol. Screen. *14*, 273-281.

Yin, H., Deng, Z., Li, X., Li, Y., Yin, W., Zhao, G., Jiang, D., Sun, C., and Zhou, Y. (2019). Down-regulation of STIP1 regulate apoptosis and invasion of glioma cells via TRAP1/AKT signaling pathway. Cancer Genet. *237*, 1-9.

Young, J. C., Hoogenraad, N. J., and Hartl, F. U. (2003). Molecular chaperones Hsp90 and Hsp70 deliver preproteins to the mitochondrial import receptor Tom70. Cell *112*, 41-50.

Zanata, S. M., Lopes, M. H., Mercadante, A. F., Hajj, G. N., Chiarini, L. B., Nomizo, R., Freitas, A. R., Cabral, A. L., Lee, K. S., Juliano, M. A., de Oliveira, E., Jachieri, S. G., Burlingame, A., Huang, L., Linden, R., Brentani, R. R., and Martins, V. R. (2002). Stress-inducible protein 1 is a cell surface ligand for cellular prion that triggers neuroprotection. EMBO J. *21*, 3307-3316.

Zhai, E., Liang, W., Lin, Y., Huang, L., He, X., Cai, S., Chen, J., Zhang, N., Li, J., Zhang, Q., He, Y., Zeng, Z., Chen, M., Xu, L., and Peng, S. (2018a). HSP70/HSP90-organizing protein contributes to gastric cancer progression in an autocrine fashion and predicts poor survival in gastric cancer. Cell. Physiol. Biochem. *47*, 879-892.

Zhai, N., Jia, H., Ma, M., Chao, Y., Guo, X., and Li, H. (2018b). Characteristics of *AccSTIP1* in *Apis cerana cerana* and its role during oxidative stress responses. Cell Stress Chaperones *23*, 1165-1176.

Zhang, K., Duan, M., Zhang, L., Li, J., Shan, L., Zheng, L., and Liu, J. (2022). HOP1 and HOP2 are involved in salt tolerance by facilitating the brassinosteroid-related nucleo-cytoplasmic partitioning of the HSP90-BIN2 complex. Plant Cell Environ. *45*, 3551-3565.

Zhang, Z., Quick, M. K., Kanelakis, K. C., Gijzen, M., and Krishna, P. (2003). Characterization of a plant homolog of hop, a cochaperone of hsp90. Plant Physiol. *131*, 525-535.

Zhao, R., Davey, M., Hsu, Y. C., Kaplanek, P., Tong, A., Parsons, A. B., Krogan, N., Cagney, G., Mai, D., Greenblatt, J., Boone, C., Emili, A., and Houry, W. A. (2005). Navigating the chaperone network: integrative map of physical and genetic interactions mediated by the Hsp90 chaperone. Cell *120*, 715-727.

Zheng, C., Atlas, E., Lee, H. M. T., Jao, S. L. J., Nguyen, K. C. Q., Hall, D. H., and Chalfie, M. (2020). Opposing effects of an F-box protein and the HSP90 chaperone network on microtubule stability and neurite growth in *Caenorhabditis elegans*. Development *147*, dev189886.

Zheng, L., Roeder, R. G., and Luo, Y. (2003). S phase activation of the histone H2B promoter by OCA-S, a coactivator complex that contains GAPDH as a key component. Cell *114*, 255-266.

Zininga, T., Makumire, S., Gitau, G. W., Njunge, J. M., Pooe, O. J., Klimek, H., Scheurr, R., Raifer, H., Prinsloo, E., Przyborski, J. M., Hoppe, H., and Shonhai, A. (2015). *Plasmodium falciparum* Hop (PfHop) interacts with the Hsp70 chaperone in a nucleotide-dependent fashion and exhibits ligand selectivity. PLoS ONE *10*, e0135326.