Hop/Sti1 FACTS & LITERATURE

(necessarily incomplete!)

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

General:

- Reviews: Frydman and Höhfeld, 1997; Odunuga et al., 2004; Smith, 2004
- yeast Sti1 and mammalian Hop are 42% identical.
- upregulated by viral transformation (Honoré et al., 1992) and in colon cancer (Kubota et al., 2010).
- 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).
- 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:

- *Δsti1* in yeast: ts and cs (Nicolet and Craig, 1989). Altered mitochondrial morphology at 37°C (Hoseini et al., 2016).
- Sti1 overexpression suppresses *cut4* mutants in S. pombe (Cut4 is a component of the cyclosome) (Yamashita et al., 1996).
- in budding yeast: synthetic lethality and allele-specific complementation between *HSP90* and *STI1* (Chang et al., 1997), and synthetic lethality with *Δcpr7* (Duina et al., 1996), *mps1-1* (Jones et al., 1999), *Δsse1* (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 *Δsti1* (Chang et al., 1997; Carrigan et al., 2004). Synthetic growth defects at 18°C and 37°C in *Δsti1 Δsba1* (Fang et al., 1998). *Δsti1* 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).

- Sti1 overexpression cannot suppress lethality of *Δcns1* (Dolinski et al., 1998; Marsh et al., 1998) and Cns1 cannot suppress synthetic lethality of *Δsti1 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). *Δsti1* normal for the propagation of *{PSI$^+$}* and *{URE3}* prions (Kumar et al., 2015).
- A *Δsti1* 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).
- Hop, and other TRP-containing proteins, fished out in a 2-hybrid with the Hsc70 substrate binding domain (Liu et al., 1999a).
- A *Δsti1* 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 *Δydj1 Δsti1* 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).
- A *tpk2* ts allele is synthetically lethal with *Δsti1*, but can be partially rescued by a dominant *CDC37* mutation (Ren 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 *Δsti1* (Kaganovich et al., 2008).
- *Δsti1* strains are hypersensitive to molybdate (Millson et al., 2009).
- *Δsti1* 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).
- *C. elegans*: 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).
- Overexpression promotes expression of USP2 in transgenic silk worms (Hong et al., 2010).
- Maternal Hop is important for canalization in Drosophila by preventing transposon expression through a complex with Piwi and Hsp90 (Gangaraju et al., 2011). Required in germ line nurse cells to allow piRNA biogenesis and transposon silencing (Karam et al., 2017).
- Loss of function of Hop enhances tau toxicity in a fly model (Ambegaokar and Jackson, 2011).
- 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).
- 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).
- *hop3* loss-of-function mutant of *Arabidopsis thaliana* shows reduced pollen germination and hypersensitivity to ER stress (Fernández-Bautista et al., 2017).

Other *in vivo* analyses:

- Overexpression and antibody injections in Xenopus oocytes: anti-Hop delays attenuation; attenuation accelerated by Hop overexpression (Bharadwaj et al., 1999).
- Drug sensitivity: *Δsti1* and even more so *Δsse1 Δsti1* yeast strains are hypersensitive to Hsp90 drugs (Liu et al., 1999b; Piper et al., 2003; see also Song and Masison, 2005). *Δsti1* 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).
- 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 and cell migration (Willmer et al., 2013).
- 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).
- Epichaperome disruption in certain types of cancers by Hsp90α/β KD or inhibition or KD of Hop or Aha1 renders cells more resistant to Hsp90 inhibitors (Rodina et al., 2016).
- Knock-down in tomato stabilizes HsfB1 (Röth et al., 2017).
- Overexpressed and secreted in hepatocellular carcinoma patients (Chen et al., 2017).
- 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).

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).
- 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).

- 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).
- 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).
- 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).

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).
- Stoichiometry: Hop dimer binds two molecules of Hsp70 in the absence of Hsp90, but only one in the ternary complex (Hernández et al., 2002).
- 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 C. 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).
- 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).

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).

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 *Δsti1* 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).
- 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 *Δydj1 Δsti1* 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).

- 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).

Extracellular:

- Evidence for Hop secretion by tissue culture cells (Eustace and Jay, 2004; Lima et al., 2007) 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).

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).

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).

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