

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).
- ◆ 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).
- ◆ differential presence of different domains across evolution (see Flom et al., 2007).
- ◆ Evolutionary plasticity of Hsp90 and cochaperones (Johnson and Brown, 2009).

Genetics:

- ◆ $\Delta sti1$ in yeast: ts and cs (Nicolet and Craig, 1989).
- ◆ 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 $\Delta cpr7$ (Duina et al., 1996), *mps1-1* (Jones et al., 1999), $\Delta sse1$ (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 $\Delta sti1$ (Chang et al., 1997; Carrigan et al., 2004). Synthetic growth defects at 18°C and 37°C in $\Delta sti1 \Delta sba1$ (Fang et al., 1998). $\Delta sti1$ 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).
- ◆ Sti1 overexpression cannot suppress lethality of $\Delta cns1$ (Dolinski et al., 1998; Marsh et al., 1998) and Cns1 cannot suppress synthetic lethality of $\Delta sti1 hsp82$ (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), 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.

- ◆ 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 glucocorticoid receptor signaling and this can be complemented with human Hop (Carrigan et al., 2004; Nelson et al., 2004).
- ◆ 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).
- ◆ *C. elegans*: knock-down in an *hsf1* mutant leads to sterility (defects in gonadal development) (Gaiser et al., 2009), and a *sti1* mutant has a shortened lifespan and an impaired heat stress response (Song et al., 2009).
- ◆ 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).
- ◆ Loss of function of Hop enhances tau toxicity in a fly model (Ambegaokar and Jackson, 2011).

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: $\Delta sti1$ and even more so $\Delta sse1 \Delta sti1$ yeast strains are hypersensitive to Hsp90 drugs (Liu et al., 1999b; Piper et al., 2003; see also Song and Masison, 2005).
- ◆ Antibodies inhibit import into lysosomes *in vitro* (Agarraberes and Dice, 2001).
- ◆ 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). There are both PrP^c-dependent and independent pathways for neuroprotection and control of proliferation in the developing retina (Arruda-Carvalho et al., 2007). 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 $\alpha 7$ nicotinic acetylcholine receptor for which PrP^c may act as receptor or co-receptor (Beraldo et al., 2010).
- ◆ 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 (Longshaw et al., 2009).
- ◆ see [below](#) for use of novel inhibitors of interaction with Hsp90.
- ◆ Nitrosylation or knock-down improves CFTR $\Delta F508$ 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).

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).
- ◆ 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).

- ◆ 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 (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).

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).
- ◆ 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 Hsp46 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).

- ◆ 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 μ M without and with ATP, respectively (Wegele et al., 2003).
- ◆ Binding constants for Hsp90 and Hsp70 are 90 nM and 1.3 μ M, respectively, but the latter affinity increases to 250 nM in the ternary complex (Hernández et al., 2002).
- ◆ in complexes with Hsc70 (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).
- ◆ 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, 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 Hsp90 α /Hsp90 β -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 Ca²⁺-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).

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.

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).
- ◆ 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 *Δyjd1 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).
- ◆ Analysis of coevolution with Hsp90 and Hsp70 suggest additional functional domains (Travers and Fares, 2007).
- ◆ Bipartite NLS overlaps TPR2a (Daniel et al., 2008).

Extracellular:

- ◆ Hsp90 complex with secreted co-chaperones p23, Hop, Hsp70 and Hsp40 increases activation of MMP-2 (ATP-independent!) (Sims et al., 2011).

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).

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