p23 FACTS & LITERATURE

(necessarily incomplete!)

Reviews:

- Methodological reviews: Buchner et al., 1998
- General reviews: Morimoto, 2002; Felts and Toft, 2003; Picard, 2006a; Biebl and Buchner, 2023.
- p23 and steroid receptors: Cato et al., 2014
- chromatin and DNA-related function (Gvozdenov et al., 2019).
- in neurodegeneration (Bohush et al., 2019).
- tissue-specificity of co-chaperones and p23-like ones (Dean and Johnson, 2021).
- Hsp90 complex in malaria (Shonhai et al., 2021).

General:

- Note that the official gene name is PTGES3 in mammals, and that it is also called TEBP and cPGES. In budding yeast, the ortholog is called Sba1.
- small acidic protein, present in all tissues and from yeast to humans (Johnson et al., 1994). For expression specifically in male mouse reproductive organs, see Cheung-Flynn et al., 2005.
- there are two homologs, p23 and tsp23 (now called AARSD1 or p23^{H}AlaXp), at least in human; expression in heart and skelettal muscle is mutually exclusive (Freeman et al., 2000; see also Echeverría et al., 2016).
- predominantly cytoplasmic, but also found in the nucleus (Tanioka et al., 2000; Stavreva et al., 2004; Picard, 2006b). Recruited to stress granules along with Hsp90 and several co-chaperones (Pare et al., 2009). Goes to the nucleus in quiescent yeast (Tapia and Morano, 2010). Some differences in cytoplasmic-nuclear ratio during *Toxoplasma gondii* life cycle (Echeverria et al., 2010). p23 as part of a Hsp90-FKBP52-p23 complex forms an intranuclear perinuclear ring in undifferentiated neurons and redistributes during differentiation including to intermediate filaments (Quintá et al., 2010); both differentiation and disassembly are triggered by FK506 (Quintá and Galigniana, 2012). Influenza infection induces nuclear localization (Digard et al., 2011).
- functionally missing in wheat germ lysate, but can be complemented (Hutchison et al., 1995). Limiting component of the Hsp90 chaperone complex in retic. lysate and Sf9 cells (Morishima et al., 2003).
- p23 has been mistaken for the unrelated protein ALG-2 (apoptosis-linked gene 2) because the antibody clone Ab 22 recognizes p23 not ALG-2 (Mollerup et al., 2003) -> some of the literature must be reinterpreted, specifically:
    - low levels in normal tissues, upregulated in primary tumors, and even more in metastases (Krebs et al., 2002).
    - cerebral ischemia upregulates p23 correlating with DNA fragmentation (Li et al., 2000).

  - induction of apoptosis by CD95 crosslinking -> p23 co-IPs with CD95 and becomes cleaved to a shorter form (Jung et al., 2001; and Mollerup et al., 2003).
  - p23 is down-regulated in atherosclerotic plaques and in THP-1 macrophage cells upon treatment with aggregated LDL (Martinet et al., 2003).
  - FAK-2 (=PYK2) co-IPs (Schmidt et al., 2003).
  - hnRNPA2/B1 co-IPs (Mollerup et al., 2003).
- By global analysis in yeast, the Hsp90 complex including Sba1 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).
- There are two orthologs in *Arabidopsis* (Zhang et al., 2010). Expression is strongly heat-inducible in orchardgrass (Cha et al., 2009).
- Evolutionary plasticity of Hsp90 and cochaperones (Johnson and Brown, 2009). *Plasmodiidae* and *Trypanosomatidae* seem to have two p23s, of which groups A and B resemble more the human and yeast proteins, respectively (Batista et al., 2015; see also Silva et al., 2017).

Genetics:

- budding yeast p23 (= **Sba1**) knock-out has no major phenotype except that steroid receptor response is more sensitive to benzoquinone ansamycins; sensitivity is rescued both by yeast and by human p23 (Bohen, 1998); v-Src signaling is reduced (Bohen, 1998; Fang et al., 1998); cold-sensitive and synthetic interaction with Δ*sti1* at 18°C and 37°C (Fang et al., 1998). Δ*sba1* cells are sensitive to 3-aminotriazol (i.e. general control response defective) (Donzé and Picard, 1999). Sba1 overexpression and deletion of *SBA1* result in increased chromosome loss (Ouspenski et al., 1999). Required for accumulation of human PKR (Donzé et al., 2001). Others don't see increased sensitivity of a Δ*sba1* strain to Hsp90 inhibitors at 22°C (Piper et al., 2003). p23 partially suppresses GR signaling defects of certain Hsp82 mutants (Hawle et al., 2006). Sba1 is required for telomere maintenance and affects telomerase occupancy *in vivo* (Toogun et al., 2007). Analysis by synthetic gene array with Δ*sba1* (Echtenkamp et al., 2011). Not required for *{PSI$^+$}* and *{URE3}* prions (Kumar et al., 2015). Δ*sba1* is synthetic lethal with *rsc7* and *sth1*, and Δ*sba1 sth1* double mutants are hypersensitive to ethanol at higher temperature (Echtenkamp et al., 2016). Genomic map of Sba1/p23 and RSC component Sth1 overlap (Echtenkamp et al., 2016). Differentially required for the activity of exogenous clients (Sahasrabudhe et al., 2017). Poor complementation by human Hsp90α compared to Hsp90β mapped to Hsp90 N-terminus, and contributions of Sba1, Cpr6/7 to promote the closed state of α relative to β and yeast Hsp90 (Reidy and Masison, 2020). Comprehensive analysis of co-chaperone double mutants for growth and specific clients (Biebl et al., 2020). p23 tail helix (with remainder of tail) is necessary to suppress growth defect and GR activity (Noddings et al., 2022). Deletion of *SBA1* strongly affects loading and closing mutants of Hsp90 (Mercier et al., 2023).
- overexpression of yeast or human p23 in yeast, and human p23 in MCF7 cells increases estrogen receptor α (ER) activation (Knoblauch and Garabedian, 1999).
- Overexpression of Sba1 is growth inhibitory in a Δ*hsc82* strain, and this depends on Hsp90 binding (Oxelmark et al., 2003). *sgt* and *cns1* point mutants are hypersensitive to overexpression of Sba1, which must be able to bind Hsp90 (Johnson et al., 2014).

- Wos2 is the *S. pombe* homolog (complemented by Sba1); its overexpression suppresses Wee1 and is synthetically lethal with *cdc2* and an *hsp90* (*swo1*) mutation; a Δ*wos2* strain is not thermotolerant (Muñoz et al., 1999).
- Sba1 (or human p23) are required for full function of the dioxin receptor (AhR) in yeast (Cox and Miller III, 2002; Cox and Miller III, 2003), and overexpression suppresses inhibition by Hsp90 inhibitors (Cox and Miller III, 2003) and signaling defect of Hsp90 mutant (Cox and Miller III, 2004).
- genome-wide 2-hybrid screen in yeast reveals a few candidate direct or indirect interactors, including Cpr6, Cns1, Ppt1, Plb1, Dot5, Taf1, Adr1 (Millson et al., 2004).
- *C. elegans*: Requirements not clear as determined by RNA interference (see gene ZC395.10 in www.wormbase.org); "not essential" all the way to even "embryonic lethal". Encoded by gene *daf-41* whose mutation promotes dauer at elevated temperatures, heat stress resistance, and increased and shortened lifespans at elevated and reduced temperatures, respectively (Horikawa et al., 2015). 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 *daf-41* (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 (Zheng et al., 2020).
- Mouse: functional disruption of the p23 gene results in perinatal lethality with underdeveloped lungs and skin defects; glucocorticoid receptor function is impaired in null MEFs (Grad et al., 2006; Lovgren et al., 2007; see also Nakatani et al., 2007). Null embryos and MEFs display slight growth defect; prostaglandin pattern does not support prostglandin E2 synthase function for p23 (Lovgren et al., 2007) except that null embryo lungs, but not other tissues, have lower levels of PGE2 (Nakatani et al., 2007). AhR still works normally in heterozygous adults and null embryos (Flaveny et al., 2009). A transgenic mouse with overexpression of p23 develops hydronephrosis with altered expression of AhR target genes (Lee et al., 2011). Further characterization of skin defect reveals impaired cell-autonomous differentiation of keratinocytes and defective GR signaling in keratinocytes (Madon-Simon et al., 2017). Mice with mutation of very C-terminal PXLE motif (see below) are viable, but phenocopy effect of the Tibetan mutations in *PHD2* on the hypoxic hyperventilatory response (Song et al., 2020).
- p23/Sba1 expression protects yeast, mammalian cells (Forafonov et al., 2008; see also Seraphim et al., 2015), and *Leishmania* (Hombach et al., 2015) against Hsp90 inhibitors
- Overexpression of orchardgrass p23 augments thermotolerance of Δ*sba1* yeast strain (Cha et al., 2009).
- A role of Sba1/p23 in secretion and Golgi function (Echtenkamp et al., 2011) is supported by: (i) p23 is overrepresented at Golgi; (ii) absence of Sba1/p23 renders cells more sensitive to brefeldin A; (iii) absence of Sba1/p23 increases amount of α-1,6-mannose modified proteins; (iv) presence of Sba1/p23 has an inhibitory effect on secretion.
- p23 null MEFs have reduced cell motility and slightly lower levels of vinculin (Echtenkamp et al., 2011).
- The Sba1 network indicates a role for it in DNA repair, supported by the fact that yeast and MEFs without Sba1/p23 are hypersensitive to genotoxic agents (Echtenkamp et al., 2011).

- The only obvious phenotype of a P23 knock-out in *Leishmania* is an increased sensitivity to Hsp90 inhibitors (Hombach et al., 2015).
- *Arabidopsis*: p23 single and double knock-outs display reduced root growth, apparently because of impaired phloem and cell-to-cell transport of auxin (D'Alessandro et al., 2015), a function also previously associated with the Hsp90 complex (Kamphausen et al., 2002; Pérez-Pérez et al., 2004; Wang et al., 2013). Phosphorylation of p23-1 on S201 by CK2 is required for normal root development (D'Alessandro et al., 2019).
- p23 expression is downregulated by infection of the chestnut blight fungus (*Cryphonectria parasitica*) with Cryphonectria hypovirus 1 (CHV1) combined with tannic acid; p23 null strain has severely retarded growth, is hypovirulent for CHV1, and hypersensitive to Hsp90 inhibitors (Ko et al., 2023).
- Δ*wos2 Cryptococcus neoformans* displays defective oxidative stress responses and reduced virulence (Ball et al., 2024).

Other *in vivo* analyses:

- Overexpression and antibody injections in Xenopus oocytes: anti-p23 activates HSF1, and anti-p23 delays attenuation (Bharadwaj et al., 1999).
- Overexpression of Sba1, human p23 and tsp23 (= Aarsd1S) differentially affect ligand efficacies of several nuclear receptors in yeast and HeLa cells; Sba1 behaves like p23; effects are mediated by hormone binding domains and require prolonged exposure to ligand (Freeman et al., 2000).
- Sba1/p23 stimulates activity of estrogen receptor α in yeast and mammalian cells (Knoblauch and Garabedian, 1999), inhibits glucocorticoid receptor (Wochnik et al., 2004). p23 overexpression stimulates recruitment (and activity) of ERα at direct target sites and adhesion and invasion of MCF7 cells on fibronectin (Oxelmark et al., 2006). Gene expression profiles of such cells resemble those of invasive breast cancer and p23 expression correlates with higher disease recurrence and mortality in breast cancer patients (Simpson et al., 2010). Some effects are dependent on ERα and p23 also increases ERα cistrome (Simpson et al., 2012).
- Overexpression stimulates PPARα activity (Sumanasekera et al., 2003).
- Role in disassembly of transcriptional complexes: p23 disrupts TR transcription complexes in vitro; in vivo Hsp90 and p23 are recruited to chromatin-bound glucocorticoid receptor; promoter-tethered p23 and to varying extents Hsp90 inhibit adjacent GR, TR, NFκB, and AP-1 (Freeman and Yamamoto, 2002).
- Antisense oligos reduce levels of p23 and telomerase activity (Chang et al., 2002).
- Reduction with antisense oligos in rat spinal cord reduces nociceptive behavior (Hofacker et al., 2005).
- Apoptotic stimuli induce p23 cleavage and degradation; p23 can be C-terminally truncated by caspases 3, 7 and 8, and this is enhanced by geldanamycin (Gausdal et al., 2004; Mollerup and Berchtold, 2005). ER-stress induces caspase 3 and/or 7 cleavage of p23, and p23 plays a protective role against ER stress (Rao et al., 2006). *In vitro*, p23 was cleaved much more efficiently by caspase 7 than by caspase 3 (Walsh et al., 2008). Novobiocin analogs induce p23 cleavage by caspases (Radanyi et al., 2009). The C-terminally truncated p23 reduces Hsp90 phosphorylation and activity, for example for telomerase, possibly by recruiting more PP5 and thus

reducing Hsp90 phosphorylation (Woo et al., 2009). Inhibitory effects of gedunin effects are amplified by caspase 7 cleavage of p23 (Patwardhan et al., 2013).

- FRAP analyses: Hsp90 binding determines intracellular dynamics of p23 -> bulk of wild-type p23 is bound to Hsp90 in a variety of complexes whereas p23 unable to bind Hsp90 (W106A of human p23) moves by free diffusion (Picard, 2006b).
- Hsp90 complexes promoting folding (with p23) and degradation (in presence of Hsp90 inhibitor and/or with CHIP) compete with each other for phospho-tau folding versus degradation based on RNAi experiments (Dickey et al., 2007).
- Use of split Renilla luciferase assay to track p23/Hsp90 interaction in cells and mice, minus and plus Hsp90 inhibitors (Chan et al., 2008).
- p23 knock-down increases ERα turnover (Berry et al., 2008).
- FKBP51 overexpression stimulates recruitment of p23 to AR-Hsp90 complex and recombinant FKBP51 promotes p23 binding to Hsp90 in PPIase-dependent fashion (Ni et al., 2010).
- Analysis in yeast of effects of deleting p23 (Δ*sba1*) or inhibiting Hsp90 pharmacologically on gene expression patterns (Echeverría et al., 2011).
- Overexpression increases hormone binding capacity and chromatin recruitment of androgen receptor (AR) in Hsp90-independent way, and levels are increased in malignant prostate cancer (Reebye et al., 2012). Also modulates cytosolic apo-AR levels, and promotes cell motility (Cano et al., 2015).
- Levels increased in lung cancer; human p23 acts as transcription factor for COX-2 by direct promoter binding, independently of Hsp90; DNA binding requires residues R88, R93, and K95, and tumor-stimulated succinylation of residues K7, K33, and K79 promotes nuclear localization and function (Yu et al., 2023).
- Expression increased in most types of cancer (Wang et al., 2023).
- Deletion of p23/*SBA1* in yeast and mammalian cells leads to a compensatory increase in Gcn5 and Hdac1 expression, and major global changes in DNase I hypersensitive sites (Zelin et al., 2012).
- p23 and Gcn5 block transcription factors by stimulating release from DNA and acetylation of released factor, respectively; in addition, Gcn5 depends on p23 to gain access to the transcription factors but its acetylation activity is also blocked by direct interaction with p23 (Zelin et al., 2012).
- p23 KD compromises Hsf1 activation, reduces Hsf1-mediated maladaptive stress response and improves trafficking of functional CFTR mutant to cell surface (Roth et al., 2014).
- KD impairs superoxide production by Nox5 (Chen et al., 2015).
- CRISPR/Cas9 KD in the brain blocks opioid anti-nociception by preventing MAPK activation through the mu opioid receptor (Lei et al., 2019).
- KD of p23 or Hsp90 or inhibition of Hsp90 block necroptosis of pulmonary artery endothelial cells (Yu et al., 2020).
- Mapping of tail regions that are required for GR activation identified a far C-terminal helical region (Biebl et al., 2021). p23 tail helix (with remainder of tail) is necessary to suppress growth defect and GR activity in budding yeast (Noddings et al., 2022

Biochemistry:

- tetrameric (Bose et al., 1996) or dimeric (Weikl et al., 1999) or monomeric (Prodromou et al., 2000; Weaver et al., 2000) or both dimeric and monomeric (Hildenbrand et al., 2011)? Dimer might be a crystal artefact and is not necessary for chaperone function (Weaver et al., 2000).
- p23 interacts preferentially with nuclear receptor-DNA complexes *in vitro* and stimulates receptor-DNA dissociation in a Grip1 peptide inhibitable fashion (Freeman et al., 2000).
- Crystal structure of free human p23 (Weaver et al., 2000). Full-length structure of yeast Hsp82 in ATP-bound mode and complex with p23/Sba1 shows intimate contacts involving multiple regions of p23 and both the N-terminal and middle domains of Hsp90; p23 sits as monomer (2x per Hsp90 dimer) between Hsp90 monomers and favors conformation with closed lid (Ali et al., 2006). Computational study of dynamics and allosteric communication in Hsp90 complexes with Aha1 and p23 (Blacklock and Verkhivker, 2013).
- human p23 has been proposed to be identical to a cytosolic prostaglandin E2 synthase (cPGES); tyrosine 9 is essential (Tanioka et al., 2000). Hsp90 enhances cPGES activity in vitro, and in vivo stimuli that increase cPGES activity enhance association with Hsp90 and both are inhibited by GA (Tanioka et al., 2003). Knock-out or knock-down in cells increases PGE2 levels by reducing the inactivating enzyme 15-PGDH (Nakatani et al., 2011).
- Phosphorylation by CK2 on S113 and S118 (human) correlates with increased cPGES activity and Hsp90 association, and conversely Hsp90 association stimulates phosphorylation by CK2 (Kobayashi et al., 2004). *Arabidopsis* p23 proteins are phosphorylated *in vitro* by CK2 (Tosoni et al., 2011; D'Alessandro et al., 2019).
- NMR analysis of p23-Hsp90 complex; no effect of ATPγS and interactions with middle domain of Hsp90 (Martinez-Yamout et al., 2006).
- Sba1 keeps telomerase DNA binding dynamic and thereby promotes telomerase function (Toogun et al., 2007). Sba1/p23 promotes release of (idle) chromatin remodeler RSC from DNA and RSC nucleosome remodeling in the presence of ATP: it specifically targets the subunit Rsc3 (Echtenkamp et al., 2016). Destabilizes assembly of INO80 and SWR-C complexes with DNA cooperatively with Hsp90; Hsp90 and p23 dissociate SWR-C from F-actin and bias INO80 to binding F-actin in the presence of H2A.Z-containing nucleosomes (Wang et al., 2020).
- not required for reconstitution of functional Chk1 with Hsp90, Hsp70, Hsp40, Cdc37 and CK2 (Hop enhances) (Arlander et al., 2006; Felts et al., 2007).
- p23/Sba1 inhibits binding of GA to Hsp90 *in vitro* (Forafonov et al., 2008).
- SAXS analysis of *Leishmania* p23 shows elongated structure (Batista et al., 2015). The two *Leishmania* p23s have similar but not identical biochemical activities, e.g. in regulating Hsp90 and preventing temperature-induced aggregation (Batista et al., 2015).
- 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).

- p23 is differentially required for assembly of GR vs. MR HBD complexes *in vitro*, and conformation of GR in budding yeast (Sahasrabudhe et al., 2017). Not required for maturation of GR HBD through NudC pathway *in vitro* (Biebl et al., 2022).
- *Plasmodium falciparum* has two p23 proteins, which are only 13% identical, but inhibit the Hsp90 ATPase and have intrinsic chaperone activity (Silva et al., 2017).
- Directly binds Smyd2 in absence of Hsp90 (Obermann, 2018).
- Binds polyA+ RNA directly, dependent on C-terminal 30 amino acid tail (Liepelt et al., 2016). Binding to 3' UTR of mRNAs, notably *KIF15* mRNA, with stabilizing effect; upon LPS induction of macrophages, Hsp90-CK2 compete with mRNA for p23 binding (de Vries et al., 2021).
- Stuy of human Hsp90α mutants of phosphorylation sites Y38, 61, or 197 shows differential impact on interaction with p23 (Huo et al., 2024).
- With FKBP51 forms a protective ternary complex with tau, which delays tau aggregation slightly more than p23 alone (Chakraborty and Zweckstetter, 2025).

Complexes:

- binds directly to Hsp90 in an ATP-dependent fashion (Johnson and Toft, 1995; Johnson et al., 1996; see also Prodromou et al., 2000; Weaver et al., 2000; McLaughlin et al., 2006). Without ATP affinity is 120 µM (Siligardi et al., 2004). Binding is blocked by geldanamycin (Johnson and Toft, 1995) and novobiocin (Marcu et al., 2000). ATP-dependence is due to ATP-induced dimerization of Hsp90 (Prodromou et al., 2000; Siligardi et al., 2004). p23 inhibits basal and substrate-stimulated rate of ATP hydrolysis (McLaughlin et al., 2002; McLaughlin et al., 2006) and stabilizes the nucleotide-bound state of Hsp90 (Sullivan et al., 2002; McLaughlin et al., 2006). Two molecules of p23/Sba1 bind a dimer of Hsp90 and trap it in the ATP hydrolysis state (Richter et al., 2004; see also McLaughlin et al., 2006). Cocrystal clearly shows 2 molecules of Sba1 per Hsp90 dimer (Ali et al., 2006). Released by hyperacetylation of Hsp90 (Kovacs et al., 2005; Kekatpure et al., 2009). Binding competed by Aha1 and Hop but not Cdc37 (also binds N-terminal domain) or Cpr6 (Harst et al., 2005) but others see p23 in Aha1 complexes (Sun et al., 2012). Evidence for association with Hsp90-FKBP52-Hop complexes (Hildenbrand et al., 2011). Cpr6, but not Cpr7, promotes association of Aha1, which in turn drives Hsp90 to a partially closed state; together, Cpr6 and Aha1 displace Sti1, and p23 finally the release of Aha1 (Li et al., 2013). With eukaryotic Hsp90, co-chaperones such as p23 can impose directionality, with an asymmetric interaction of the two molecules of p23 with the Hsp90 homodimer and the specifics of the nucleotide turnover (Ratzke et al., 2014). p23 has higher affinity for Hsp90 dimer over Hsp90 oligomers, and promotes a shift of the oligomer-dimer equilibrium towards dimer (Lepvrier et al., 2015). p23 promotes Hsp90 NTD closure following NTD rotation (Lopez et al., 2021). Single-molecule analyses with Ste11 as client show equilibrium of interactions with only Cdc37/Hsp90, but progression to closed complex (energy-driven directionality) with Aha1, Sba1, and ATP (Vollmar et al., 2024).
- essential for assembly of stable steroid receptor heterocomplexes (Johnson and Toft, 1994; Dittmar et al., 1996).
- binding to GR-Hsp90 heterocomplexes is ATP-independent (Dittmar et al., 1997) (not compatible with more recent data, e.g. Kirschke et al., 2014).
- does not bind Hsp90-Hop-Hsp70 heterocomplexes (Dittmar et al., 1997; see also Kirschke et al., 2014).

- Stable intermediate consists of $(FKBP51)_1(GR)_1(Hsp90)_2(p23)_2$; when FKBP52 replaces FKBP51 to form dynamic transfer complex, p23 is expelled (Ebong et al., 2016), consistent with IP results with cell extracts (Schülke et al., 2010).
- binds to cytosine-5 methyltransferase (MTase) (Zhang and Verdine, 1996).
- in Hsp90 complexes with mutant p53 (Dasgupta and Momand, 1997; Whitesell et al., 1998). Also direct but weak interaction through acidic tail with DBD of p53 (Wu et al., 2018).
- also in GR complexes in yeast; released with hormone (Bohen, 1998).
- associated with reovirus protein σ1; association blocked by GA (Gilmore et al., 1998).
- yeast Sba1 binds Hsp82: stabilized by molybdate, dependent on non-hydrolyzable ATP *in vitro* and blocked by Macbecin or GA (Fang et al., 1998).
- various yeast Hsp82 point mutants (A97I, G170D, S485Y, T525I) cannot bind Sba1 *in vitro* (Fang et al., 1998).
- yeast p23 (Sba1) can bind both yeast and mammalian Hsp90, but yeast Hsp90 cannot bind mammalian p23 (Scheibel et al., 1999); and yet human p23 stimulates activity of a Hsp90 substrate in yeast (Knoblauch and Garabedian, 1999).
- in complexes with Hsp90 with active telomerase (Holt et al., 1999; Forsythe et al., 2001).
- binds Hsf1 trimer and probably also monomer (Xenopus system) (Bharadwaj et al., 1999).
- reverse transcriptase of duck hepatitis B virus (see below).
- associated with death domain kinase RIP along with Hsp90 (Lewis et al., 2000).
- CHIP reduces amounts of Hsp90-associated p23 (Connell et al., 2001).
- Evidence for substrate-stimulated assembly of four component complex with Hsp90-$p50^{Cdc37}$-FKBP52-p23 (Hartson et al., 2000). Others find no evidence for ternary complexes between Cdc37, Hsp90 and Sba1 (Siligardi et al., 2004).
- Harc <u>not</u> found in p23 complexes (Scholz et al., 2001).
- In complexes with PKR; PKR misfolded in presence of GA may bind p23 without Hsp90 (Donzé et al., 2001).
- FAK-2 (=PYK2) co-IPs (Schmidt et al., 2003).
- hnRNPA2/B1 co-IPs (Mollerup et al., 2003).
- p23 co-IPs with CD95 (Jung et al., 2001; and Mollerup et al., 2003).
- co-IPs with Flt3 (and Hsp90) (Yao et al., 2003).
- XAP-2 overexpression displaces p23 from AhR-Hsp90 complex (Hollingshead et al., 2004).
- co-IP with PUMA, possibly without Hsp90 (Rao et al., 2006).
- Hsp90 and many co-chaperones including Aha1, p23, and FKBP8 are part of the CFTR interactome, and p23 levels correlate with folding/export of CFTR ΔF508 (Wang et al., 2006; Okiyoneda et al., 2010).
- 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).
- RAR1 and SGT1 bind overlapping surfaces that are distinct from the p23 and Aha1 binding sites (Kadota et al., 2008; Zhang et al., 2008). Full-length SGT1 but not its CS domain alone compete with p23 for Hsp90 binding (Kadota et al., 2008). Aarsd1 competes with p23 (Echeverría et al., 2016).
- Interacts with Nup62 (Echeverría et al., 2009).
- Proteomic analysis in *Toxoplasma gondii* identifies a whole series of potential interactors (Echeverria et al., 2010).

- Plant p23's may not inhibit Hsp90 ATPase (Zhang et al., 2010).
- Protein microarray analysis suggests a role in ribosome biogenesis; indeed, yeast and MEFs without Sba1/p23 are hypersensitive to hygromycin and Sba1 enhances the release of maturation factors from pre-60S complexes (Echtenkamp et al., 2011).
- The composite Sba1 interaction network shows relatively little overlap with that of Hsp82, but there is a remarkable number of multiprotein complexes where Sba1 and Hsp82 affect adjacent subunits (Echtenkamp et al., 2011).
- Co-IPs with Bax (Vogel et al., 2012).
- Interacts with AR in Hsp90-independent way (Reebye et al., 2012).
- Interacts with Gcn5 (Zelin et al., 2012).
- Colocalizes with purinosomes (French et al., 2013).
- Binds prolyl hydroxylase domain protein 2 (PHD2) through the conserved very C-terminal P-X-L-E motif thereby recruiting PHD2 to Hsp90-bound HIF1α; a knock-down of p23 augments HIF1α levels (Song et al., 2013). There is a Tibetan variant of PHD2 where this interaction with p23 is abolished (Song et al., 2014). An erythrocytosis-associated mutation in the zinc finger of PHD2 abolishes interaction (Song et al., 2019). Effect of the Tibetan mutations in the *PHD2* gene of humanized mice on the hypoxic hyperventilatory response is phenocopied with mutation of very C-terminal PXLE motif of p23 (Song et al., 2020). Tibetan PHD2 variant does not affect PXLE-mediated interaction with ribosomal chaperone nascent polypeptide complex-α (NACA) explaining why Tibetans are not predisposed to erythrocytosis (Song et al., 2022).
- Promotes release of Hsp70 and association of Hsp90 with GR (Kirschke et al., 2014).
- Global proteomic analysis reveals a variety of interactions and notably with Argonaute proteins and IRS4 (Taipale et al., 2014).
- PKM2 complex with Hsp90-Hop-p23 stabilizes mutant EGFR (Yang et al., 2015).
- TAP purification of Sba1 interactors from *C. albicans* (O'Meara et al., 2019).
- Swr1 of SWR-C and Ino80 in yeast (Wang et al., 2020).
- Assembly of GR HBD complexes with *C. elegans* and human proteins, including p23, reveals cooperativity, and unexpected disruptive effects of p23 and Hop (Kaziales et al., 2020).
- Cryo-EM structure of GR-Hsp90 maturation complex shows p23-client contact, specifically the hydrophobic surface of the p23 tail helix binds the GR HBD surface at a hydrophobic patch that is conserved across evolution and steroid receptors, and the C-terminal strand of GR, potentially allosterically reorienting the GR helix 12 in the agonist-bound position (Noddings et al., 2022). Characterization of p23-containing GR-Hsp90 complexes *in vivo* by crosslinking of photoactivatable amino acid analogs at a large number of sites shows direct contacts of p23 with GR, and Hsp90-dependence of these interactions, and rapid disruption of the GR-Hsp90 complex, and of the direct GR contacts with p23 upon treatment with dexamethasone or the antagonist RU486 or geldanamycin (Baischew et al., 2023).
- When p23 enters the GR-LBD complex, which still contains Hop, the interplay between Hop DP2, p23 (including direct contacts between DP2 and the p23 C-terminal region), and the client releases Hop TPR2B from the Hsp90 middle domain, enabling Hsp90 closure (Dahiya et al., 2022).
- Hsp90-independent complexes with cyclophilin A (Daneri-Becerra et al., 2021).
- In an Hsp90 complex with GSK3β (Tang et al., 2022).

p23 chaperone:

- prevents thermal aggregation and loss of activity, more potent but similar to Hsp90 in stabilizing non-native proteins (Bose et al., 1996); keeps substrates in folding-competent state (Bose et al., 1996; Freeman et al., 1996). Orchardgrass p23 prevents thermal aggregation, too (Cha et al., 2009).
- essential for RNP formation of reverse transcriptase of duck hepatitis B virus along with Hsp90; binds RT directly; coincorporated into nucleocapsids (Hu et al., 1997). Accelerates and improves in vitro assembly of functional RT in purified system (Hu and Anselmo, 2000).
- p23 required for ligand-dependence of Hsp90 release from AhR by Arnt (Kazlauskas et al., 1999). Not released upon ligand binding without Arnt (Kazlauskas et al., 2001). Stimulates DNA binding competence in Hsp90-dependent fashion (Shetty et al., 2003). p23 may stabilize AhR in an Hsp90-independent way (Pappas et al., 2018).
- p23 as coupling factor: stimulates ATP-hydrolysis dependent release of substrates from Hsp90 (Young and Hartl, 2000; see also Kaziales et al., 2020).
- 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).
- C-terminally truncated p23 that is produced by caspases has reduced anti-aggregation activity *in vitro* (Mollerup and Berchtold, 2005) and affects several Hsp90-dependent activities (Woo et al., 2009).

Mapping of p23 domains:

- two domains (human p23): a stably folded N-terminal β-sheet domain and a mainly unstructured highly acidic C-terminal tail of about 30 to 50 aa; the latter is needed for chaperone activity but not for binding to Hsp90 (Weikl et al., 1999; Weaver et al., 2000). N-terminal part of C-terminal tail contains a 13-residue helix; within it their is a conserved motif FXXMMN, which can be found in NCoA3, which may allow this transcriptional coactivator to interact with GR in place of p23 through a second contact site (Noddings et al., 2022).
- in yeasts and plants, the acidic tail is interrupted by a GM/A-rich segment.
- C-terminus not required for stimulation of substrate release of Hsp90 (Young and Hartl, 2000).
- C-terminus, and notably AA 123-145, of Sba1 are required for ER signaling in yeast; mutations that abolish Hsp90 binding or render it ATP-independent compromise it (Oxelmark et al., 2003). Hsp90 binding but not chaperone activity required for repression of glucocorticoid receptor (Wochnik et al., 2004).
- Point mutations that affect Sba1 stability and function; a C-terminal frameshift that behaves like a dominant-negative mutant (Oxelmark et al., 2003).
- Structural model for interaction with Hsp90 based on evolutionary tracing (Zhu and Tytgat, 2004).
- Both N-termini are accessible in p23-Hsp90 complexes and can be tagged with fluorescent proteins without interfering with binding (Picard et al., 2006).
- Chaperone domain is required for regulation of telomerase (Toogun et al., 2007) and stimulating RSC mobility and function (Echtenkamp et al., 2016).

- Chaperone domain/activity not required for protection of Hsp90 against inhibitors (Forafonov et al., 2008).
- CS domain of p23 can replace that of B-Ind1 for complex formation with NS5A, Hsp90 and FKBP8, and conversely for p23 function in inhibiting GR (Taguwa et al., 2009).
- GNMGGLx7 sequence repeats and portion of N-terminal domain (-->???) of *Plasmodium falciparum* p23 not required for Hsp90 binding (Chua et al., 2010).
- Very C-terminal P-X-L-E motif required for binding PHD2 (Song et al., 2013).
- Analysis of structural properties and of effects on Hsp90 inhibitor sensitivity and thermotolerance in yeast of C-terminal truncations of human p23 (Seraphim et al., 2015).
- Cleaved by caspase-7 in acidic tail at PEVD142↓G within an intrinsically disordered region allowing transient interaction with the caspase (Martini et al., 2017).
- Interaction domain with SMYD2 maps to the sequence motif (M/I/L/V)PXL of the very C-terminus of p23, which it shares with Hsp90 where it lies about ten amino acids N-terminal of the MEEVD (Obermann, 2018).
- Core domain without tail is insufficient for inhibiting the Hsp90 ATPase; requires adjacent conserved F121 and W124 (of yeast Sba1), which can interact with core domain (Biebl et al., 2021).
- Tail also contains a more C-terminal α-helical region, which can make transient contacts with M and C domains of Hsp90, notably in the internal client binding cleft, and can then directly interact with GR in the p23-Hsp90-GR ternary complex; this α-helical domain is required for GR activation (Biebl et al., 2021). C-terminal tail makes direct contact with Hop, including through DP2 (Dahiya et al., 2022).
- DNA binding requires residues R88, R93, and K95, and tumor-stimulated succinylation of residues K7, K33, and K79 promotes nuclear localization and transcription factor function (all independently of Hsp90) (Yu et al., 2023).
- Major binding site for FKBP51 is near the C-terminal end of the structured domain of p23, but the C-terminal tail also contributes; on FKBP51, p23 recognizes the TPR domain, where it competes with the MEEVD of Hsp90, and the p23 tail may bind the FK2/TPR interface region (Chakraborty and Zweckstetter, 2025).

Pharmacology:

- Celastrol binds non-covalently to p23 and induces fibrillization and as a consequence loss of p23 functions *in vivo* (Chadli et al., 2010).
- Gedunin is a specific p23 inhibitor and selectively affects p23-dependent functions (Hsp90 binding, GR and PR function, ...); it may bind the CS domain in a C-terminus dependent fashion (Patwardhan et al., 2013).
- Ailanthone binds p23 with low µM affinity, prevents Hsp90 interaction and induces the degradation of clients such as AR (He et al., 2016).
- Small molecule inhibitor and direct binder M16 inhibits both succinylation of p23 and its transcription factor activity (Yu et al., 2023).

Extracellular:

- Evidence for p23 secretion by tissue culture cells (Eustace and Jay, 2004).

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

p23 relatives:

- CS-domain proteins: within the 90 N-terminal amino acids p23 shares a common fold (antiparallel β-sandwich with 7 strands) and about 10% sequence identity with a large family of proteins including the small Hsps (Garcia-Ranea et al., 2002). This Cys-His rich domain (CHORD and Sgt1 {CS} domain) is shared, for example, with Siah-1-interacting protein (SIP) and Sgt1, which also contains a TPR domain (Dubacq et al., 2002). Human (and mouse) B-ind1, a potentiator of Rac1 (Courilleau et al., 2000). NudC, which binds Hsp90 with its CS domain and inhibits the ATPase activity (Zhu et al., 2010). The p23 C-terminus contains significant homologies with regions outside of the active site of the putative tyrosine phosphatase PTPLA. Binds Hsp90 through FXXW motif (Taguwa et al., 2008). Human tsp23 (see Freeman et al., 2000), now referred to as AARSD1 and $p23^{H}$AlaXp in its long form (Nawaz et al., 2011; Echeverría et al., 2016).
- NMR structure of SGT1 CS domain shows extensive similarities with p23 (Botër et al., 2007).

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