p23 FACTS & LITERATURE

(necessarily incomplete!)

Reviews:

- Felts and Toft, 2003; see also Morimoto, 2002 and Picard, 2006a

General:

- 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 seems to be mutually exclusive (Freeman et al., 2000).
- 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). 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).
- ♦ Expression is strongly heat-inducible in orchardgrass (Cha et al., 2009).
- ♦ Evolutionary plasticity of Hsp90 and cochaperones (Johnson and Brown, 2009).

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 *Δsti1* at 18°C and 37°C (Fang et al., 1998). *Δsba1* 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 *Δsba1* 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 *Δsba1* (Echtenkamp et al., 2011).
- ♦ overexpression of yeast or human p23 in yeast, and human p23 in MCF7 cells increases estrogen receptor (ER) activation (Knoblauch and Garabedian, 1999).
- ♦ Overexpression of Sba1 is growth inhibitory in a *Δhsc82* strain, and this depends on Hsp90 binding (Oxelmark et al., 2003).
- ♦ 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 *Δwos2* 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).
- ♦ Requirements in C. elegans not clear as determined by RNA interference (see gene ZC395.10 in www.wormbase.org): "not essential" all the way to even "embryonic lethal".
- ♦ 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).
- ♦ p23/Sba1 expression protects yeast and mammalian cells against Hsp90 inhibitors (Forafonov et al., 2008).

- Overexpression of orchardgrass p23 augments thermotolerance of *Δsba1* 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).

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 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).
- 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).

- 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 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 (*Δsba1*) or inhibiting Hsp90 pharmacologically on gene expression patterns (Echeverría et al., 2011).

Biochemistry:

- Methodological reviews: Buchner et al., 1998
- 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).
- human p23 has been proposed to be identical to a cytosolic <u>prostaglandin E2 synthase</u> (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). Phosphorylated in vitro by CK2 (Tosoni et al., 2011).
- 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).
- <u>not</u> 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).

- Celastrol binds non-covalently to p23 and induces fibrillization and as a consequence loss of p23 functions *in vivo* (Chadli et al., 2010).

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). Evidence for association with Hsp90-FKBP52-Hop complexes (Hildenbrand et al., 2011).
- binding to GR-Hsp90 heterocomplexes is ATP-independent (Dittmar et al., 1997).
- does not bind Hsp90-Hop-Hsp70 heterocomplexes (Dittmar et al., 1997).
- 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 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).
- 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).

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 assembly of stable steroid receptor heterocomplexes (Johnson and Toft, 1994; Dittmar et al., 1996).
- 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 as coupling factor: stimulates ATP-hydrolysis dependent release of substrates from Hsp90 (Young and Hartl, 2000).
- 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).
- 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).
- 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).

Extracellular:

- 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 (Nawaz et al., 2011).

- NMR structure of SGT1 CS domain shows extensive similarities with p23 (Botër et al., 2007).

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