Chapter 2
Functions of the Hsp90-Binding FKBP Immunophilins

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Abstract Hsp90 functionally interacts with a broad array of client proteins, but in every case examined Hsp90 is accompanied by one or more co-chaperones. One class of co-chaperone contains a tetratricopeptide repeat domain that targets the co-chaperone to the C-terminal region of Hsp90. Within this class are Hsp90-binding peptidylprolyl isomerases, most of which belong to the FK506-binding protein (FKBP) family. Despite the common association of FKBP co-chaperones with Hsp90, it is now clear that the client protein influences, and is influenced by, the particular FKBP bound to Hsp90. Examples include Xap2 in aryl hydrocarbon receptor complexes and FKBP52 in steroid receptor complexes. In this chapter, we discuss the known functional roles played by FKBP co-chaperones and, where possible, relate distinctive functions to structural differences between FKBP members.

Keywords Immunophilin · FKBP · Hsp90 · Steroid hormone receptor

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Introduction

Immunophilins are a large, functionally diverse group of proteins that are defined by their ability to bind immunosuppressive ligands. The immunophilins minimally contain a peptidyl-prolyl cis-trans isomerase (PPIase; also termed rotamase) domain to which the immunosuppressive drugs bind. Early investigations into the PPIase enzymatic activity led to the belief that the immunosuppressive drugs elicited their effects by inhibiting the PPIase activity. However, some compounds binding the PPIase active site efficiently inhibit PPIase activity without inducing immunosuppression, so PPIase activity is not critical for immune responses. It is now known that effector domains on the immunosuppressive drugs project from the PPIase pocket. This allows the immunophilin-drug complex to bind tightly to and inhibit calcineurin or target of rapamycin, signal transduction proteins required for immune responses (see Hamilton and Steiner 1998 for a detailed review on the mechanisms by which immunophilins and their ligands suppress immune responses).

Since the initial identification of the immunophilin proteins, multiple family members have been identified in all major branches of life. Some immunophilins are small proteins containing only a single PPIase domain while others are large multidomain proteins that contain one or more PPIase domains, as well as additional functional domains. The immunophilins are divided into two groups based on their ability to bind different immunosuppressive ligands: the FK506 binding proteins (FKBP), which also bind rapamycin, and the cyclosporin-A binding proteins or cyclophilins (CyP). The PPIase domains of FKBP and cyclophilins are structurally distinct and likely evolved independently. On the other hand, some members of either the FKBP or cyclophilin families contain a structurally similar tetratricopeptide repeat (TPR) domain that targets binding to heat shock protein 90 (Hsp90).

Hsp90 is an abundant molecular chaperone that interacts with a broad array of protein clients that regulate numerous important cellular pathways. Among the known Hsp90 clients are transcription factors (e.g., steroid hormone receptors, heat shock transcription factor 1, aryl hydrocarbon receptor), both serine/threonine and tyrosine kinases (e.g., Raf and Src-related kinases), and key regulatory enzymes (e.g., nitric oxide synthase and telomerase). A compilation of known Hsp90 clients maintained by Didier Picard at Univ. of Geneva can be accessed at: http://www.picard.ch/downloads/Hsp90interactors.pdf.

In concert with other chaperone proteins, Hsp90 facilitates client folding and proteolytic stability but can also promote client degradation. In the case of steroid receptors, Hsp90 and its associated co-chaperones also regulate receptor activity. Hsp90 binding to steroid receptors must be preceded by transient receptor interactions with Hsp40, Hsp70, and associated co-chaperones. Hsp90, which is recruited as a dimer in the latter stages of complex assembly, binds directly to the receptor ligand binding domain and stabilizes a receptor conformation that is competent for hormone binding. Proteins that are associated with Hsp90 in the functionally mature

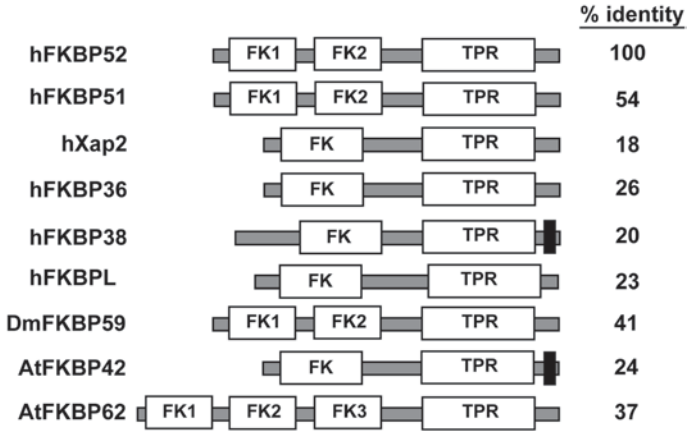

Fig. 2.1 Domain organization of representative Hsp90-binding TPR-containing FKBPs from vertebrate, insect, and plant sources were selected for comparison of domain organizations. The proteins are human FKBP52 (acc. # NP_002005), human FKBP51 (acc. # Q13451), human FKBPL (acc. # NP_071393.2), human Xap2 (acc. # O00170), human FKBP36 (acc. # NP_003593), human FKBP38 (acc. # NP_036313.3), *Drosophila melanogaster* FKBP59 (acc. # AAF18387), *Arabadopsis thaliana* FKBP42 (acc. # CAC00654), and *Arabadopsis thaliana* FKBP62 (acc. # AAB82062). The percent amino acid identity of each compared to human FKBP52 was determined from ClustalW2 alignments (http://www.ebi.ac.uk/clustalw). Each protein shown has at least one FKBP12-like domain (FK), which in some cases has peptidylprolyl isomerase activity and is the binding site for the immunosuppressant drug FK506, and one tetratricopeptide repeat domain (TPR), which is typically an Hsp90 binding site. The black box in the C-terminus of AtFKBP42 is a transmembrane domain used for anchoring the protein to the plasma and vacuolar membranes

receptor complex are p23, a co-chaperone that stabilizes Hsp90 binding to receptor, and any one of several TPR co-chaperones, including the immunophilin/PPIases FKBP52 (also termed p59, Hsp56, p50, HBI, FKBP59, and FKBP4), FKBP51 (also termed p54, FKBP54, and FKBP5), and CyP40, or the protein phosphatase PP5. As discussed below, receptor activity can vary depending on the particular TPR co-chaperone in mature receptor heterocomplexes.

The domain organization for several TPR co-chaperones is compared in Fig. 2.1. These co-chaperones compete for a common binding site in the C-terminal region of Hsp90 that includes the highly conserved -MEEVD sequence that terminates Hsp90. Co-crystallographic structures have shown how an MEEVD pentapeptide associates with the TPR binding pocket (Scheufler et al. 2000; Wu et al. 2004). Although the TPR domains for each of these co-chaperones are structurally similar and interact in a similar manner with Hsp90, the client protein bound by Hsp90 can influence the rank order of co-chaperone recruitment to Hsp90-client complexes (reviewed in Riggs et al. 2004). For instance, PP5 and FKBP51 are preferred components in glucocorticoid receptor (GR) complexes, FKBP51 is preferred in progesterone receptor (PR) complexes, and CyP40 is relatively enhanced in estrogen receptor (ER) complexes (Silverstein et al. 1997; Barent et al. 1998). On the other

hand, another TPR-containing FKBP, the hepatitis B virus protein X associated protein 2 (Xap2; also termed AIP, ARA9, and FKBP37) shows little interaction with steroid receptors but is strongly associated with the aryl hydrocarbon receptor-Hsp90 complex (Ma and Whitlock 1997; Meyer et al. 1998). The distinctive patterns of preference for co-chaperone association in client complexes is one line of evidence that the co-chaperones bound to Hsp90 can also interact with the Hsp90-bound client.

In addition to FKBP52, FKBP51, and XAP2, several other FKBP family members contain TPR domains that are known or likely to bind Hsp90. FKBP36 is structurally similar to XAP2 but is required for male fertility and homologous chromosome pairing in meiosis (Crackower et al. 2003). FKBP38 is a unique family member that is anchored to the mitochondrial and endoplasmic reticulum membranes, and is involved in a variety of processes including protein folding and trafficking, apoptosis, neural tube formation, cystic fibrosis transmembrane conductance regulator (CFTR) trafficking, and viral replication (reviewed in Edlich and Lucke 2011). FK506-binding protein like (FKBPL) protein is a divergent member of the FKBP family that can associate and functionally regulate steroid hormone receptors, has antiangiogenic properties, has a role in the DNA damage response, and controls tumor growth (reviewed in Robson and James 2012). *Drosophila melanogaster* express a TPR-containing immunophilin (DmFKBP59) that has high similarity to FKBP52/51 in vertebrates (Goel et al. 2001; Zaffran 2000). Plants have several FKBP genes that encode TPR domains; for example, in *Arabidopsis thaliana* there are 4 such genes: AtFKBP42, AtFKBP62, AtFKBP65 and AtFKBP72 (Romano et al. 2005; He et al. 2004). Although prokaryotic and Archaeal genomes also contain FKBP family members (Maruyama et al. 2004), none of these genes encode a TPR domain.

Structure/Function Relationships of Steroid Receptor-Associated FKBPs

X-ray crystallographic structures have been resolved for full-length FKBP51 and for overlapping fragments of FKBP52 (Fig. 2.2). FKBP51 and FKBP52 share greater than 60% amino acid sequence similarity, and individual domains do not differ markedly between FKBP51 and FKBP52. Both share a similar TPR domain composed of three tandem repeats of the degenerate 34-amino acid motif, which is a typical characteristic of TPR proteins (Blatch and Lassle 1999). Each repeat adopts a helix-turn-helix conformation and adjacent units stack in parallel to form a saddle-shaped domain with a concave binding pocket for Hsp90. In addition to the TPR domain, both FKBP51 and FKBP52 have two N-terminal domains, each of which is structurally similar to FKBP12. FK506-binding and PPIase activities reside in the most N-terminal domain (FK1), which has a pocket and active site residues similar to FKBP12. Due to several amino acid differences, the second domain (FK2) lacks drug binding and PPIase activity (Sinars et al. 2003).

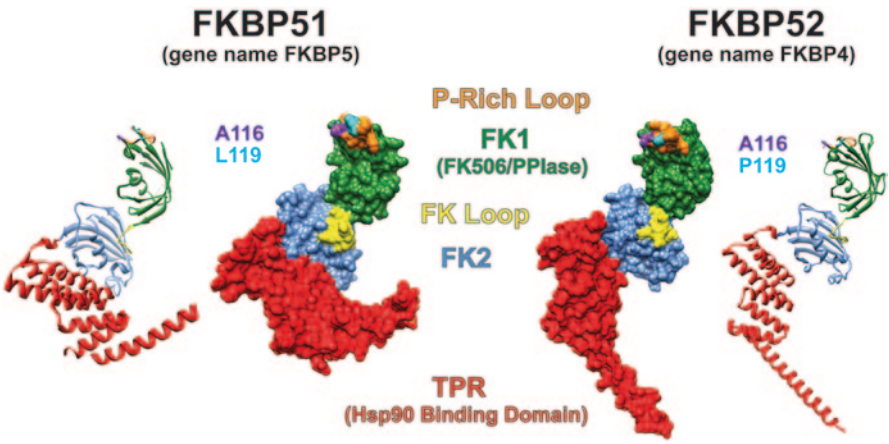

Fig. 2.2 Structural and functional characteristics of FKBP51 and FKBP52. Both ribbon and molecular surface depictions of the X-ray crystallographic structures for human FKBP51 (A; protein data bank number 1KT0) and a composite of two partial structures for human FKBP52 (B; protein data bank numbers 1Q1C and 1P5Q) are shown. In either protein the two FKBP12-like domains (FK1 and FK2, *green* and *blue* respectively) are indicated, the first of which has FK506 binding and PPIase activities. PPIase activity is not required for receptor regulation. The proline-rich loop (*orange*) that overhangs the PPIase catalytic pocket is critical for FKBP52 function and is responsible for the functional difference between FKBP51 and FKBP52. Two functionally critical residues (A116 and L119 in FKBP51 and A116 and P119 in FKBP52) within this loop are highlighted. The FK1 domain, the proline-rich loop in particular, is hypothesized to serve as an interaction surface within the Hsp90-receptor heterocomplex. A loop structure containing a CKII phosphorylation site in the hinge region between FK1 and FK2 is pointed out (*yellow*). The C-terminal TPR domain (*red*) consists of three helix-loop-helix motifs that form the Hsp90 binding pocket. Structures of the individual domains are highly similar between the two proteins, but the angle between FK2 and TPR domains of FKBP51 is more acute and probably more constrained than in FKBP52. The FKBP51 and FKBP52 structure models shown were constructed using UCSF Chimera version 1.5

The most striking difference in crystal structures relates to apparent domain:domain orientations. The FKBP52 structure shown in Fig. 2.2 is a composite model derived from merging the separate FK1-FK2 and FK2-TPR structures. The composite model suggests that the FKBP52 TPR domain is aligned in a more linear fashion with the FK domains rather than in the kinked conformation seen with FKBP51 (Fig. 2.2). In fact, the static orientations shown in crystal structures are likely more dynamic in solution, but the different crystal orientations are perhaps telling. Amino acid side chains unique to FKBP51 form a salt bridge between FK2 and TPR that would stabilize the domain:domain interaction in FKBP51 relative to FKBP52, which lacks this salt bridge. The apparently more malleable structure of FKBP52 might allow interactions within the receptor heterocomplex that are strained in FKBP51.

Significant progress has been made in understanding functionally important domains and residues on FKBP52 that contribute to the distinct ability to regulate steroid hormone receptor activity. Random mutagenesis studies in *S. cerevisiae*

demonstrated that two point mutations (A116V and L119P) in the FKBP51 FK1 domain, which does not potentiate steroid hormone receptor activity under normal conditions, confer full receptor potentiating ability to FKBP51, similar to that of FKBP52 (Riggs et al. 2007). This suggests that FKBP51 and FKBP52 functionally diverged at some point in evolution by only a few residues. A recent study suggests that there are differences in conformational dynamics between FKBP51 and FKBP52 within the proline-rich loop (Mustafi et al. 2014). 15N NMR relaxation measurements demonstrated that only the proline-rich loop in FKBP51 displays significantly larger line broadening, which is completely suppressed in the presence of the L11P mutation. These data suggest not only that differences in the proline-rich loop confer distinct functions to FKBP51 and FKBP52, but also that the proline-rich loop is functionally important for FKBP52 regulation of receptor activity. The current hypothesis holds that the FKBP52 proline-rich loop serves as an interaction surface, and the interaction partner is likely the receptor hormone binding domain (Sivils et al. 2011; De Leon et al. 2011).

Recent evidence by Bracher et al. demonstrate that the FK1-FK2 domains portray a flexible hinge that may account for regulatory differences between FKBP51 and FKBP52 (Bracher et al. 2013). It is hypothesized that the FK2 domain of FKBP52 contains an activation mechanism based on the calmodulin-binding motif at the C-terminus, yet this region is unable to bind FK506 and rapamycin, and lacks PPIase activity (Chambraud et al. 1993; Pirkl and Buchner 2001; Rouviere et al. 1997).

FKBP51 and FKBP52 also differ in the hinge region connecting FK1 and FK2 domains (FK loop). The FK loop of FKBP52 contains a -TEEED- sequence that has been identified as an *in vitro* substrate for casein kinase II; the corresponding sequence in FKBP51, -FED-, lacks the threonine phosphorylation site. Phosphorylation of FKBP52 is potentially important since the phospho-protein is reported to lose Hsp90 binding (Miyata et al. 1997). This difference was further tested using comparative analysis of FKBP51 and FKBP52 FK linker sequences (Cox et al. 2007). While the phosphomimetic mutation T143E had no effect on FKBP52 binding to Hsp90 in this study, the mutation did abrogate FKBP52 regulation of receptor activity. It is predicted that phosphorylation of residue T143 in the FKBP52 FK linker reorients the entire FK1 conformation, thereby eliminating FK1 interactions with the receptor hormone binding domain.

Cellular and Physiological Functions of Hsp90-Associated FKBPs

FKBP52

FKBP52 is expressed in most vertebrate tissues and cell lines, although its expression can be up-regulated by heat stress (Sanchez 1990), by estrogen in MCF-7 breast

cancer cells (Kumar et al. 2001), and by the homeobox transcription factor HoxA-10 in the peri-implantation mouse uterus (Daikoku et al. 2005). FKBP52 associates with steroid receptor complexes in an Hsp90-dependent manner, but FKBP52 is not required in a defined cell-free assembly system for receptor to reach the mature conformation that is competent for hormone binding (Dittmar et al. 1996; Kosano et al. 1998). Nonetheless, FKBP52 in cells potentiates hormone-dependent reporter gene activation by GR (Riggs et al. 2003), AR (Cheung-Flynn et al. 2005), and PR (Tranguch et al. 2005). Potentiation of hormone signaling can be related to an increase in receptor affinity for hormone (Riggs et al. 2003; Davies et al. 2005), but there may be additional mechanisms by which FKBP52 enhances receptor activity.

In concordance with hormone binding affinity changes, domain-swapping experiments between GR and ER, which is not potentiated by FKBP52, demonstrated that FKBP52 potentiation is localized to the ligand binding domain of GR (Riggs et al. 2003). FKBP52-dependent potentiation of receptor activity is abrogated in point mutants that are defective for Hsp90 binding, and potentiation is blocked by the PPIase inhibitor FK506 (Riggs et al. 2003; Cheung-Flynn et al. 2005). One model to explain these findings is that Hsp90 recruits FKBP52 to the receptor heterocomplex such that the FK1 PPIase can effectively catalyze isomerization of one or more proline substrates in the receptor ligand binding domain. However, studies have shown that point mutations within the FKBP52 PPIase pocket that eliminate PPIase activity have no effect on FKBP52 potentiation of receptor activity (Riggs et al. 2007). Thus, FK506-mediated inhibition of FKBP52 function likely occurs through the inhibition of FK1 interactions as opposed to inhibition of PPIase enzymatic activity. As discussed above, the FKBP52 FK1 domain as a whole is functionally important and the proline-rich loop that overhangs the PPIase pocket could serve as a functionally important interaction surface that contacts the receptor hormone binding domain within the receptor-chaperone heterocomplex. A structure-based screen for small molecules targeting an alternative surface of the androgen receptor hormone binding domain identified a series of fenamic acid molecules that allosterically affect coactivator binding at the activation function 2 (AF2) site through interaction with a surface cleft termed binding function 3 (BF3) (Estebanez-Perpina et al. 2007). Steroid hormone receptor structural comparisons identified this region to be a highly conserved regulatory surface that could serve as a therapeutic target for hormone-dependent diseases (Buzon et al. 2012). Interestingly, mutations within the AR BF3 surface (F673P, P723S, and C806Y) result in increased dependence on FKBP52 for function. In addition, a drug termed MJC13 that specifically inhibits FKBP52-regulated AR activity is predicted to target the BF3 surface (De Leon et al. 2011). Thus, the BF3 surface is a putative FKBP52 interaction and/or regulatory surface, and FKBP52 interaction with the receptor BF3 surface could allosterically affect receptor interactions at the AF2 site. In addition to the AR BF3 surface, recent studies suggest that the Helix 1–3 (H1-H3) loop in the GR LBD is an important site of FKBP regulation. Glucocorticoid insensitivity in guinea pig has been linked to sequence differences in the H1-H3 loop and substitution of the guinea pig H1-H3 loop into rat GR resulted in increased FKBP51-mediated repression of receptor activity. It is hypothesized that changes in the H1-H3 loop result in

changes within the GR-Hsp90 heterocomplex that favor FKBP51 repression over FKBP52 potentiation (Cluning et al. 2013).

FKBP52 has been shown by *in vitro* studies to have a chaperone activity that is independent of Hsp90 binding or PPIase (Bose et al. 1996; Pirkl and Buchner 2001). Like Hsp90 and numerous other chaperone components, FKBP52 can hold misfolded proteins in a non-aggregated state that is amenable to refolding. The possibility that chaperone holding activity displayed by FKBP52 plays some role in altering receptor activity cannot be dismissed, but this appears unlikely since holding activity is highly redundant among chaperone components. Furthermore, holding activity, unlike FKBP52-dependent potentiation of receptor activity, is neither PPIase- nor Hsp90-dependent. Unfortunately, no one has identified an FKBP52 mutation that disrupts holding activity in a discrete manner.

In an effort to extend biochemical and cellular data to the physiological level FKBP52 gene knockout (52KO) mice were generated, independently, by two groups (Cheung-Flynn et al. 2005; Yong et al. 2007). The mutant mice have striking reproductive phenotypes that can be attributed, at least in part, to loss of steroid receptor activity. Male 52KO mice are infertile and display abnormal virilization with persistent nipples, ambiguous external genitalia, and dysgenic seminal vesicles and prostate (Cheung-Flynn et al. 2005; Yong et al. 2007). These developmental defects are consistent with androgen insensitivity in these tissues. Testicular morphology, descent, histology, and spermatogenesis are normal and androgen production and release from testes is unimpaired; these developmental features are not highly androgen-dependent. On the other hand, sperm isolated from the epididymis have abnormal tail morphology and reduced motility suggestive of a defect in sperm maturation within the epididymis, a process that is androgen-dependent. Cellular studies confirm that FKBP52 is required for full AR function, which provides a rational explanation for androgen insensitivity in tissues of 52KO males.

52KO females have no gross morphological abnormalities, yet are completely infertile (Tranguch et al. 2005). Oocyte formation and release are not markedly impaired, and oocytes are competent for *in vitro* and *in vivo* fertilization. Infertility is due, at least in part, to a maternal failure of embryonic implantation and uterine decidualization. During the early stages of pregnancy, the 52KO uterus does not display the usual molecular or physiological markers for implantation. These events are largely dependent on progesterone actions, and both molecular and cellular studies confirm that FKBP52 is required for full PR activity. Additionally, FKBP52 is related to the etiology of endometriosis given that 52KO mice display increased endometrial lesions, inflammation, cell proliferation, and angiogenesis, and FKBP52 protein levels are reduced in human endometrial tissues (Hirota et al. 2008).

FKBP52 is critical for reproductive development and success in both male and female mice and its role can be traced to support of AR and PR function. Although GR-related phenotypes are not readily apparent, cellular and biochemical studies suggest that 52KO animals should display phenotypes related to reduced GR activity. Given that abnormal Mendelian ratios are not observed for heterozygous crosses,

the 52KO phenotype does include partial embryonic lethality. This combined with the reproductive defects leads to difficulty in obtaining sufficient numbers of 52KO animals for experiments. Thus, heterozygous fkbp52-deficient mice (52+/–) were generated to determine the *in vivo* roles for FKBP52 in GR-mediated physiology. 52+/– mice displayed phenotypes associated with reduced GR signaling including increased susceptibility to high-fat diet-induced hepatic steatosis, hyperglycemia, hyperinsulinemia, and behavioral alterations under basal and chronic stress conditions (Wadekar et al. 2004; Warrier et al. 2010).

Although FKBP52 does not alter ER function in cellular studies and 52KO mice show no signs of estrogen insensitivity, FKBP52 expression is upregulated by estrogens and FKBP52 is over-expressed in breast tumors (Ward et al. 1999). In addition, the FKBP52 gene is methylated in ER-negative, but not in ER-positive breast cancer cells (Ostrow et al. 2009). Thus, a few studies have identified FKBP52 as a potential regulator of at least ER expression in breast cancer.

Despite the fact that FKBP52 was initially discovered in the immune system, it is ubiquitously expressed and particularly abundant in the central nervous system. Thus, it is not surprising that FKBP52 is involved in neurodegenerative tauopathies including Alzheimer's (AD) and Pick's disease, fronto-temporal dementia and Parkinsonism linked to chromosome 17 (FTDP), and progressive supranuclear palsy (Haelens et al. 2007; Hernandez and Avila 2007). The defining neuropathological characteristic of tauopathies is the aberrant aggregation of insoluble hyperphosphorylated microtubule-associated protein (MAP) tau within the neurons, which is termed neurofibrillary tangles (NFTs) and is also referred to as paired helical filaments (PHF) (Cao and Konsolaki 2011). Recent studies have shown FKBP52's direct interaction with tau, particularly with its hyperphosphorylated form, has antagonistic effects on tubulin polymerization and microtubule assembly (Chambraud et al. 2007; Chambraud et al. 2010). In addition, FKBP52 was recently shown to induce Tau-P301L oligimerization and assembly into filaments (Giustiniani et al. 2014). More importantly, knockdown of FKBP52 was shown to restore axonal outgrowth and branching caused by Tau-P301L expression, thereby validating FKBP52 as an attractive therapeutic target in tauopathies. FKBP52 is known to be involved in subcellular rearrangement. Studies by Quintá et al. demonstrated that the overexpression of FKBP52 can induce neuronal differentiation and neurite outgrowth (Quintá et al. 2010).

Recent reports have shown that copper (Cu) contributes to the neuropathology of AD by interacting with copper binding domains of amyloid precursor proteins (APPs) and beta-amyloid (Aβ) peptides causing the formation of amyloid plaques and disrupting metal ion homeostasis (Barnham and Bush 2008; Drago et al. 2008; Kong et al. 2007). FKBP52 is involved in the regulation of cellular Cu homeostasis by interacting directly with the copper transport protein Atox1 (Sanokawa-Akakura et al. 2004), which is part of the Cu efflux machinery in neurons. In addition, both genetic and cellular data in Drosophila suggest a novel role for FKBP52 in the regulation of intracellular Cu homeostasis via binding to APP, thus, modulating the toxicity level of Aβ peptides (Sanokawa-Akakura et al. 2010).

S100A proteins belong to the EF-hand type calcium (Ca^{2+}) sensing protein family that are linked to regulation of various intracellular processes and are often expressed in a cell- and tissue-specific fashion (Santamaria-Kisiel et al. 2006; Wright et al. 2009). Based on biochemical evidence, it has been demonstrated that S100A1 and S100A6 interact with FKBP52 by competing with Hsp90 for the TPR domain in a Ca^{2+}-dependent manner (Shimamoto et al. 2010). Cellular data has linked S100A1s involvement in the neuronal cell dysfunction/death that occurs in AD by reducing APP expression and stabilizing the intracellular Ca^{2+} homeostasis (Zimmer et al. 2005). It seems that the function of FKBP52 can be regulated by Ca^{2+} homeostasis within the cell leading to effects on the phosphorylation of tau and pathology in AD. Interestingly, a Drosophila orthologue of FKBP52 termed FKBP59 was found to interact with the Ca^{2+} channel protein TRPL in photoreceptor cells and to influence Ca^{2+} influx (Goel et al. 2001). Subsequent studies revealed that FKBP52 similarly interacts with a subset of rat transient receptor potential channel (TRPC) proteins that form Ca^{2+} channels in the mammalian brain (Sinkins et al. 2004). The C-terminus of FKBP52 contains a predicted calmodulin binding domain, which enables the protein to bind to calmodulin-Sepharose in a Ca^{2+}-dependent manner, the biological function of which is still unknown (Silverstein et al. 1999).

Apart from the well-established roles of FKBP52 in steroid hormone receptor function, FKBP52, as with other Hsp90 co-chaperones, has been identified in a variety of client-Hsp90 heterocomplexes such as those containing kinases, aryl hydrocarbon receptor, and heat shock transcription factor; however, many of these interactions might reflect passive, transient association of the protein with Hsp90 and have no functional impact on client activity. FKBP52 is also linked to various Hsp90-independent interactions. Aside from the aforementioned Hsp90-independent interactors, FKBP52 has been found to interact directly with the interferon regulatory factor 4 (Mamane et al. 2000), which regulates gene expression in B and T lymphocytes, forms a complex with tyrosine kinase receptor RET51, which is involved in the development and maintenance of the nervous system (Fusco et al. 2010) and FKBP associated protein 48 (Chambraud et al. 1996), which influences proliferation of Jurkat T cells (Krummrei et al. 2003). Each of these interactions was found to be disrupted by FK506 and to target the FKBP52 PPIase domain to specific proline sites in each partner protein. Phenotypes potentially related to these interactions have not yet been assessed in 52KO mice. Not only does FKBP52 interact with proteins, but also FKBP52 is capable of directly binding adeno-associated virus DNA and regulating replication of the viral genome (Qing et al. 2001; Zhong et al. 2004). The relevant DNA binding site in FKBP52 has not been identified.

FKBP51

FKBP51/p54/FKBP54 was originally identified as a component of chicken PR complexes (Smith et al. 1990; Smith et al. 1993a; Smith et al. 1993b) and is now

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