ELSEVIER

Available online at www.sciencedirect.com
SCIENCE DIRECT®

The International Journal of Biochemistry & Cell Biology 37 (2005) 42–47

IJBCB

www.elsevier.com/locate/biocel

FKBP52

Todd H. Davies[1], Edwin R. Sánchez*

Department of Pharmacology, Medical College of Ohio, 3035 Arlington Avenue, Toledo, OH 43614-5804, USA

Received 15 January 2004; received in revised form 19 March 2004; accepted 19 March 2004

Abstract

The large molecular-weight immunophilin, FKBP52, is a known target of the immunosuppressive drug FK506. FKBP52 exhibits peptidyl-prolyl *cis–trans* isomerase (PPIase) activity, which is inhibited by the binding of FK506—properties that it shares with the smaller but better-studied immunophilin, FKBP12. Unlike FKBP12, however, FKBP52 does not mediate the immunosuppressive actions of FK506 and, due to its larger size, contains additional numerous functional domains. One such structure is a series of tetratricopeptide repeat (TPR) domains, which serve as binding sites for the ubiquitous and abundant molecular chaperone, Hsp90. It is this property as a TPR protein that best characterizes the known cellular roles of FKBP52. Here, we review the structural features of FKBP52 and relate them to the evolving and diverse functions of this protein. Although the most recognized role of FKBP52 is in regulation of steroid receptor signaling, other less well-known functions are also discussed.
© 2004 Elsevier Ltd. All rights reserved.

Keywords: Immunophilin; Tetratricopeptide repeat protein; FKBP; FK506; Steroid receptor; Chaperone; Hsp90

1. Introduction

FKBP52 belongs to a subclass of immunophilin proteins, FK506-binding proteins (FKBPs), based on its ability to bind the immunosuppressive drug FK506. The FK506-binding site of FKBP52 contains peptidyl-prolyl *cis–trans* isomerase (PPIase) activity. PPIase (also known as rotamase activity) is a chaperoning function that catalyzes the conversion of prolyl–peptide bonds from *trans*- to *cis*-proline, often a rate-limiting step in protein folding (Schiene & Fischer, 2000). The active PPIase domain shares 55% sequence homology with its smaller, but better-studied cousin FKBP12 (Callebaut et al., 1992). FKBP52 was discovered, not as a lone chaperone, but as a component of unliganded steroid receptor heterocomplexes—an interaction that occurs through heat shock protein 90 (Hsp90). Since then, a number of large molecular-weight immunophilins (FKBP52, FKBP51, and Cyp40) have been identified more by their abilities to bind Hsp90 via tetratricopeptide repeat (TPR) domains than by individual chaperoning activities.

Since its discovery in 1985, FKBP52 has gone through many designations. Faber and co-workers found FKBP52 while creating an antibody to the EC1 epitope of the 9S progesterone receptor (PR) complex of rabbit uterus (Nakao, Myers, & Faber, 1984; Tai et al., 1986). EC1 turned out to be on a 59-kDa protein, initially termed p59 by the Faber laboratory, which bound Hsp90 (Sanchez, Faber,

* Corresponding author. Tel.: +1-419-383-4182;
fax: +1-419-383-2871.
E-mail address: esanchez@mco.edu (E.R. Sánchez).
[1] Present address: Department of Molecular and Integrative Physiology, University of Michigan, 7744 Medical Science II Building, 1301 East Catherine Street, Ann Arbor, MI 48109-0622, USA.

1357-2725/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2004.03.013

Henzel, & Pratt, 1990). In addition to PR, p59 was found to be part of untransformed steroid complexes for the estrogen (ER), androgen (AR), and glucocorticoid (GR) receptors (Renoir, Radanyi, Faber, & Baulieu, 1990; Tai et al., 1986). Using Faber's EC1 antibody, Sanchez discovered a homologous 56-kDa protein, which he called p56, interacting with GR in human IM-9 cells (Sanchez et al., 1990). This smaller isoform in IM-9 cells was soon discovered to be inducible by both heat and chemical stress, and was relabeled Hsp56 (Sanchez, 1990). A short while later, two laboratories followed the discovery of high molecular-weight FK506-binding proteins (Fretz et al., 1991) by identifying Hsp56 (Yem et al., 1992) and p59 (Tai, Albers, Chang, Faber, & Schreiber, 1992) as an FK506-binding immunophilin. Several laboratories have had different designations for this hsp90-binding immunophilin: FKBP52 or hFKBP52 (Peattie et al., 1992), FKBP51 (not to be confused with a distinct relative now designated FKBP51) (Wiederrecht et al., 1992), FKBP59 (Tai et al., 1992), HBI (heat shock protein-binding immunophilin) (Callebaut et al., 1992), and p59-HBI (Chambraud et al., 1993). Although FKBP52 is now the standard nomenclature for this many-monikered protein, it has recently been discovered that the adeno-associated virus (AAV) D-sequence-binding protein, ssD-BP, is also FKBP52 (Qing et al., 2001), illustrating the versatility of this particular immunophilin.

2. Structure

Lebeau et al. (1992) first cloned the cDNA sequence of FKBP52 from rabbit liver. Since then, sequence, hydrophobicity and crystal structure analyses have shown the immunophilin to be composed of four distinct domains (Fig. 1). The first two domains include a functional site for peptidyl-prolyl *cis/trans* isomerase (PPIase) activity and a PPIase-like region, both similar in structure to the PPIase domain of FKBP12. Three tetratricopeptide repeat (TPR) domains occupy the third structural domain, while the fourth C-terminal domain contains a putative binding site for calmodulin.

The first 138 amino acids from the N-terminus constitutes the PPIase domain of FKBP52 and exhibits PPIase activity on peptide substrates in a protease-coupled assay when expressed alone (Chambraud et al., 1993). Similarly to FKBP12, FK506 binding also occurs in the first domain of the larger FKBP (Yem et al., 1993). Unlike FKBP12, however, FKBP52 does not inhibit calcineurin when bound to immunosuppressive ligands (Lebeau, Myagkikh, Rouviere-Fourmy, Baulieu, & Klee, 1994; Wiederrecht et al., 1992; Yem et al., 1993). A single amino acid, Lys121, corresponding to Ile90 of FKBP12, is responsible for this lack of calcineurin binding (Li et al., 2003).

Despite the lack of calcineurin association, interactions with other proteins, including itself as a dimer, are known to be dependent on the first domain of FKBP52. Although it is widely believed that only one molecule of immunophilin binds Hsp90 in a mature complex, FKBP52 does dimerize (Wiederrecht et al., 1992). The site for dimerization is probably near or embedded within the PPIase domain, as a proteolytic fragment containing the first domain behaves as a dimer independent of the rest of the protein (Yem et al., 1993). Hsp90 binding by immunophilins

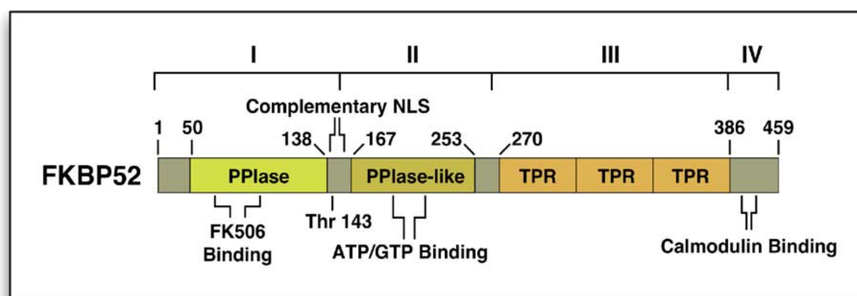

Fig. 1. Functional domains of human FKBP52. PPIase, peptidyl-prolyl *cis–trans* isomerase activity site. TPR, tetratricopeptide repeat domains responsible for interaction with Hsp90. For all other aspects, see text.

has been well studied and, even though a growing number of Hsp90 client proteins have been found to associate with FKBP52, the relationship between this immunophilin and the GR is best understood. Within the steroid receptor heterocomplex, Domain I of FKBP52 is necessary for potentiation of GR transactivity and is, therefore, thought to be responsible for direct receptor interaction (Riggs et al., 2003). However, direct interaction between a steroid receptor and FKBP52 has only been shown in a purified solution with GST-hGR in which addition of PPIase domain or TPR domain fragments failed to inhibit a weak immunophilin/GR binding (Silverstein et al., 1999). The PPIase domain, however, is clearly needed for dynein association to the GR complex (Galigniana, Radanyi, Renoir, Housley, & Pratt, 2001).

While the second domain also shares homology with FKBP12 (28%), the PPIase activity is marginal (Chambraud et al., 1993) and this domain has not been shown to bind FK506. A noteworthy aspect of Domain II, other than the close relation to a PPIase activity site, is a consensus ATP/GTP-binding sequence between amino acids 199 and 222 (Callebaut et al., 1992; Le et al., 1993). Whether the nucleotide-binding site functions in vivo is yet to be determined. Although few activities have been found in Domain II, functional sequences between the first two domains exist. Thr-143 in the hinge region between Domains I and II is phosphorylated by casein kinase-2 (CK2) and prevents binding of FKBP52 to Hsp90 (Miyata et al., 1997). An eight amino acid sequence, also found in this hinge region, is electrostatically complementary to receptor nuclear localization sequences (NLS) and antibodies to the sequence slow translocation of liganded GR to the nucleus (Czar, Lyons, Welsh, Renoir, & Pratt, 1995).

There is strong evidence that association of FKBP52 to all steroid receptors requires the three TPR regions located in Domain III (Radanyi, Chambraud, & Baulieu, 1994; Russell, Whitt, Chen, & Chinkers, 1999). TPRs are highly degenerate 34 amino acid sequences that mediate protein-protein interactions (Goebl & Yanagida, 1991). FKBP52, along with the other GR-associated immunophilins and PP5, bind to the C-terminal EEVD sequence of Hsp90 through electrostatic interactions (Scheufler et al., 2000). Point mutations to any of several basic sequences within the TPR domains can prevent binding to Hsp90 (Russell et al., 1999). Despite its prolyl isomerase activity, co-chaperone activity by FKBP52 seems to be independent of the protein's PPIase domain (Bose, Weikl, Buglm, & Buchner, 1996) and dependent instead on the TPR domains via a mechanism that requires Hsp90 binding (Pirkl, Fischer, Modrow, & Buchner, 2001).

Beyond the TPR-domains are two putative calmodulin (CaM) binding sites occupying the C-terminus of FKBP52 (Domain IV). FKBP52 also contains PEST sequences usually found in CaM-binding proteins (Massol, Lebeau, Renoir, Faber, & Baulieu, 1992). The calmodulin inhibitor, phenoxybenzamine, greatly decreases GR hormone binding, although it is not certain whether this is through FKBP52 or Hsp90 (Ning and Sanchez, 1995, 1996). Deletion of this region reduces the binding affinity of FKBP52 to Hsp90 (Cheung-Flynn, Roberts, Riggs, & Smith, 2003).

3. Biological function

It has been known for some time that FKBP52 can be found associated with steroid receptors (Pratt & Toft, 1997) and other proteins (Nair et al., 1996) in a complex with Hsp90. FKBP52 can only stably bind a client protein if Hsp90 is present (Czar et al., 1994a, 1994b). FKBP52 has been shown to affect GR-mediated transactivity. Riggs et al. (2003) have shown a potentiation of GR-mediated reporter gene expression by human FKBP52 in *S. cerevisiae*, which does not express a homolog to any known FKBP. A corresponding increase in GR hormone-binding function was also noticed. In the same experiments, no increase in hormone binding and transactivity was seen with FKBP51, PP5, or over-expressed Cpr7 (yeast homolog of Cyp40). A constitutively-active GR mutant failed to be potentiated by FKBP52, suggesting that the effect is pre-transcriptional. In mammalian cells, the displacement of FKBP51, which has been shown to decrease steroid binding activity when associated with GR (Denny, Valentine, Reynolds, Smith, & Scammell, 2000; Reynolds, Ruan, Smith, & Scammell, 1999), could explain the potentiation, but no FKBP51 homolog is known to exist in yeast. Thus, FKBP52 may itself be capable of maintaining GR in a high affinity state for hormone.

A role for FKBP52 in translocation of steroid receptors is accepted by many. The cytoplasmic fraction of

FKBP52 localizes to microtubules (Czar et al., 1994a, 1994b; Perrot-Applanat, Cibert, Geraud, Renoir, & Baulieu, 1995) and dynein co-purifies with FKBP52 (Czar et al., 1994a, 1994b). Association of dynein to FKBP52 is dependent on the PPIase domain, while GR co-immune purification with the motor protein requires both Domains I and III of FKBP52. This suggests that the immunophilin is serving as an adaptor between dynein, which binds at the PPIase site, and the GR/Hsp90 complex, which binds at the TPR-domain (Galigniana et al., 2002; Silverstein et al., 1999). The role of FKBP52 in translocation of receptors to the nucleus has been strengthened by the recent discovery of a switching mechanism in which hormone causes exchange of FKBP51 for FKBP52 in GR complexes (Davies, Ning, & Sanchez, 2002). This exchange also leads to co-recruitment of dynein motor protein and movement of GR as a complex to the nucleus of intact cells (Fig. 2). Thus, it is now likely that differential incorporation of TPR proteins into steroid receptor complexes may form the basis for subcellular trafficking of receptors.

While the activities of FKBP52 in the Hsp90 chaperone system are relatively well documented, there is still much to be learned about this protein. As stated, FKBP52 can accompany GR into the nucleus (Davies et al., 2002), but most of what is known about Hsp90/immunophilin interactions occurs in the cytoplasm. Yet, the majority of FKBP52 is located in the nucleus (Czar et al., 1994a, 1994b; Perrot-Applanat et al., 1995). Two recently discovered phenomena may shed some light on unknown functions of FKBP52. First, Gold, Densmore, Shou, Matzuk, and Gordon (1999) discovered that axonal elongation in neurons can be stimulated by FK506 through a mechanism that likely involves FKBP52. Qing et al. (2001) found that the single-stranded, D-sequence-binding protein (ssD-BP), a protein that binds the D-sequence of the adeno-associated viral genome to prevent second strand synthesis, is FKBP52. Tyrosine phosphoryla-

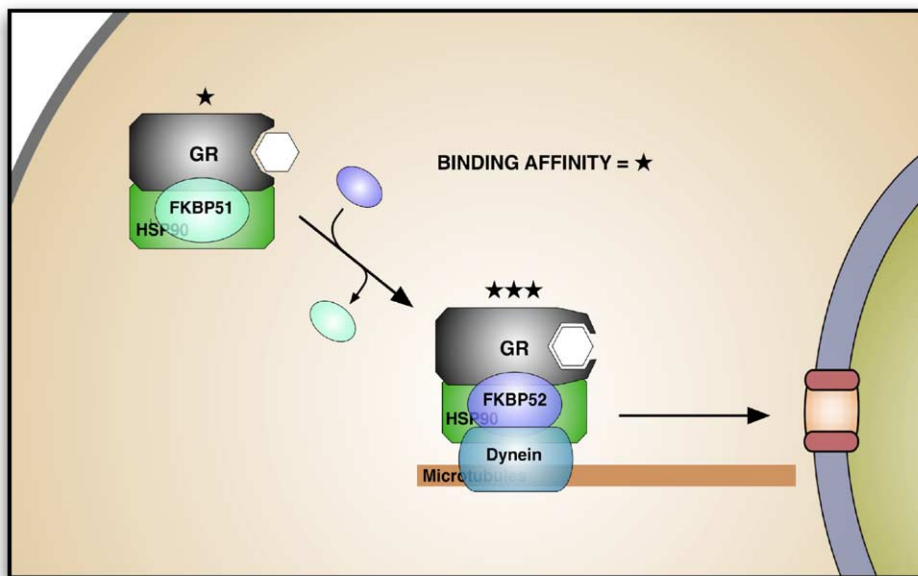

Fig. 2. Role of FKBP52 in steroid receptor function and trafficking. Cytoplasmic glucocorticoid receptor (GR) complexes are known to contain FKBP52 and the closely-related immunophilin, FKBP51. GR complexed with FKBP52 exhibits a higher hormone-binding affinity for steroidal hormone than receptors complexed with FKBP51. In some systems, FKBP51 appears to be the predominant immunophilin in hormone-free GR complexes, and binding of hormone causes exchange of FKBP51 for FKBP52. Following this exchange, FKBP52 serves to promote translocation of receptor to the nucleus due to its interaction with the motor protein, Dynein. Although the most recognized role of FKBP52 is in control of steroid receptor responses, other evolving roles for FKBP52 exist, including control of axonal elongation and viral replication (see text).

tion of FKBP52/ssD-BP by epidermal growth factor receptor tyrosine kinase (EGF-RTK) is required for D-sequence binding to inhibit viral replication of AAV. Moreover, a T-cell protein tyrosine phosphatase (TC-PTP) has been identified that reverses both the tyrosine phosphorylation of FKBP52/ssD-BP and the inhibitory effect on AAV replication (Qing et al., 2003). In this latest incarnation, FKBP52, a protein with no recognizable DNA-binding domain, apparently now acts as a single-stranded DNA-binding protein to protect cells from replication of viral genomes. It is likely, therefore, that many other functions, especially in the nucleus, will be discovered about this multipurpose immunophilin.

Acknowledgements

This work was supported by National Institutes of Health grant (DK48367) to E.R.S.

References

Bose, S., Weikl, T., Bugl, H., & Buchner, J. (1996). Chaperone function of Hsp90-associated proteins. *Science*, *274*, 1715–1717.

Callebaut, I., Renoir, J. M., Lebeau, M. C., Massol, N., Burny, A., & Baulieu, E. E. et al., (1992). An immunophilin that binds M(r) 90,000 heat shock protein: main structural features of a mammalian p59 protein. *Proceedings of the National Academy of Sciences, USA*, *89*, 6270–6274.

Chambraud, B., Rouviere-Fourmy, N., Radanyi, C., Hsiao, K., Peattie, D. A., & Livingston, D. J. et al., (1993). Overexpression of p59-HBI (FKBP59), full length and domains, and characterization of Pplase activity. *Biochemical and Biophysical Research Communications*, *196*, 160–166.

Cheung-Flynn, J., Roberts, P. J., Riggs, D. L., & Smith, D. F. (2003). C-terminal sequences outside the tetratricopeptide repeat domain of FKBP51 and FKBP52 cause differential binding to Hsp90. *Journal of Biological Chemistry*, *278*, 17388–17394.

Czar, M. J., Lyons, R. H., Welsh, M. J., Renoir, J. M., & Pratt, W. B. (1995). Evidence that the FK506-binding immunophilin heat shock protein 56 is required for trafficking of the glucocorticoid receptor from the cytoplasm to the nucleus. *Molecular Endocrinology*, *9*, 1549–1560.

Czar, M. J., Owens-Grillo, J. K., Dittmar, K. D., Hutchison, K. A., Zacharek, A. M., & Leach, K. L. et al., (1994a). Characterization of the protein-protein interactions determining the heat shock protein (hsp90 hsp70 hsp56) heterocomplex. *Journal of Biological Chemistry*, *269*, 11155–11161.

Czar, M. J., Owens-Grillo, J. K., Yem, A. W., Leach, K. L., Deibel Jr., M. R., & Welsh, M. J. et al., (1994b). The hsp56 immunophilin component of untransformed steroid receptor complexes is localized both to microtubules in the cytoplasm and to the same nonrandom regions within the nucleus as the steroid receptor. *Molecular Endocrinology*, *8*, 1731–1741.

Davies, T. H., Ning, Y. M., & Sanchez, E. R. (2002). A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. *Journal of Biological Chemistry*, *277*, 4597–4600.

Denny, W. B., Valentine, D. L., Reynolds, P. D., Smith, D. F., & Scammell, J. G. (2000). Squirrel monkey immunophilin FKBP51 is a potent inhibitor of glucocorticoid receptor binding. *Endocrinology*, *141*, 4107–4113.

Fretz, H., Albers, M. W., Galat, A., Standaert, R. F., Lane, W. S., & Burakoff, S. J. et al., (1991). Rapamycin and FK506 binding proteins (immunophilins). *Journal of American Chemical Society*, *113*, 1409–1411.

Galigniana, M. D., Harrell, J. M., Murphy, P. J., Chinkers, M., Radanyi, C., & Renoir, J. M. et al., (2002). Binding of hsp90-associated immunophilins to cytoplasmic dynein: direct binding and in vivo evidence that the peptidylprolyl isomerase domain is a dynein interaction domain. *Biochemistry*, *41*, 13602–13610.

Galigniana, M. D., Radanyi, C., Renoir, J. M., Housley, P. R., & Pratt, W. B. (2001). Evidence that the peptidylprolyl isomerase domain of the hsp90-binding immunophilin FKBP52 is involved in both dynein interaction and glucocorticoid receptor movement to the nucleus. *Journal of Biological Chemistry*, *276*, 14884–14889.

Goebl, M., & Yanagida, M. (1991). The TPR snap helix: a novel protein repeat motif from mitosis to transcription. *Trends in Biochemical Sciences*, *16*, 173–177.

Gold, B. G., Densmore, V., Shou, W., Matzuk, M. M., & Gordon, H. S. (1999). Immunophilin FK506-binding protein 52 (not FK506-binding protein 12) mediates the neurotrophic action of FK506. *Journal of Pharmacology and Experimental Therapeutics*, *289*, 1202–1210.

Le, B. S., Renoir, J. M., Radanyi, C., Chambraud, B., Joulin, V., & Catelli, M. G. et al., (1993). The mammalian heat shock protein binding immunophilin (p59/HBI) is an ATP and GTP binding protein. *Biochemical and Biophysical Research Communications*, *195*, 600–607.

Lebeau, M. C., Massol, N., Herrick, J., Faber, L. E., Renoir, J. M., & Radanyi, C. et al., (1992). P59, an hsp 90-binding protein. Cloning and sequencing of its cDNA and preparation of a peptide-directed polyclonal antibody. *Journal of Biological Chemistry*, *267*, 4281–4284.

Lebeau, M. C., Myagkikh, I., Rouviere-Fourmy, N., Baulieu, E. E., & Klee, C. B. (1994). Rabbit FKBP-59/HBI does not inhibit calcineurin activity in vitro. *Biochemical and Biophysical Research Communications*, *203*, 750–755.

Li, P., Ding, Y., Wu, B., Shu, C., Shen, B., & Rao, Z. (2003). Structure of the N-terminal domain of human FKBP52. *Acta Crystallographica Section D: Biological Crystallography*, *59*, 16–22.

Massol, N., Lebeau, M. C., Renoir, J. M., Faber, L. E., & Baulieu, E. E. (1992). Rabbit FKBP59-heat shock protein binding immunophillin (HBI) is a calmodulin binding protein. *Biochemical and Biophysical Research Communications*, *187*, 1330–1335.

Miyata, Y., Chambraud, B., Radanyi, C., Leclerc, J., Lebeau, M. C., & Renoir, J. M. et al., (1997). Phosphorylation of the immunosuppressant FK506-binding protein FKBP52 by casein kinase II: regulation of HSP90-binding activity of FKBP52. *Proceedings of the National Academy of Sciences, USA*, *94*, 14500–14505.

Nair, S. C., Toran, E. J., Rimerman, R. A., Hjermstad, S., Smithgall, T. E., & Smith, D. F. (1996). A pathway of multi-chaperone interactions common to diverse regulatory proteins: estrogen receptor, Fes tyrosine kinase, heat shock transcription factor Hsf1, and the aryl hydrocarbon receptor. *Cell Stress Chaperones*, *1*, 237–250.

Nakao, K., Myers, J. E., & Faber, L. E. (1984). Development of a monoclonal antibody to the rabbit 8.5S uterin progestin receptor. *Canadian Journal of Biochemistry and Cell Biology*, *63*, 33–40.

Ning, Y. M., & Sanchez, E. R. (1995). Evidence for a functional interaction between calmodulin and the glucocorticoid receptor. *Biochemical and Biophysical Research Communications*, *208*, 48–54.

Ning, Y. M., & Sanchez, E. R. (1996). In vivo evidence for the generation of a glucocorticoid receptor-heat shock protein-90 complex incapable of binding hormone by the calmodulin antagonist phenoxybenzamine. *Molecular Endocrinology*, *10*, 14–23.

Peattie, D. A., Harding, M. W., Fleming, M. A., Decenzo, M. T., Lippke, J. A., & Livingston, D. J. et al., (1992). Expression and characterization of human FKBP52, an immunophilin that associates with the 90-kDa heat shock protein and is a component of steroid receptor complexes. *Proceedings of the National Academy of Sciences, USA*, *89*, 10974–10978.

Perrot-Applanat, M., Cibert, C., Geraud, G., Renoir, J. M., & Baulieu, E. E. (1995). The 59 kDa FK506-binding protein, a 90 kDa heat shock protein binding immunophilin (FKBP59-HBI), is associated with the nucleus, the cytoskeleton and mitotic apparatus. *Journal of Cell Sciences*, *108*, 2037–2051.

Pirkl, F., Fischer, E., Modrow, S., & Buchner, J. (2001). Localization of the chaperone domain of FKBP52. *Journal of Biological Chemistry*, *276*, 37034–37041.

Pratt, W. B., & Toft, D. O. (1997). Steroid receptor interactions with heat shock protein and immunophilin chaperones. *Endocrinological Review*, *18*, 306–360.

Qing, K., Hansen, J., Weigel-Kelley, K. A., Tan, M., Zhou, S., & Srivastava, A. (2001). Adeno-associated virus type 2-mediated gene transfer: role of cellular FKBP52 protein in transgene expression. *Journal of Virology*, *75*, 8968–8976.

Qing, K., Li, W., Zhong, L., Tan, M., Hansen, J., & Weigel-Kelley, K. A. et al., (2003). Adeno-associated virus type 2-mediated gene transfer: role of cellular T-cell protein tyrosine phosphatase in transgene expression in established cell lines in vitro and transgenic mice in vivo. *Journal of Virology*, *77*, 2741–2746.

Radanyi, C., Chambraud, B., & Baulieu, E. E. (1994). The ability of the immunophilin FKBP59-HBI to interact with the 90-kDa heat shock protein is encoded by its tetratricopeptide repeat domain. *Proceedings of the National Academy of Sciences, USA*, *91*, 11197–11201.

Renoir, J. M., Radanyi, C., Faber, L. E., & Baulieu, E.-E. (1990). The non-DNA-binding heterooligomeric form mammalian steroid hormone receptors contains a hsp90-bound 59-kilodalton protein. *Journal of Biological Chemistry*, *265*, 10740–10745.

Reynolds, P. D., Ruan, Y., Smith, D. F., & Scammell, J. G. (1999). Glucocorticoid resistance in the squirrel monkey is associated with overexpression of the immunophilin FKBP51. *Journal of Clinical Endocrinology and Metabolism*, *84*, 663–669.

Riggs, D. L., Roberts, P. J., Chirillo, S. C., Cheung-Flynn, J., Prapapanich, V., & Ratajczak, T. et al., (2003). The Hsp90-binding peptidylprolyl isomerase FKBP52 potentiates glucocorticoid signaling in vivo. *EMBO Journal*, *22*, 1158–1167.

Russell, L. C., Whitt, S. R., Chen, M. S., & Chinkers, M. (1999). Identification of conserved residues required for the binding of a tetratricopeptide repeat domain to heat shock protein 90. *Journal of Biological Chemistry*, *274*, 20060–20063.

Sanchez, E. R. (1990). Hsp56: a novel heat shock protein associated with untransformed steroid receptor complexes. *Journal of Biological Chemistry*, *265*, 22067–22070.

Sanchez, E. R., Faber, L. E., Henzel, W. J., & Pratt, W. B. (1990). The 56-59-kilodalton protein identified in untransformed steroid receptor complexes is a unique protein that exists in cytosol in a complex with both the 70- and 90-kilodalton heat shock proteins. *Biochemistry*, *29*, 5145–5152.

Scheufler, C., Brinker, A., Bourenkov, G., Pegoraro, S., Moroder, L., & Bartunik, H. et al., (2000). Structure of TPR domain-peptide complexes: critical elements in the assembly of the Hsp70-Hsp90 multichaperone machine. *Cell*, *101*, 199–210.

Schiene, C., & Fischer, G. (2000). Enzymes that catalyse the restructuring of proteins. *Current Opinion in Structural Biology*, *10*, 40–45.

Silverstein, A. M., Galigniana, M. D., Kanelakis, K. C., Radanyi, C., Renoir, J. M., & Pratt, W. B. (1999). Different regions of the immunophilin FKBP52 determine its association with the glucocorticoid receptor, hsp90, and cytoplasmic dynein. *Journal of Biological Chemistry*, *274*, 36980–36986.

Tai, P. K., Albers, M. W., Chang, H., Faber, L. E., & Schreiber, S. L. (1992). Association of a 59-kilodalton immunophilin with the glucocorticoid receptor complex. *Science*, *256*, 1315–1318.

Tai, P. K. K., Maeda, Y., Nakao, K., Wakim, N. G., Duhring, J. L., & Faber, L. E. (1986). A 59-kilodalton protein associated with progestin, estrogen, androgen, and glucocorticoid receptors. *Biochemistry*, *25*, 5269–5275.

Wiederrecht, G., Hung, S., Chan, H. K., Marcy, A., Martin, M., & Calaycay, J. et al., (1992). Characterization of high molecular weight FK506 binding activities reveals a novel FK506 binding protein as well as a protein complex. *Journal of Biological Chemistry*, *267*, 21753–21760.

Yem, A. W., Reardon, I. M., Leone, J. W., Heinrikson, R. L., & Deibel Jr., M. R. (1993). An active FK506-binding domain of 17000 Daltons is isolated following limited proteolysis of chicken thymus HSP56. *Biochemistry*, *32*, 12571–12576.

Yem, A. W., Tomasselli, A. G., Heinrikson, R. L., Zurcher-Neely, H., Ruff, V. A., & Johnson, R. A. et al., (1992). The Hsp56 component of steroid receptor complexes binds to immobilized FK506 and shows homology to FKBP-12 and FKBP-13. *Journal of Biological Chemistry*, *267*, 2868–2871.