Published in final edited form as:

Curr Mol Pharmacol. 2015 ; 9(1): 48–65.

FK506-Binding Proteins and Their Diverse Functions

Mingming Tong and Yu Jiang*

Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

Abstract

FK506 binding proteins (FKBPs) are a family of highly conserved proteins in eukaryotes. The prototype of this protein family, FKBP12, is the binding partner for immunosuppressive drugs FK506 and rapamycin. FKBP12 functions as a *cis/trans* peptidyl prolyl isomerase (PPIase) that catalyzes interconversion between prolyl *cis/trans* conformations. Members of the FKBP family contain one or several PPIase domains, which do not always exhibit PPIase activity yet are all essential for their function. FKBPs are involved in diverse cellular functions including protein folding, cellular signaling, apoptosis and transcription. They elicit their function through direct binding and altering conformation of their target proteins, hence acting as molecular switches. In this review, we provide a general summary for the structures and diverse functions of FKBPs found in mammalian cells.

Keywords

FK506; immunophilin; peptidyl prolyl *cis/trans* isomerase; FK506 binding proteins; calcineurin; mTOR

1. INTRODUCTION

FK506 binding proteins (FKBPs) are a large family of proteins that possess peptidyl prolyl *cis/trans* isomerase (PPIase) domains. The founding member of this family is FKBP12, which is a 108 amino acid peptide containing the minimal sequence for a PPIase [1, 2]. It binds to FK506 and rapamycin and mediates the immunosuppressive action of the drugs [3, 4]. Other members were subsequently identified in yeast, plants and mammals, based on their sequence similarity to FKBP12. A glance at human genome reveals at least 15 polypeptides that contain PPI domains similar to FKBP12 (Fig. 1). The closest homolog of FKBP12 is FKBP12.6, which displays 83% sequence identity to FKBP12 [5]. Many large FKBPs contain several PPIase domains. For instance, FKBP52 possesses two PPIase domains and FKBP65 has four [6, 7]. All FKBPs, except FKBP12 and FKBP12.6, possess additional functional domains (Fig. 1). The most common one is tetratricopeptide (TPR) domain, a sequence motif that is often involved in mediating protein-protein interactions.

*Address correspondence to this author at the Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213; Tel: 412-648-3390; yuj5@pitt.edu.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

Some FKBP s also contain Ca^{2+} binding regions, such as Ca^{2+} /Calmodulin (CaM) binding domain and EF-hand motif. Several FKBP s function in the endoplasmic reticulum (ER) and contain ER targeting and retention motifs. FKBP38 and FKBP19 are two unique members which contain a transmembrane domain that targets them to membrane structures [8, 9]. Despite the presence of PPIase domain, not all members exhibit the ability to catalyze interconversion of prolyl *cis/trans* conformations or to bind with FK506. However, the PPI domain appears to be essential for their function. It has been suggested that the domain binds to X-proline sites (where X can be any amino acid) in target proteins and alters their conformation through a PPIase-like activity, hence acting as a molecular switch [10].

2. STRUCTURES AND FUNCTIONS OF FK506 BINDING PROTEINS

2.1. FKBP12

FKBP12 is a 12 kDa cytosolic protein that is abundantly expressed in all tissues. It possesses the enzymatic activity for catalyzing peptidyl prolyl *cis/trans* isomerization and functions as molecular chaperone in facilitating protein folding [1, 2].

2.1.1. FKBP12 as an Immunophilin—FKBP12 was originally identified as the target of FK506 and rapamycin [1]. Both drugs bind noncovalently to FKBP12 and inhibit its PPIase activity [3]. However, the inhibition of FKBP12 *per se* does not contribute to their immunosuppressive activity. Instead, the binding with FKBP12 allows the drugs to subsequently interact with the mechanistic targets of their action in immunosuppression. The FK506-FKBP12 complex specifically interacts with calcineurin (CaN), a Ca^{2+} -dependent serine-threonine phosphatase [11–14], whereas the rapamycin-FKBP12 complex targets mammalian target of rapamycin (mTOR) [15–17].

In T lymphocytes, CaN is a key component in the T-cell receptor mediated signaling that is required for T activation [11, 18]. It is activated by CaM in response to the increasing calcium concentration following activation of the T-cell receptor by antigen stimulation [11]. Activated CaN dephosphorylates nuclear factor of activated T cells (NFAT) resided in the cytoplasm, allowing it to translocate into the nucleus, where it cooperates with other nuclear transcription factors to initiate the transcription program for T cell activation [18]. The FK506-FKBP12 complex binds to CaN and blocks the access of NFAT to its catalytic site, preventing NFAT dephosphorylation and consequently, T cell activation [18] (Fig. 2).

The Rapamycin-FKBP12 complex inhibits cytokine stimulated T lymphocyte proliferation [3, 19–22]. Cytokines, such as interleukin-2 (IL-2), produced by activated T cells, bind to the cell surface receptors to activate the PI3K/AKT pathway and the downstream effector, mTOR [22–24]. Activated mTOR phosphorylates ribosomal protein 6 kinase (S6K) and eukaryotic initiation factor 4E binding protein 1 (4EBP1), two factors involved in translation initiation, resulting in an increase in protein synthesis, which in turn promotes cell growth and proliferation [22, 24]. The rapamycin-FKBP12 complex specifically binds to mTOR and interferes with its kinase function, thus blocking the cytokine-stimulated protein synthesis (Fig. 2).

In clinic FK506 is currently a first-line immunosuppressive drug in prevention of allograft rejection and treatment of severe autoimmunity [25]. Because it specifically targets CaN, FK506 is often referred as a calcineurin inhibitor. The major side effect associated with FK506 is nephrotoxicity, caused by blocking the function of CaN [26]. Rapamycin, which acts by distinct mechanism, is devoid of nephrotoxicity and hence offers an alternative in immunotherapy [22]. While the clinic application of Fk506 is limited to immunosuppression, rapamycin and its analogs are currently used in treating various cancers, owing to its effect in blocking cell proliferation [27–29].

2.1.2. FKBP12 and Ca²⁺ Release Channels—Following the identification of FKBP12 as the receptor for immunosuppressive drugs, extensive studies have been focused on uncovering the normal physiologic function of this small cytosolic protein. One surprising finding from those studies was that the protein not only resides in cytosol but also associates with many membrane receptors. In muscle cells FKBP12 has been found to interact with the major Ca²⁺ release channels of the sarcoplasmic reticulum (SR) ryanodine receptors (RyRs) [30–33]. These channel receptors mediate the release of Ca²⁺ from the sarcoplasmic reticulum into the cytoplasm during muscle contraction [30, 34]. The receptor exists as a tetramer, which binds to four molecules of FKBP12, one for each subunit [34] (Fig. 3). The binding is sensitive to FK506 or rapamycin, which displaces FKBP12 from the receptor [34]. In the absence of FKBP12, RyR receptors are correctly assembled and presented on the sarcoplasmic reticulum, suggesting that FKBP12 does not act as a molecular chaperone for the assembly and presentation of the receptors [31]. However, removal of FKBP12 from the receptors by FK506 or rapamycin results in a ‘leaky’ channel with an increase in open probability and conductance, which leads to depletion of Ca²⁺ store and consequently reduction in muscle contractility [35]. These observations have led to the suggestion that FKBP12 stabilizes channel conformation and increases the threshold for channel opening [36]. However, how FKBP12 binding affects the stability of the receptors is unclear. An early study suggested that the PPIase activity of FKBP12 was not required [37]. This PPIase independent action of FKBP12 is reminiscent of its action in FK506 mediated inhibition of CaN [11]. A closer examination of the association between FKBP12 and RyRs revealed the presence of CaN in the complex, which was disrupted by FK506 and rapamycin [38]. This observation raises a possibility that FKBP12 may control the phosphorylation state of the receptors through the CaN associated with the receptors.

FKBP12.6, the closest isoform of FKBP12, also plays a role in regulating RyR Ca²⁺ release channels in a manner similar to that of FKBP12 [5]. However, these two FKBP12s appear to have different specificity to different types of RyRs. FKBP12 is more selective for RyR1 in skeletal muscle, whereas FKBP12.6 preferentially targets RyR2 in cardiac muscle [5, 39, 40] (Fig. 3).

2.1.3. FKBP12 and IP₃R—FKBP12 also associates with another type of Ca²⁺ channel receptors named as inositol 1, 4,5-trisphosphate receptors (IP₃R), which are structurally and functionally related to RyRs [41] (Fig. 3). The receptor mediates the release of Ca²⁺ from the endoplasmic reticulum (ER) into cytosol and mitochondria in response to inositol trisphosphate (IP₃) [42]. The effect of FKBP12 on IP₃Rs appears to be the same as that on

RyRs, which stabilizes the receptors [41]. When FKBP12 is stripped from the receptors by FK506 or rapamycin, a leaky channel is created [41]. As in the case for RyRs, CaN is found in complex with FKBP12 and IP₃Rs [43]. Because IP₃R is phosphorylated at multiple sites [44, 45], the significance of its association with a phosphatase is apparent. Indeed, CaN has been shown to modulate the phosphorylation status of the receptors. Importantly, changes in the phosphorylation status of the receptors appear to alter their calcium flux properties [43]. However, it remains unclear whether FKBP12 controls IP₃R simply by targeting CaN to the receptors or its binding to the receptors may also contribute to the regulation.

In addition to binding with Ca²⁺ channel receptors, FKBP12 also interacts with type I receptor for transforming growth factor- β (TGF- β) [46]. In this case, FKBP12 serves as a natural ligand and binds to a glycine- and serine-rich motif of TGF- β receptor 1 (TGF- β R1). The binding does not directly inhibit the receptor but blocks its phosphorylation by TGF- β R2, hence trapping the receptor in an inactive state [46]. This mechanism is believed to provide a safeguard against leaky signaling activity of the receptors. As in the case for calcium channel receptors, the association of FKBP12 with TGF- β R1 is sensitive to FK506 and rapamycin. It has been shown that rapamycin is able to reverse the inhibitory action of FKBP12 on the receptors, presumably by removing FKBP12 from TGF- β R1 [47].

2.2. FKBP38

FKBP38 was originally isolated based on its sequence similarity to FKBP12 [48, 49]. It was later identified as a gene that was downregulated in Schwannomas as the tumor cells progressed into advanced stages [49]. The initially isolated cDNA contained an open reading frame encoding a protein of 355 amino acids (38 kDa) but the initial ATG was later found to be 58 codons upstream [48, 50]. The full size of FKBP38 is 413 amino acids with a predicted size of 45 kDa [50]. But on SDS page it shows an apparent molecular weight of 57 kDa [50, 51]. In addition to the PPIase domain that marks all members of FKBP family, FKBP38 contains several other sequence domains, including three TPR domains located at the C-terminal half of the protein, followed by a putative Ca²⁺/CaM binding domain, and a transmembrane domain at the very C-terminus [48, 49] (Fig. 1). This transmembrane domain is responsible for anchoring FKBP38 to ER and mitochondrial membranes¹¹.

FKBP38 is unique among the members of the FKBP family in that its PPIase activity is Ca²⁺/CaM dependent [52]. Interestingly, while a putative Ca²⁺/CaM binding motif is located at the C-terminus near the transmembrane domain, Ca²⁺/CaM binds has been found to bind to the N-terminal region of FKBP38 [53]. This binding releases the inhibitory effect of the N-terminal region on the PPIase domain of FKBP38, which potentiates the PPIase activity of FKBP38 and enhances its interaction with target proteins [53, 52].

The importance of FKBP38 in cell growth was first indicated by the inverse correlation between the levels of FKBP38 and the rate of cell growth. For cells derived from malignant Schwannomas, a faster growth rate was found to accompany a lower level of FKBP38 [49], indicating that FKBP38 may negatively mediate cell growth in Schwannomas. A similar phenomenon was also observed in melanoma cells [54]. These observations have led to the suggestion that FKBP38 may function as a tumor suppressor [54]. In addition, a high expression level of FKBP38 also correlates with a reduced cell size in cells overexpressing

TSC1 tumor suppressor gene [55]. All these attributes indicate that FKBP38 is an important regulator for cell growth and proliferation. In the past several years, the action mechanism of FKBP38 in controlling cell growth has begun to emerge [49, 54, 55]. It is now well-established that FKBP38 regulates cell growth and proliferation through multiple mechanisms, including regulation of mTOR, apoptosis and hypoxia response [8, 52, 56–58].

2.2.1. FKBP38 and mTOR—The mammalian target of rapamycin, mTOR, is a serinethreonine protein kinase that controls a wide spectrum of cellular events by integrating various environmental cues, such as growth factors, changes in energy levels and fluctuations in nutrient conditions [59, 60]. The kinase exists in two distinct complexes named as mTOR complex 1 (mTORC1) and 2 (mTORC2). mTORC1 is the major downstream component of the PI3K and AKT pathway that controls cell growth and proliferation [61]. Rapamycin, in complex with FKBP12, specifically blocks mTORC1 activity and inhibits cell growth [62]. mTORC1 activity is negatively regulated by the TSC1 and TSC2 tumor suppressor complex, which functions as a GTPase activating protein for a Ras-like small GTPase, Rheb [63]. The TSC1/2 complex stimulates the intrinsic GTPase activity of Rheb, thus negatively regulating Rheb. In TSC deficient cells the inactivation of the TSC1/2 complex results in the accumulation of GTP-bound Rheb, which in turn stimulates mTORC1 [64].

FKBP38 has been shown to act as the endogenous inhibitor of mTOR [58]. In cells the level of FKBP38 expression has been reported to correlate inversely with the activity of mTORC1 [65–67]. When FKBP38 is overexpressed, it inhibits growth factor or amino acids-stimulated mTORC1 activity. On the other hand, FKBP38 knockdown causes an increase in mTORC1 activity and renders mTORC1 activity partially insensitive to growth factor deprivation and amino acid starvation. The inhibitory effect of FKBP38 on mTORC1 is also recapitulated *in vitro* using purified recombinant FKBP38, which strongly inhibits mTORC1 kinase activity toward 4EBP1. The inhibition does not require rapamycin, although the drug appears to further augment the inhibitory effect [58]. These observations support the notion that FKBP38 is an endogenous inhibitor of mTORC1.

FKBP38 binds directly to mTOR. Deletion analysis shows that the PPIase domain of FKBP38 mediates the binding. The minimal region in mTOR responsible for binding with FKBP38 comprises amino acids 1967–2191, which overlaps the FKBP12-rapamycin binding region (amino acids 2015–2114), indicating that FKBP38 affects mTORC1 in a way similar to that of the FKBP12-rapamycin complex. In accordance with this notion, FKBP38, like the FKBP12-rapamycin complex, targets only mTORC1 but not mTORC2 [58].

The inhibitory effect of FKBP38 on mTOR can be antagonized by Rheb, which interacts directly with FKBP38 and prevents it from binding with mTOR [58, 68]. The interaction of Rheb with FKBP38 depends on its nucleotide binding status. *In vitro* GTP-bound Rheb exhibits much higher binding affinity toward FKBP38 than GDP-bound Rheb. Rheb interacts with FKBP38 through its switch I region, the region commonly referred to as the effector domain that is required for a small GTPases to interact with its effectors. Mutations within the region affect the ability of Rheb to interact with FKBP38, rendering the small GTPase incapable of stimulating mTORC1 activity [68]. This effector domain-mediated and

GTP-dependent binding is a common mechanism for members of the Ras family of small GTPases to interact with their targets [69], hence indicating that FKBP38 is a *bona fide* effector of Rheb. This FKBP38-dependent regulation supports a notion that Rheb stimulates mTORC1 by disrupting FKBP38 from mTOR [58].

How does Rheb block the interaction of FKBP38 with mTOR? It has been found that Rheb binds to the PPIase domain in FKBP38 which is the same region for mTOR binding. However, the interactions of Rheb and mTOR with FKBP38 do not appear to be mutually exclusive. A dominant inactive mutant of Rheb is able to bind with FKBP38 without dissociating mTOR, indicating that Rheb regulates FKBP38 allosterically in a GTP-dependent manner and consequently alters its interaction with mTOR [68].

The interaction of Rheb with FKBP38 in cells is regulated by both growth factors and nutrient conditions [58]. Under growth factor derivation condition or when amino acid supply is limited, FKBP38 binds to mTOR and down-regulates its activity. The presence of growth factors and amino acids promotes accumulation of GTP-bound Rheb, which interacts with FKBP38 and releases mTOR from its inhibition [58] (Fig. 4). Growth factors, such as insulin, promote Rheb activation by activating the PI3K/AKT pathway, which reduces the GAP activity of the TSC1/2 complex, allowing GTP-bound Rheb to accumulate. However, how amino acid conditions affect Rheb GTP binding state is poorly understood. It has been suggested that amino acids control Rheb localization, hence its access to its effectors [60].

In addition to Rheb, the interaction of FKBP38 with mTORC1 is also controlled by phosphatidic acid (PA), a secondary messenger that is produced by phospholipase D through hydrolysis of phosphatidylcholine [70]. PA binds directly to mTORC1 and stimulates its activity [71–73]. A recent study has shown that PA binds to the same region in mTOR as does FKBP38. The binding reduces the affinity of mTOR for FKBP38, thus contributing to the PA-stimulated mTOR activation [72].

2.2.2. FKBP38 and Apoptosis—Bcl-2 and Bcl-X_L are two major anti-apoptotic proteins that localize to various subcellular locations, including the cytoplasm, nucleus, ER and mitochondria. To perform their apoptotic function, these two proteins have to be recruited to mitochondria, where they bind to pro-apoptotic proteins, Bak and Bax, and prevent their oligomerization on mitochondrial outer membrane [74]. The mitochondrial recruitment of these two anti-apoptotic proteins is mediated by FKBP38, which resides on mitochondria via its C-terminal transmembrane domain [8]. Overexpressing FKBP38 results in accumulation of Bcl-2 and Bcl-X_L on mitochondria, and consequently, renders cells resistance to various apoptotic inducers. On the other hand, downregulation of FKBP38 by shRNA reduces the amount of the Bcl-2 and Bcl-X_L on mitochondria and sensitizes the cells to apoptosis [8, 75]. In addition, the level of Bcl-2 is also reduced when FKBP38 expression level is low, indicating that the presence of FKBP38 also stabilizes Bcl-2 [75]. It is believed that binding with FKBP38 protects Bcl-2 from the caspase-dependent cleavage [76]. Interestingly, during mitophagy, a process for selectively removal damaged or excessive mitochondria through autophagosomes [77], FKBP38 and Bcl-2 are able to escape the destruction by translocating to ER membrane [78]. This process is believed to prevent

apoptosis from initiation during mitophagy [78]. However, how cells are able to selectively remove the proteins remains unclear.

FKBP38 binds to an N-terminal unstructured loop in Bcl-2 located between the Bcl-2 homology (BH) domains 3 and 4. The PPIase domain is required, although the three TPR domains may also contribute to the binding [8, 79]. However, a recent finding from a NMR analysis suggests that another region (amino acids 119–131) is involved in binding with FKBP38 [80]. It is possible that multiple regions in Bcl-2 are involved in its interaction with FKBP38. Alternatively, the interaction is a dynamic process that changes in response to other cues, such as Ca^{2+} concentration.

Two factors are involved in regulating the interaction of FKBP38 with the two anti-apoptotic proteins, Rheb and Ca^{2+} concentration. The mechanism by which Rheb controls the interaction of FKBP38 with the anti-apoptotic proteins mirrors the one for mTOR regulation. It has been shown that Rheb in its GTP-bound form is able to interact with FKBP38 and prevents it from association with Bcl-2 *in vitro* [81]. In cultured cells deprived of growth factor or amino acids the interaction between Bcl-2 and FKBP38 is strongly enhanced. Re-addition of the missed ingredients to culture medium or simply overexpressing Rheb reduces the interaction [81]. This Rheb-dependent regulation provides a link that allows both growth factor and nutrient signals to control apoptosis (Fig. 4). The growth factor and nutrient sensitive interaction of FKBP38 with the two anti-apoptotic proteins may constitute a protective mechanism that prevents a premature apoptosis initiation during growth factor deprivation or nutrient limitation, allowing time for other stress response mechanisms, such as autophagy, to launch. This notion is consistent with the observation that both FKBP38 and Bcl-2 are selectively removed from mitochondria during mitophagy [78].

Ca^{2+} is another factor that plays a critical role in mediating the binding of FKBP38 with Bcl-2. An elevated Ca^{2+} concentration has been shown to enhance the interaction of FKBP38 with Bcl-2 [52]. FKBP38 exhibits a capacity for binding with $\text{Ca}^{2+}/\text{CaM}$, which form a complex with FKBP38 and change its the affinity for Bcl-2 [52]. However, the regions in FKBP38 responsible for the binding remain controversial. A putative $\text{Ca}^{2+}/\text{CaM}$ binding site is located at the C-terminal region of FKBP38 (Fig. 1). However, a recent study shows that $\text{Ca}^{2+}/\text{CaM}$ bind to the N-terminal extension (1–32) in FKBP38. It has been suggested that binding with $\text{Ca}^{2+}/\text{CaM}$ removes the N-terminal extension away from the PPIase domain, allowing it to interact with Bcl-2 [53]. Despite these observations, the physiologic significance of $\text{Ca}^{2+}/\text{CaM}$ mediated interaction of FKBP38 with Bcl-2 in apoptotic regulation is unclear.

Phosphorylation represents another mechanism in mediating the interaction of FKBP38 with Bcl-2. An early study showed that JNK was able to phosphorylate Bcl-2 at the unstructured loop that is involved in binding with FKBP38 [79, 82]. Phosphorylation at this site decreases its interaction with FKBP38. This JNK mediated phosphorylation may play a role in autophagy, as it affects the formation of the Bcl-2/Beclin 1 complex [79].

2.2.3. FKBP38 Mediates a Crosstalk between mTOR and Bcl-2—A recent study has uncovered a novel crosstalk between mTOR and Bcl-2 which may have an implication in cancer development. It was found that changes in the expression levels of Bcl-2 and Bcl-X_L had a dramatic effect on mTORC1 signaling activity. mTORC1 activity increased when Bcl-X_L was overexpressed but decreased when Bcl-2 or Bcl-X_L was downregulated. The effects of the two antiapoptotic proteins on mTORC1 are independent of the antiapoptotic function of the proteins. Because FKBP38 is able to bind both mTOR and Bcl-2/X_L, it is conceivable that it may mediate the crosstalk. Indeed, mutants of the Bcl proteins defective for binding with FKBP38 are incapable of affecting mTORC1 activity [83]. During normal cell proliferation, such a crosstalk may not play a significant role in cell growth and survival, as the levels of Bcl-2 and Bcl-X_L remain relative unchanged. However, during cancer development, the levels of the two proteins are often highly elevated, as a way for the cancer cells to escape apoptosis [74]. The overexpressed Bcl-2 and Bcl-X_L may thus promote mTORC1 activity in addition to their function for enhancing cell survival.

2.2.4. FKBP38 in Hypoxia Response—FKBP38 has been found to associate with PHD2, a prolyl-4-hydroxylase domain-containing enzyme (PHDs) that catalyzes hydroxylation of two conserved prolyl residues in hypoxia-inducible transcription factor 1 alpha (HIF1 α) [56]. HIF1 α is a key factor in regulation of hypoxia response and plays a central role in angiogenesis and tumor development. The PHD-dependent hydroxylation of HIF1 α targets it for proteasomal degradation [84]. FKBP38 specifically interacts with PHD2 but not with other isoforms of PHD. The interaction is mediated by the N-terminal region of FKBP38 outside of the PPIase domain. In glioblastoma multiforme cells an increase in PHD2 level was found to correlate with a down-regulation of FKBP38, indicating that FKBP38 plays a negative role in regulating the stability of PHD2 [85]. Consistent with the notion, FKBP38 has been suggested to act as an adaptor protein to target PHD2 for proteasomal degradation [57].

Perturbation of FKBP38 function in apoptosis appears to underlie some pathogenesis of human diseases. The hepatitis C virus non-structural protein NS5A, which contains three BH domains and localizes to mitochondria, is structurally related to Bcl-2. This viral protein inhibits apoptosis through interaction with FKBP38, which is believed to contribute to the survival of the virus infected cells [86]. Presenilins 1 and 2, two proteins whose functions have been implicated in familial Alzheimer's disease (FAD), promote the degradation of FKBP38 and Bcl-2 and inhibit FKBP38 mediated mitochondrial recruitment of Bcl-2 [87].

2.3. FKBP52

FKBP52 was isolated as a co-chaperone of heat-shock protein 90 (Hsp90) of steroid receptor complex [88, 89]. The protein resides in both the cytoplasm and nucleus. In the cytoplasm FKBP52 exists in complex with steroid receptors as well as with Hsp70 and Hsp90 [90]. FKBP52 elicits its role in steroid receptor regulation by stabilizing the steroid receptors as well as by promoting their shuttling into the nucleus from the cytoplasm [91, 92] (Fig. 5). The pattern of FKBP52 distribution in the cytoplasm is reminiscent that of cytoskeleton, which is due to its binding with microtubule motor protein dynein [93]. In the presence of Hsp90 FKBP52 forms a complex with receptor proteins and bring the receptors to

microtubule motor protein dynein. Dynein together with associated microtubule then facilitate the nuclear translocation of the receptor proteins [92, 94] (Fig. 5).

FKBP52 is comprised of two PPIase domains, three TRP domains, and two C-terminal putative binding Ca^{2+} /CaM binding sites [6] (Fig. 1). The first PPIase domain (FK1) toward N-terminus exhibits enzymatic activity on its target proteins, which is inhibited by FK506 and rapamycin [95]. This PPIase domain is responsible for the interaction with steroid receptors and important for receptor activity [96, 97]. The PPIase domain also mediates the interaction between dynein and the steroid receptor complex [98]. The second PPIase domain (FK2) is remotely related to FKBP12 (share ~17% identical sequence). It is devoid of enzymatic activity and incapable of binding with FK506 and rapamycin [99]. An ATP and GTP binding site is found within this domain [100]. In the presence of Ca^{2+} /CaM, binding of ATP at the site promotes FKBP52 phosphorylation [101]. Phosphorylation in the hinge region between FK1 and FK2 by casein kinase-2 inhibits the binding of FKBP52 with Hsp90 [102]. The three TPR domains are also involved in the association of FKBP52 with the steroid receptors and Hsp90 [103]. The two C-terminal Ca^{2+} /CaM binding sites appear to be involved in the interaction of FKBP52 with Hsp90, as deletion of this region reduces the affinity of the interaction between the two proteins [104, 105].

2.3.1. FKBP52 in Steroid Receptor Regulation—FKBP52 plays a critical role in reproduction in rodents. It acts as a positive regulator for glucocorticoid, progesterone, and androgen receptors, but not for estrogen and mineralocorticoid receptors [96, 106, 107]. Male mice without FKBP52 are infertile. The animals display severe defects in reproductive tissues consistent with androgen insensitivity, including ambiguous external genitalia and dysgenic prostate. In addition, androgen receptor levels are reduced in testis and epididymis of the knockout animals [107]. The androgen insufficiency and insensitivity are believed to underlie the many birth defects in the reproductive system of the FKBP52 deficient animals [107–109]. FKBP52 has been found to be a component of androgen receptor complex, in which FKBP52 promotes the receptor mediated transcriptional activity. In addition, binding with FKBP52 appears to stabilize androgen receptor, as the receptor level is reduced when FKBP52 is downregulated by siRNA [107, 110, 111]. The positive effect of FKBP52 in androgen receptor-mediated transactivation requires FK1 domain and is sensitive to FK506 [107].

In female mice FKBP52 knockout also causes infertility, due to defects in uterine receptivity during implantation. The defects are caused by loss of activity of progesterone receptors in the uterus [106, 112]. The absence of FKBP52 results in reduced progesterone receptor transcriptional activity and down-regulation of the receptor regulated gene expression [106]. In addition, FKBP52 knockout female mice are susceptible to oxidative stress and prone to the growth of endometriotic lesions with increased inflammation and angiogenesis [113]. A downregulation of peroxiredoxin (PRDX6), an antioxidant, in FKBP52 deficient animals is believed to contribute the defects [114].

A role of FKBP52 in regulation of glucocorticoid receptor was first tested using yeast cells. It was found that FKBP52 stabilized glucocorticoid receptors and increased hormone-binding affinity of the receptors. The effect of FKBP52 on the receptors requires its PPI

activity and binding with Hsp90 [96]. In FKBP52-knockout mice, no obvious defects in glucocorticoid receptor regulated processes have been detected, indicating that FKBP52 is not an essential regulator of glucocorticoid receptor activity [115]. However, an analysis of glucocorticoid receptor activity at reporter genes shows significant reduction in receptor activity in mouse embryonic fibroblasts (MEF) of FKBP52 knock-out mice [115].

2.4. FKBP51

FKBP51 shares 60% sequence homology with FKBP52 and contains similar structural features, including two PPIase domains, three TPR domains, and a Ca^{2+} /CaM binding motif [116] (Fig. 1). Like FKBP52, the first PPIase domain of FKBP51 displays enzymatic activity and is sensitive to FK506 and rapamycin [117]. The second PPIase domain lacks PPIase activity [116] and does not bind FK506 [118]. The C-terminal TRP domains serve as the region for the association with Hsp90 [118].

2.4.1. FKBP51 in Regulation of Steroid Receptors—FKBP51 was originally identified as a subunit of the progesterone receptor complex [119] and later found to associate with androgen, glucocorticoid, estrogen, and mineralocorticoid receptors [120]. Despite the sequence and structural similarity to FKBP52, FKBP51 does not act as a functionally redundant copy of FKBP52. In contrast, FKBP51 is a negative regulator for activity of steroid receptors, except androgen receptors. It competes with FKBP52 for binding with steroid receptors, consequently, antagonizes the positive effect of FKBP52 on these receptors [96, 121]. It has been shown that binding with FKBP51 sequesters glucocorticoid receptors in the cytoplasm and reduces its affinity for hormone-binding [122] (Fig. 5). However, the effect of FKBP51 on androgen receptors appears to be opposite of its effect on other receptors. Instead of reducing ligand binding activity, FKBP51 promotes the binding of the receptors with androgen and increases receptor transcriptional activity [123]. Interestingly, the expression of FKBP51 is regulated by androgen receptors in response to androgen. The mutual regulation of FKBP51 and the androgen receptor activity hence constitutes a positive feedback loop, which is believed to contribute to prostate cancer development [124, 125]. Therefore, targeting FKBP51 expression or activity may be an effective way to treat prostate cancers.

2.4.2. FKBP51 in $\text{NF-}\kappa\text{B}$ Regulation—In addition its role in regulation of steroid receptors, FKBP51 also involves in $\text{NF-}\kappa\text{B}$ activation as a positive regulator. In human melanoma cells knockdown of FKBP51 reduces the transactivation of $\text{NF-}\kappa\text{B}$ in the nucleus. Two different mechanisms count for the action of FKBP51 in $\text{NF-}\kappa\text{B}$ regulation, one through inhibitor of nuclear factor kappa-B ($\text{I}\kappa\text{B}$) kinase subunit alpha ($\text{IKK}\alpha$) and the other through CaN. $\text{I}\kappa\text{B}$ is a negative regulator of $\text{NF-}\kappa\text{B}$. It binds to $\text{NF-}\kappa\text{B}$ and keeps it sequestered in an inactive state in the cytoplasm. Phosphorylation of $\text{I}\kappa\text{B}$ by $\text{IKK}\alpha$ removes $\text{I}\kappa\text{B}$ from $\text{NF-}\kappa\text{B}$, allowing it to translocate into the nucleus [126]. FKBP51 has been found to associate with $\text{IKK}\alpha$ and stimulates IKK directed-phosphorylation of $\text{I}\kappa\text{B}$ [127] (Fig. 6), hence promoting $\text{NF-}\kappa\text{B}$ activation. The second mechanism involves CaN, which inhibits $\text{NF-}\kappa\text{B}$ activation by dephosphorylation of $\text{I}\kappa\text{B}$. FKBP51 has been found to inhibit CaN activity independent of FK506 [117] (Fig. 6).

2.4.3. FKBP51 in the PI3K/AKT Pathway—FKBP51 also plays a role in the PI3K/AKT pathway. In this case, FKBP51 functions as a scaffolding protein for pleckstrin homology (PH) domain leucine-rich repeat protein phosphatase (PHLPP), which dephosphorylates AKT and downregulates its activity [128]. FKBP51 facilitates the association of PHLPP with AKT and enhances PHLPP-directed dephosphorylation of AKT at position 473 [129] (Fig. 6). The N-terminal PPIase domain of FKBP51 binds to AKT and the C-terminal TPR domain binds to the phosphatase, hence bridging the phosphatase to its substrates. Expression of FKBP51 has been found to be downregulated in many types of cancers, such as pancreatic and breast cancers. This reduced FKBP51 level causes dissociation of PHLPP from AKT and, consequently, an increase in AKT phosphorylation, which may contribute to cancer development [129].

2.4.4. Mitochondrial Localized FKBP51 in Stress Response and Adipogenesis

—In 3T3-L1 fibroblasts overexpression of FKBP51 has been found to protect the cells from oxidative stress [130]. This protective effect is mediated by mitochondrial localized FKBP51, where it forms complexes with glucocorticoid receptor, Hsp90, and Hsp70 [130]. The TRP domain of FKBP51 but not the PPIase domain is required for the mitochondrial localization. In response to oxidative stress, FKBP51 translocates to the nucleus from mitochondria, indicating that FKBP51 may play a role in oxidative stress response [130].

During 3T3-L1 preadipocyte differentiation, the level of FKBP51 progressively increases. At the onset of adipogenesis, the mitochondrial localized FKBP51 redistributes to the nucleus, where it interacts with chromatin and the nuclear matrix in complex with Hsp70 [131]. This redistribution is regulated by the cAMP/Protein kinase A (PKA) pathway, likely through direct phosphorylation by PKA [131].

2.5. FKBP36

FKBP36 was identified as one of the genes deleted in patients of Williams syndrome, a dominant autosomal disorder that is characterized by aortic and arterial stenoses. FKBP36 contains an N-terminal PPIase domain and a C-terminal TPR domain (Fig. 1). It lacks PPIase activity but is able to bind with several proteins through its PPIase and TPR domains [132]. The function of FKBP36 does not appear to be associated with Williams syndrome. Instead, FKBP36 has been found to be a component of synaptonemal complex, a key factor that mediates chromosome synapsis during meiosis [133]. The absence of FKBP36 causes aspermia in male mice without any negative effects in female mice, suggesting that the protein is involved in spermatogenesis [134]. In addition, FKBP36 has been found to form separate complexes with clathrin heavy chain (CHC) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The FKBP36-CHC complex also contains Hsp72 and may play a role in controlling the clathrin-coated vesicles [135]. The association of FKBP36 with GAPDH results in inhibition of GAPDH catalytic activity and reduction in the expression level of GAPDH [136]. These findings suggest that the action mechanism of FKBP36 is similar to that of FKBP51 and FKBP52, which involves formation of multiple complexes. It appears that FKBP36 acts as a scaffolding protein through its multiple binding domains to facilitate protein interactions.

2.6. FKBP37

FKBP37 is an aryl hydrocarbon receptor-interacting protein that contains a typical PPIase domain at its N-terminus and a TPR domain at its C-terminus (Fig. 1). FKBP37 does not bind to FK506 and exhibits no PPIase activity. FKBP37 has been found to interact with Hsp90 through its PPIase and TRP domains [137].

2.7. Endoplasmic reticulum FKBP

There are six FKBP proteins known to be localized to the ER, including FKBP13, FKBP19, FKBP22, FKBP23, FKBP60, and FKBP65. These proteins contain an N-terminal ER-targeting sequence and a C-terminal ER retention motif, except FKBP19, which contains a lysine-rich C-terminal tail. These ER FKBP proteins are involved in regulation protein folding in the ER and secretory pathway.

FKBP13 is closely related to FKBP12. In comparison with FKBP12, the extra length of the protein is comprised of an N-terminal ER-targeting signal peptide and C-terminal ER retention sequence [138]. FKBP13 displays a PPIase activity that is sensitive to FK506 and rapamycin. However, it is unable to form a complex with CaN in the presence of FK506 [138, 139]. FKBP13 participates in protein folding and trafficking in the ER. It is constitutively expressed under normal condition, but can be induced in response to accumulation of unfolded proteins during ER stress [140]. FKBP13 has been found to interact with brefeldin A-inhibited guanine nucleotide-exchange protein 1 (BIG1) for ADP-ribosylation factors that are involved in regulation of membrane trafficking [141]. FK506 but not rapamycin enhances the interaction, indicating that this association may be analogous to those of FKBP12 and CaN [142]. Surprisingly, FKBP13 is also found to interact with erythrocyte membrane cytoskeletal protein 4.1G outside of ER, indicating a novel function of FKBP13 in the membrane cytoskeleton [143].

FKBP19 is mainly expressed secretory tissues and is believed to function in protein folding and secretion. In addition to the PPIase domain, it possesses a cleavable leucine-rich N-terminal sequence, a putative transmembrane domain, and a lysine-rich C-terminal tail often found in ER membrane proteins [9]. The PPIase domain binds FK506 weakly *in vitro*. FKBP19 is highly expressed in the tumor tissue of hepatocellular carcinoma, suggesting that it may play a role in hepatic tumor development [144].

The other members of the ER FKBP group all contain two EF-hand motifs that bind to Ca^{2+} . In FKBP22, the EF-hand motifs mediate the dimerization of the protein [145, 146]. In FKBP23, the motifs are involved in regulating its interaction with the immunoglobulin (Ig) heavy-chain-binding protein (BiP), a molecular chaperone of Hsp70 family [147]. This interaction is mediated through the PPIase domain of FKBP23 but is regulated by Ca^{2+} concentration through the EF-hand motifs [147]. It is likely that the EF-hand motif imparts a Ca^{2+} dependent regulation on the function of these proteins.

Two members of the ER FKBP group, FKBP60 and FKBP65, are unique in that both contain four tandem PPIase domains [7, 148]. FKBP60 displays PPIase activity which is inhibited by FK506. It binds Ca^{2+} *in vitro*, presumably through its C-terminal EF-hand motifs, and is phosphorylated *in vivo* [148]. FKBP65 modulates the folding of collagen and

interacts with tropoelastin, both of which are proline-rich proteins in the extracellular matrix of tissues [149]. FKBP65 is degraded following ER stresses along with the Ca^{2+} release from ER. The EF-hand Ca^{2+} binding motifs of FKBP65 influence the stability of FKBP65 [150].

2.8. FKBP25

FKBP25 is a nuclear DNA-binding protein in FKBP family that is predominantly localizes to the nucleus. It is involved in regulating transcription and chromatin structure. The FKBP25 comprises a hydrophilic helix-loop-helix (HLH) motif at its N-terminus, PPIase domain at its C-terminus, and a nuclear targeting sequence [151]. The HLH motif is responsible for binding to DNA [152]. Its PPIase domain shares 43% homology with FKBP12 and displays PPIase activity, which is sensitive to rapamycin and FK506 [151]. FKBP25 physically interacts with the histone deacetylases HDAC1 and HDAC2 as well as the HDAC-binding transcriptional regulator YY1 [153]. The expression of FKBP25 can be repressed in a P53-dependent manner [154]. FKBP25 is also involved in regulating ubiquitination and degradation of oncogene MDM2 and P53 expression [155].

2.9. FKBP133

FKBP133, also named as WAFL, comprises a Wiskott-Aldrich syndrome protein homology region1(WH1) and a PPIase domain [156]. FKBP133 is mainly expressed in the developing nervous system. It localizes to the growth cones of dorsal root ganglion neurons and influences the growth cone size and the number of filopodia. Overexpressing FKBP133 protects neurons from Semaphorin-3A induced collapse response [156]. At cellular level the protein is involved in modulation of early endosomes at the actin and microtubule dynamics [157].

3. NEURONAL FUNCTIONS OF FKBP AND THEIR IMPLICATIONS IN THE PATHOPHYSIOLOGY OF NEUROLOGICAL DISEASES

The peripheral and central nervous systems are highly enriched in FKBP [158–159]. Abundant expression of several FKBP have been detected in neurons, including FKBP12, FKBP38, FKBP51, FKBP52 and FKBP65, which are collectively termed as neuroimmunophilins [160]. The initial interest in these neuroimmunophilins arose from the observations that FK506 possessed neurotrophic and neuroprotective effects in cultured neurons and in animal models. Early studies focused mainly on FKBP12 and calcineurin, the mechanistic target of FK506 in immunosuppression, which is also highly expressed in neuron and glial cells [161]. However, it was subsequently found that the mechanisms underlying the neurotrophic and neuroprotective effects of FK506 are far more complicated than initially expected, of which neither FKBP12 nor CaN appears to play a direct role.

3.1. FKBP in Neuroprotection and Regeneration

The observation that FKBP12 was strongly expressed in the nervous system fueled studies into the neurological effects of immunophilin ligand FK506 [159]. Several studies demonstrated that FK506 possessed neurotrophic and neuroprotective properties. In cultured

PC12 cells and rat sensory ganglia FK506 enhanced neurite outgrowth [162]. In a rat model of peripheral nerve injury, administration of FK506 increased functional recovery and nerve regeneration [163]. A neuronal protective effect of FK506 was also observed in an *in vivo* model of focal cerebral ischemia, in which case administration of FK506 was found to exhibit a profound protective effect against neuronal damage. The protective effect was not seen with another CaN inhibitor, CsA, indicating that it was not caused by inhibition of CaN [164]. Subsequently, several non-immunosuppressive FK506 analogs were developed and tested for their neurological effects in a variety of animal models. It was found that the nonimmunosuppressive analogs retained their activity in neuroprotection and recovery, ruling out CaN as the mediator of the neurotrophic effect for the immunophilin ligands [165–167]. Surprisingly, the neurotrophic properties of FK506 were also preserved in FKBP12 deficient primary neurons, indicating that FKBP12 might not be involved [168]. Consistent with the notion, it was later found that immunophilin ligands devoid of FKBP12 binding activity retained their ability to promote neurite outgrowth and regeneration [169].

Because FK506 binds to other neuroimmunophilins in addition to FKBP12, several studies examined the role of some large neuroimmunophilins in FK506 mediated neurotrophic effect. In a rat model of transient focal cerebral ischemia, inhibition of FKBP38 by a cycloheximide derivative, N-(N',N'-dimethylcarboxamidomethyl) cycloheximide, was able to reduce neuronal damage and enhance neuroregeneration. Since FKBP38 is also a target of FK506, this finding indicates that this immunophilin may mediate the neurotrophic effect of FK506 [170]. In human neuroblastoma SH-SY5Y cells, the neurotrophic action of FK506 was blocked by FKBP52 specific antibody, which had led to the suggestion that FKBP52, rather than FKBP12, might mediate the action of FK506 [171]. However, a recent study using inhibitors selective against FKBP51 but not FKBP52 showed that inhibition of FKBP51 enhanced neurite outgrowth in neuronal cultures, indicating that FKBP51 was responsible for the neuronal effect of FK506 [172]. The action of FKBP51 in neurite growth has been suggested to be mediated through the steroid hormone receptor signaling. Selective inhibition of FKBP51 enhances glucocorticoid receptor activation by increasing the receptor sensitivity to the hormone [173]. In animal models, in addition to the neurotrophic effect, inhibition of FKBP51 was found to improve stress-coping behavior [172]. This finding is consistent with the role of FKBP51 in stress-associated psychiatric diseases. Polymorphisms in this gene have been found to be associated with risks for developing depressive behavior in human [174]. Targeting FKBP51 may thus represent a potential therapeutic strategy for treating depression and other stress-related disorders.

3.2. FKBP5s in Neurodegenerative Diseases

The functions of neuroimmunophilins are implicated in some neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD). FKBP12 has been shown to associate with α -synuclein, a small soluble protein predominantly localized in presynaptic termini. In PD, α -synuclein aggregates and forms cytoplasmic proteinaceous inclusion bodies (Lewy bodies) that interfere with the function of dopaminergic neurons [175]. *In vitro* FKBP12 was found to bind and facilitate α -synuclein aggregation [176]. In cultured neurons knockdown of FKBP12 was able to reduce oxidative stress induced formation of α -synuclein aggregates and protect neurons from stress-induced cell death [177]. These

observations indicate that FKBP12 may play a role PD pathophysiology through regulation of α -synuclein aggregation. Two other FKBP, FKBP51 and FKBP52, are implicated in the pathophysiology of AD for their role in regulation of tau, a microtubule associated protein that stabilizes microtubule [178]. Hyperphosphorylated tau forms intraneuronal aggregates called neurofibrillary tangles which contribute to the degradation of the neurons in the regions of brain involved in learning and memory in AD patients [179]. FKBP52 binds to hyperphosphorylated Tau and blocks its ability to induce microtubule assembly [180]. When interacts with the pathological mutant of Tau (P301L), FKBP52 also promotes tau oligomerization [181]. In contrast, FKBP51, in complex with HSP90, binds to tau and promotes its dephosphorylation and reassociation with microtubule [182]. While these *in vitro* studies suggest a potential role for the neuroimmunophilins in PD and AD, the lacking of data from appropriate animal models of PD and AD hinders the evaluation of their pathological relevance in the neurodegenerative diseases.

4. FKBP_s IN CANCER DEVELOPMENT

Given the diverse functions of FKBP_s in intracellular signaling, it is not surprising that many of the proteins are found to be involved in cancer development. Among them, FKBP51 has emerged as a key regulator in several cancers, including prostate cancer, leukemia, melanoma and pancreatic cancer [129, 183–185]. In prostate cancer FKBP51 plays a positive role in cancer progression. This cancer promoting function of FKBP51 is associated with its regulation of androgen dependent transcription [123, 186]. FKBP51 has been found to associate androgen receptor (AR) and overexpression of FKBP51 stimulates AR transcriptional activity and cell proliferation [187]. In androgen independent prostate cancer cells, high level of FKBP51 is believed to sustain AR signaling in the absence of androgen [188]. In melanomas FKBP51 expression correlates with the invasiveness and aggressiveness of the cancer [189]. It has been shown that FKBP51 exhibits anti-apoptosis activity and protects the cancer cells from irradiation induced cell death [127, 189]. This pro-survival function of FKBP51 is mediated through NF- κ B [190]. In response to irradiation FKBP51 stimulates NF- κ B activation, which suppresses apoptosis by stimulating X-linked inhibitor of apoptosis (XIAP) and downregulating Bax [189]. FKBP51 may also promote melanoma cell migration and invasion by increasing TGF- β signaling and activation of epithelial-to-mesenchymal transition (EMT) genes [191, 192]. In contrast to the positive role in prostate cancer and melanoma, FKBP51 appears to play a negative role in pancreatic cancer [193, 194]. Analysis of tumor samples of pancreatic cancer revealed a downregulation in the expression level of FKBP51 [129]. In a pancreatic cancer xenograft mice model, knockdown of FKBP5 was found to promote tumor growth and enhance resistance to gemcitabine, a chemotherapeutic agent. The negative effect of FKBP51 on pancreatic cancer is mediated through phosphatase PHLPP. It has been shown that FKBP51 associates with the phosphatase and stimulates its activity, which in turn dephosphorylates AKT and its pro-survival function [129]. This cancer cell specific effect of FKBP51 is consistent with its multifaceted activities in many signaling events. Depending on the signaling events that are dominant in different types of cancer cells, FKBP51 may exhibit different effects on cancer growth. In addition to FKBP51, several other FKBP_s have also been implicated in cancer development, including FKBP38. In Schwannomas cell lines the

expression level of FKBP38 has been found to correlate inversely with the rate of cell growth [49]. In a melanomas xenografts model, over-expression of FKBP38 was found to reduce tumor growth [54]. Study of the gene expression in a prostate cancer xenograft model also revealed an inverse correlation between the expression level of FKBP38 and the progression of tumors during androgen depletion treatment [195]. The tumor suppressive activity of FKBP38 is consistent with its negative role in regulation of mTOR. In many types of cancer cells an enhanced mTOR signaling activity is essential for tumor growth and progression. As an inhibitor of mTOR, an increase in FKBP38 expression is expected to reduce mTOR activity and hence inhibits tumor growth [196].

5. CONCLUSION

Since the isolation of FKBP12 as an immunophilin that displays PPIase activity 25 years ago, many proteins sharing sequence similarity to FKBP12 have been identified from yeast to human, hence constituting the family of FKBP. The members of this conserved protein family are involved in diverse biological functions. In all the cases examined, the PPIase domain of the FKBP appears to be essential for their function. In addition to protein folding and chaperone functions, the PPIase domain in many FKBP is involved in mediating protein-protein interaction. It has been suggested that the PPIase activity of the domain acts as a molecular switch that allosterically regulates the conformation of the target proteins by catalyzing the interconversion of prolyl *cis/trans* isomerization [10]. Together with the TPR domains, which are commonly found in FKBP, one FKBP is able to interact with multiple proteins, allowing it to function as a scaffolding protein to nucleate the formation of large protein complexes [197]. In addition, The Ca^{2+} /CaM and EF-hand motifs impart Ca^{2+} dependent regulation into the action of FKBP. In such a way, FKBP act as a group of molecular switches that control many cellular functions.

The prospect for targeting FKBP in disease prevention and treatment, particularly in neurodegenerative disorders, has been a central theme in field of FKBP related studies, since the discovery of FKBP12 as the mediator for the therapeutic effects of FK506 and rapamycin. However, the ensuing effort has so far met limited success. A few nonimmunosuppressive FK506 analogs that made to clinical trials have failed due to lack of therapeutic efficacy [198, 199]. However, accumulating data from the last decade have allowed a better understanding the roles of each FKBP in many diverse cellular processes and signaling events. The gained insights are to guide future development of therapeutic agents that specifically target individual member of FKBP.

ACKNOWLEDGEMENTS

The authors would like to thank laboratory members for stimulating discussion and comments during the preparation of the manuscript. This work is supported by NIH grant (CA169186) to YJ.

Biography

Yu Jiang

REFERENCES

- [1]. Harding MW; Galat A; Uehling DE; Schreiber SL, A receptor for the immunosuppressant FK506 is a cis-trans peptidyl-prolyl isomerase. *Nature* 1989, 341 (6244), 758–60. [PubMed: 2477715]
- [2]. Siekierka JJ; Hung SH; Poe M; Lin CS; Sigal NH, A cytosolic binding protein for the immunosuppressant FK506 has peptidyl-prolyl isomerase activity but is distinct from cyclophilin. *Nature* 1989, 341 (6244), 755–7. [PubMed: 2477714]
- [3]. Bierer BE; Mattila PS; Standaert RF; Herzenberg LA; Burakoff SJ; Crabtree G; Schreiber SL, Two distinct signal transmission pathways in T lymphocytes are inhibited by complexes formed between an immunophilin and either FK506 or rapamycin. *Proceedings of the National Academy of Sciences of the United States of America* 1990, 87 (23), 9231–5. [PubMed: 2123553]
- [4]. Harrison RK; Stein RL, Substrate specificities of the peptidyl prolyl cis-trans isomerase activities of cyclophilin and FK-506 binding protein: evidence for the existence of a family of distinct enzymes. *Biochemistry* 1990, 29 (16), 3813–6. [PubMed: 1693856]
- [5]. Timmerman AP; Jayaraman T; Wiederrecht G; Onoue H; Marks AR; Fleischer S, The ryanodine receptor from canine heart sarcoplasmic reticulum is associated with a novel FK-506 binding protein. *Biochemical and biophysical research communications* 1994, 198 (2), 701–6. [PubMed: 8297381]
- [6]. Lebeau MC; Massol N; Herrick J; Faber LE; Renoir JM; Radanyi C; Baulieu EE, P59, an hsp 90-binding protein. Cloning and sequencing of its cDNA and preparation of a peptidedirected polyclonal antibody. *The Journal of biological chemistry* 1992, 267 (7), 4281–4. [PubMed: 1537818]
- [7]. Coss MC; Winterstein D; Sowder RC 2nd; Simek SL, Molecular cloning, DNA sequence analysis, and biochemical characterization of a novel 65-kDa FK506-binding protein (FKBP65). *The Journal of biological chemistry* 1995, 270 (49), 29336–41. [PubMed: 7493967]
- [8]. Shirane M; Nakayama KI, Inherent calcineurin inhibitor FKBP38 targets Bcl-2 to mitochondria and inhibits apoptosis. *Nature cell biology* 2003, 5 (1), 28–37. [PubMed: 12510191]
- [9]. Rulten SL; Kinloch RA; Tateossian H; Robinson C; Gettins L; Kay JE, The human FK506-binding proteins: characterization of human FKBP19. *Mammalian genome : official journal of the International Mammalian Genome Society* 2006, 17 (4), 322–31. [PubMed: 16596453]
- [10]. Lu KP; Finn G; Lee TH; Nicholson LK, Prolyl cis-trans isomerization as a molecular timer. *Nature chemical biology* 2007, 3 (10), 619–29. [PubMed: 17876319]
- [11]. Liu J; Farmer JD Jr.; Lane WS; Friedman J; Weissman I; Schreiber SL, Calcineurin is a common target of cyclophilin/cyclosporin A and FKBP-FK506 complexes. *Cell* 1991, 66 (4), 807–15. [PubMed: 1715244]
- [12]. Fruman DA; Klee CB; Bierer BE; Burakoff SJ, Calcineurin phosphatase activity in T lymphocytes is inhibited by FK 506 and cyclosporin A. *Proceedings of the National Academy of Sciences of the United States of America* 1992, 89 (9), 3686–90. [PubMed: 1373887]
- [13]. Sewell TJ; Lam E; Martin MM; Leszyk J; Weidner J; Calaycay J; Griffin P; Williams H; Hung S; Cryan J; et al., Inhibition of calcineurin by a novel FK-506-binding protein. *The Journal of biological chemistry* 1994, 269 (33), 21094–102. [PubMed: 7520438]
- [14]. Fruman DA; Bierer BE; Benes JE; Burakoff SJ; Austen KF; Katz HR, The complex of FK506-binding protein 12 and FK506 inhibits calcineurin phosphatase activity and IgE activation-

induced cytokine transcripts, but not exocytosis, in mouse mast cells. *Journal of immunology* (Baltimore, Md. : 1950) 1995, 154 (4), 1846–51.

- [15]. Heitman J; Movva NR; Hall MN, Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. *Science* (New York, N.Y.) 1991, 253 (5022), 905–9.
- [16]. Cafferkey R; Young PR; McLaughlin MM; Bergsma DJ; Koltin Y; Sathe GM; Faucette L; Eng WK; Johnson RK; Livi GP, Dominant missense mutations in a novel yeast protein related to mammalian phosphatidylinositol 3-kinase and VPS34 abrogate rapamycin cytotoxicity. *Molecular and cellular biology* 1993, 13 (10), 6012–23. [PubMed: 8413204]
- [17]. Kunz J; Henriquez R; Schneider U; Deuter-Reinhard M; Movva NR; Hall MN, Target of rapamycin in yeast, TOR2, is an essential phosphatidylinositol kinase homolog required for G1 progression. *Cell* 1993, 73 (3), 585–96. [PubMed: 8387896]
- [18]. Jain J; McCaffrey PG; Miner Z; Kerppola TK; Lambert JN; Verdine GL; Curran T; Rao A, The T-cell transcription factor NFATp is a substrate for calcineurin and interacts with Fos and Jun. *Nature* 1993, 365 (6444), 352–5. [PubMed: 8397339]
- [19]. Dumont FJ; Staruch MJ; Koprak SL; Melino MR; Sigal NH, Distinct mechanisms of suppression of murine T cell activation by the related macrolides FK-506 and rapamycin. *Journal of immunology* (Baltimore, Md. : 1950) 1990, 144 (1), 251–8.
- [20]. Kahan BD; Gibbons S; Tejpal N; Stepkowski SM; Chou TC, Synergistic interactions of cyclosporine and rapamycin to inhibit immune performances of normal human peripheral blood lymphocytes *in vitro*. *Transplantation* 1991, 51 (1), 232–9. [PubMed: 1987692]
- [21]. Kay JE; Kromwel L; Doe SE; Denyer M, Inhibition of T and B lymphocyte proliferation by rapamycin. *Immunology* 1991, 72 (4), 544–9. [PubMed: 1709916]
- [22]. Abraham RT; Wiederrecht GJ, Immunopharmacology of rapamycin. *Annual review of immunology* 1996, 14, 483–510.
- [23]. Dure M; Macian F, IL-2 signaling prevents T cell anergy by inhibiting the expression of anergy-inducing genes. *Molecular immunology* 2009, 46 (5), 999–1006. [PubMed: 18990450]
- [24]. Waickman AT; Powell JD, Mammalian target of rapamycin integrates diverse inputs to guide the outcome of antigen recognition in T cells. *Journal of immunology* (Baltimore, Md. : 1950) 2012, 188 (10), 4721–9.
- [25]. Rath T, Tacrolimus in transplant rejection. *Expert opinion on pharmacotherapy* 2013, 14 (1), 115–22. [PubMed: 23228138]
- [26]. Naesens M; Kuypers DR; Sarwal M, Calcineurin inhibitor nephrotoxicity. *Clinical journal of the American Society of Nephrology : CJASN* 2009, 4 (2), 481–508. [PubMed: 19218475]
- [27]. Mita MM; Mita A; Rowinsky EK, The molecular target of rapamycin (mTOR) as a therapeutic target against cancer. *Cancer biology & therapy* 2003, 2 (4 Suppl 1), S169–77. [PubMed: 14508096]
- [28]. Law BK, Rapamycin: an anti-cancer immunosuppressant? *Critical reviews in oncology/hematology* 2005, 56 (1), 47–60. [PubMed: 16039868]
- [29]. Gibbons JJ; Abraham RT; Yu K, Mammalian target of rapamycin: discovery of rapamycin reveals a signaling pathway important for normal and cancer cell growth. *Seminars in oncology* 2009, 36 Suppl 3, S3–s17. [PubMed: 19963098]
- [30]. Jayaraman T; Brillantes AM; Timmerman AP; Fleischer S; Erdjument-Bromage H; Tempst P; Marks AR, FK506 binding protein associated with the calcium release channel (ryanodine receptor). *The Journal of biological chemistry* 1992, 267 (14), 9474–7. [PubMed: 1374404]
- [31]. Brillantes AB; Ondrias K; Scott A; Kobrinisky E; Ondriasova E; Moschella MC; Jayaraman T; Landers M; Ehrlich BE; Marks AR, Stabilization of calcium release channel (ryanodine receptor) function by FK506-binding protein. *Cell* 1994, 77 (4), 513–23. [PubMed: 7514503]
- [32]. Carmody M; Mackrill JJ; Sorrentino V; O'Neill C, FKBP12 associates tightly with the skeletal muscle type 1 ryanodine receptor, but not with other intracellular calcium release channels. *FEBS letters* 2001, 505 (1), 97–102. [PubMed: 11557049]
- [33]. Samso M; Shen X; Allen PD, Structural characterization of the RyR1-FKBP12 interaction. *Journal of molecular biology* 2006, 356 (4), 917–27. [PubMed: 16405911]
- [34]. Timmerman AP; Ogunbumni E; Freund E; Wiederrecht G; Marks AR; Fleischer S, The calcium release channel of sarcoplasmic reticulum is modulated by FK-506-binding protein. *Dissociation*

- and reconstitution of FKBP-12 to the calcium release channel of skeletal muscle sarcoplasmic reticulum. *The Journal of biological chemistry* 1993, 268 (31), 22992–9. [PubMed: 7693682]
- [35]. Bielefeldt K; Sharma RV; Whiteis C; Yedidag E; Abboud FM, Tacrolimus (FK506) modulates calcium release and contractility of intestinal smooth muscle. *Cell calcium* 1997, 22 (6), 507–14. [PubMed: 9502200]
- [36]. MacMillan D, FK506 binding proteins: cellular regulators of intracellular Ca²⁺ signalling. *European journal of pharmacology* 2013, 700 (1–3), 181–93. [PubMed: 23305836]
- [37]. Timerman AP; Wiederrecht G; Marcy A; Fleischer S, Characterization of an exchange reaction between soluble FKBP-12 and the FKBP.ryanodine receptor complex. Modulation by FKBP mutants deficient in peptidyl-prolyl isomerase activity. *The Journal of biological chemistry* 1995, 270 (6), 2451–9. [PubMed: 7531689]
- [38]. Shin DW; Pan Z; Bandyopadhyay A; Bhat MB; Kim DH; Ma J, Ca(2+)-dependent interaction between FKBP12 and calcineurin regulates activity of the Ca(2+) release channel in skeletal muscle. *Biophysical journal* 2002, 83 (5), 2539–49. [PubMed: 12414688]
- [39]. Lam E; Martin MM; Timerman AP; Sabers C; Fleischer S; Lukas T; Abraham RT; O’Keefe SJ; O’Neill EA; Wiederrecht GJ, A novel FK506 binding protein can mediate the immunosuppressive effects of FK506 and is associated with the cardiac ryanodine receptor. *The Journal of biological chemistry* 1995, 270 (44), 26511–22. [PubMed: 7592869]
- [40]. Xin HB; Rogers K; Qi Y; Kanematsu T; Fleischer S, Three amino acid residues determine selective binding of FK506-binding protein 12.6 to the cardiac ryanodine receptor. *The Journal of biological chemistry* 1999, 274 (22), 15315–9. [PubMed: 10336416]
- [41]. Cameron AM; Steiner JP; Sabatini DM; Kaplin AI; Walensky LD; Snyder SH, Immunophilin FK506 binding protein associated with inositol 1,4,5-trisphosphate receptor modulates calcium flux. *Proceedings of the National Academy of Sciences of the United States of America* 1995, 92 (5), 1784–8. [PubMed: 7533300]
- [42]. Patterson RL; Boehning D; Snyder SH, Inositol 1,4,5-trisphosphate receptors as signal integrators. *Annual review of biochemistry* 2004, 73, 437–65.
- [43]. Cameron AM; Steiner JP; Roskams AJ; Ali SM; Ronnett GV; Snyder SH, Calcineurin associated with the inositol 1,4,5-trisphosphate receptor-FKBP12 complex modulates Ca²⁺ flux. *Cell* 1995, 83 (3), 463–72. [PubMed: 8521476]
- [44]. Supattapone S; Danoff SK; Theibert A; Joseph SK; Steiner J; Snyder SH, Cyclic AMP-dependent phosphorylation of a brain inositol trisphosphate receptor decreases its release of calcium. *Proceedings of the National Academy of Sciences of the United States of America* 1988, 85 (22), 8747–50. [PubMed: 2847175]
- [45]. Joseph SK; Ryan SV, Phosphorylation of the inositol trisphosphate receptor in isolated rat hepatocytes. *The Journal of biological chemistry* 1993, 268 (31), 23059–65. [PubMed: 8226822]
- [46]. Wang T; Donahoe PK; Zervos AS, Specific interaction of type I receptors of the TGF-beta family with the immunophilin FKBP-12. *Science (New York, N.Y.)* 1994, 265 (5172), 674–6.
- [47]. Chen YG; Liu F; Massague J, Mechanism of TGFbeta receptor inhibition by FKBP12. *The EMBO journal* 1997, 16 (13), 3866–76. [PubMed: 9233797]
- [48]. Lam E; Martin M; Wiederrecht G, Isolation of a cDNA encoding a novel human FK506-binding protein homolog containing leucine zipper and tetratricopeptide repeat motifs. *Gene* 1995, 160 (2), 297–302. [PubMed: 7543869]
- [49]. Pedersen KM; Finsen B; Celis JE; Jensen NA, muFKBP38: a novel murine immunophilin homolog differentially expressed in Schwannoma cells and central nervous system neurons *in vivo*. *Electrophoresis* 1999, 20 (2), 249–55. [PubMed: 10197430]
- [50]. Nielsen JV; Mitchelmore C; Pedersen KM; Kjaerulff KM; Finsen B; Jensen NA, Fkbp8: novel isoforms, genomic organization, and characterization of a forebrain promoter in transgenic mice. *Genomics* 2004, 83 (1), 181–92. [PubMed: 14667822]
- [51]. Bulgakov OV; Eggenschwiler JT; Hong DH; Anderson KV; Li T, FKBP8 is a negative regulator of mouse sonic hedgehog signaling in neural tissues. *Development (Cambridge, England)* 2004, 131 (9), 2149–59.

- [52]. Edlich F; Weiwad M; Erdmann F; Fanghanel J; Jarczowski F; Rahfeld JU; Fischer G, Bcl-2 regulator FKBP38 is activated by Ca²⁺/calmodulin. The EMBO journal 2005, 24 (14), 2688–99. [PubMed: 15990872]
- [53]. Kang C; Ye H; Chia J; Choi BH; Dhe-Paganon S; Simon B; Schutz U; Sattler M; Yoon HS, Functional role of the flexible N-terminal extension of FKBP38 in catalysis. Scientific reports 2013, 3, 2985. [PubMed: 24145868]
- [54]. Fong S; Mounkes L; Liu Y; Maibaum M; Alonzo E; Desprez PY; Thor AD; Kashani-Sabet M; Debs RJ, Functional identification of distinct sets of antitumor activities mediated by the FKBP gene family. Proceedings of the National Academy of Sciences of the United States of America 2003, 100 (24), 14253–8. [PubMed: 14612567]
- [55]. Rosner M; Hofer K; Kubista M; Hengstschlager M, Cell size regulation by the human TSC tumor suppressor proteins depends on PI3K and FKBP38. Oncogene 2003, 22 (31), 4786–98. [PubMed: 12894220]
- [56]. Barth S; Nesper J; Hasgall PA; Wirthner R; Nytko KJ; Edlich F; Katschinski DM; Stiehl DP; Wenger RH; Camenisch G, The peptidyl prolyl cis/trans isomerase FKBP38 determines hypoxia-inducible transcription factor prolyl-4-hydroxylase PHD2 protein stability. Molecular and cellular biology 2007, 27 (10), 3758–68. [PubMed: 17353276]
- [57]. Barth S; Edlich F; Berchner-Pfannschmidt U; Gneuss S; Jahreis G; Hasgall PA; Fandrey J; Wenger RH; Camenisch G, Hypoxia-inducible factor prolyl-4-hydroxylase PHD2 protein abundance depends on integral membrane anchoring of FKBP38. The Journal of biological chemistry 2009, 284 (34), 23046–58. [PubMed: 19546213]
- [58]. Bai X; Ma D; Liu A; Shen X; Wang QJ; Liu Y; Jiang Y, Rheb activates mTOR by antagonizing its endogenous inhibitor, FKBP38. Science (New York, N.Y.) 2007, 318 (5852), 977–80.
- [59]. Laplante M; Sabatini DM, mTOR signaling in growth control and disease. Cell 2012, 149 (2), 274–93. [PubMed: 22500797]
- [60]. Jewell JL; Russell RC; Guan KL, Amino acid signalling upstream of mTOR. Nature reviews. Molecular cell biology 2013, 14 (3), 133–9. [PubMed: 23361334]
- [61]. Shimobayashi M; Hall MN, Making new contacts: the mTOR network in metabolism and signalling crosstalk. Nature reviews. Molecular cell biology 2014, 15 (3), 155–62. [PubMed: 24556838]
- [62]. Brown EJ; Albers MW; Shin TB; Ichikawa K; Keith CT; Lane WS; Schreiber SL, A mammalian protein targeted by G1-arresting rapamycin-receptor complex. Nature 1994, 369 (6483), 756–8. [PubMed: 8008069]
- [63]. Garami A; Zwartkruis FJ; Nobukuni T; Joaquin M; Rocco M; Stocker H; Kozma SC; Hafen E; Bos JL; Thomas G, Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Molecular cell 2003, 11 (6), 1457–66. [PubMed: 12820960]
- [64]. Manning BD; Cantley LC, Rheb fills a GAP between TSC and TOR. Trends in biochemical sciences 2003, 28 (11), 573–6. [PubMed: 14607085]
- [65]. Dunlop EA; Dodd KM; Seymour LA; Tee AR, Mammalian target of rapamycin complex 1-mediated phosphorylation of eukaryotic initiation factor 4E-binding protein 1 requires multiple protein-protein interactions for substrate recognition. Cellular signalling 2009, 21 (7), 1073–84. [PubMed: 19272448]
- [66]. Sato T; Nakashima A; Guo L; Tamanoi F, Specific activation of mTORC1 by Rheb G-protein *in vitro* involves enhanced recruitment of its substrate protein. The Journal of biological chemistry 2009, 284 (19), 12783–91. [PubMed: 19299511]
- [67]. Uhlenbrock K; Weiwad M; Wetzker R; Fischer G; Wittinghofer A; Rubio I, Reassessment of the role of FKBP38 in the Rheb/mTORC1 pathway. FEBS letters 2009, 583 (6), 965–70. [PubMed: 19222999]
- [68]. Ma D; Bai X; Guo S; Jiang Y, The switch I region of Rheb is critical for its interaction with FKBP38. The Journal of biological chemistry 2008, 283 (38), 25963–70. [PubMed: 18658153]
- [69]. Bos JL, Ras-like GTPases. Biochimica et biophysica acta 1997, 1333 (2), M19–31. [PubMed: 9395281]
- [70]. Cazzolli R; Shemon AN; Fang MQ; Hughes WE, Phospholipid signalling through phospholipase D and phosphatidic acid. IUBMB life 2006, 58 (8), 457–61. [PubMed: 16916782]

- [71]. Fang Y; Vilella-Bach M; Bachmann R; Flanigan A; Chen J, Phosphatidic acid-mediated mitogenic activation of mTOR signaling. *Science (New York, N.Y.)* 2001, 294 (5548), 1942–5.
- [72]. Yoon MS; Sun Y; Arauz E; Jiang Y; Chen J, Phosphatidic acid activates mammalian target of rapamycin complex 1 (mTORC1) kinase by displacing FK506 binding protein 38 (FKBP38) and exerting an allosteric effect. *The Journal of biological chemistry* 2011, 286 (34), 29568–74. [PubMed: 21737445]
- [73]. You JS; Frey JW; Hornberger TA, Mechanical stimulation induces mTOR signaling via an ERK-independent mechanism: implications for a direct activation of mTOR by phosphatidic acid. *PloS one* 2012, 7 (10), e47258. [PubMed: 23077579]
- [74]. Youle RJ; Strasser A, The BCL-2 protein family: opposing activities that mediate cell death. *Nature reviews. Molecular cell biology* 2008, 9 (1), 47–59. [PubMed: 18097445]
- [75]. Kang CB; Feng L; Chia J; Yoon HS, Molecular characterization of FK-506 binding protein 38 and its potential regulatory role on the anti-apoptotic protein Bcl-2. *Biochemical and biophysical research communications* 2005, 337 (1), 30–8. [PubMed: 16176796]
- [76]. Choi BH; Feng L; Yoon HS, FKBP38 protects Bcl-2 from caspase-dependent degradation. *The Journal of biological chemistry* 2010, 285 (13), 9770–9. [PubMed: 20139069]
- [77]. Twig G; Elorza A; Molina AJ; Mohamed H; Wikstrom JD; Walzer G; Stiles L; Haigh SE; Katz S; Las G; Alroy J; Wu M; Py BF; Yuan J; Deeney JT; Corkey BE; Shirihai OS, Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *The EMBO journal* 2008, 27 (2), 433–46. [PubMed: 18200046]
- [78]. Saita S; Shirane M; Nakayama KI, Selective escape of proteins from the mitochondria during mitophagy. *Nature communications* 2013, 4, 1410.
- [79]. Kang CB; Tai J; Chia J; Yoon HS, The flexible loop of Bcl-2 is required for molecular interaction with immunosuppressant FK-506 binding protein 38 (FKBP38). *FEBS letters* 2005, 579 (6), 1469–76. [PubMed: 15733859]
- [80]. Haupt K; Jahreis G; Linnert M; Maestre-Martinez M; Malesevic M; Pechstein A; Edlich F; Lucke C, The FKBP38 catalytic domain binds to Bcl-2 via a charge-sensitive loop. *The Journal of biological chemistry* 2012, 287 (23), 19665–73. [PubMed: 22523079]
- [81]. Ma D; Bai X; Zou H; Lai Y; Jiang Y, Rheb GTPase controls apoptosis by regulating interaction of FKBP38 with Bcl-2 and Bcl-XL. *The Journal of biological chemistry* 2010, 285 (12), 8621–7. [PubMed: 20048149]
- [82]. Wei Y; Patingre S; Sinha S; Bassik M; Levine B, JNK1-mediated phosphorylation of Bcl-2 regulates starvation-induced autophagy. *Molecular cell* 2008, 30 (6), 678–88. [PubMed: 18570871]
- [83]. Zou H; Lai Y; Zhao X; Yan G; Ma D; Cardenes N; Shiva S; Liu Y; Bai X; Jiang Y; Jiang Y, Regulation of mammalian target of rapamycin complex 1 by Bcl-2 and Bcl-XL proteins. *The Journal of biological chemistry* 2013, 288 (40), 28824–30. [PubMed: 23960074]
- [84]. Kaelin WG Jr., The von Hippel-Lindau tumour suppressor protein: O₂ sensing and cancer. *Nature reviews. Cancer* 2008, 8 (11), 865–73. [PubMed: 18923434]
- [85]. Pistollato F; Rampazzo E; Abbadi S; Della Puppa A; Scienza R; D'Avella D; Denaro L; Te Kronnie G; Panchision DM; Basso G, Molecular mechanisms of HIF-1 α modulation induced by oxygen tension and BMP2 in glioblastoma derived cells. *PloS one* 2009, 4 (7), e6206. [PubMed: 19587783]
- [86]. Wang J; Tong W; Zhang X; Chen L; Yi Z; Pan T; Hu Y; Xiang L; Yuan Z, Hepatitis C virus non-structural protein NS5A interacts with FKBP38 and inhibits apoptosis in Huh7 hepatoma cells. *FEBS letters* 2006, 580 (18), 4392–400. [PubMed: 16844119]
- [87]. Wang HQ; Nakaya Y; Du Z; Yamane T; Shirane M; Kudo T; Takeda M; Takebayashi K; Noda Y; Nakayama KI; Nishimura M, Interaction of presenilins with FKBP38 promotes apoptosis by reducing mitochondrial Bcl-2. *Human molecular genetics* 2005, 14 (13), 1889–902. [PubMed: 15905180]
- [88]. Tai PK; Maeda Y; Nakao K; Wakim NG; Duhring JL; Faber LE, A 59-kilodalton protein associated with progesterin, estrogen, androgen, and glucocorticoid receptors. *Biochemistry* 1986, 25 (18), 5269–75. [PubMed: 3768347]

- [89]. Renoir JM; Radanyi C; Faber LE; Baulieu EE, The non-DNA-binding heterooligomeric form of mammalian steroid hormone receptors contains a hsp90-bound 59-kilodalton protein. The Journal of biological chemistry 1990, 265 (18), 10740–5. [PubMed: 2355020]
- [90]. Sanchez ER; Faber LE; Henzel WJ; Pratt WB, 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 1990, 29 (21), 5145–52. [PubMed: 2378870]
- [91]. Nair SC; Toran EJ; Rimerman RA; Hjermsstad S; Smithgall TE; Smith DF, 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 1996, 1 (4), 237–50. [PubMed: 9222609]
- [92]. Banerjee A; Periyasamy S; Wolf IM; Hinds TD Jr.; Yong W; Shou W; Sanchez ER, Control of glucocorticoid and progesterone receptor subcellular localization by the ligand-binding domain is mediated by distinct interactions with tetratricopeptide repeat proteins. Biochemistry 2008, 47 (39), 10471–80. [PubMed: 18771283]
- [93]. Ruff VA; Yem AW; Munns PL; Adams LD; Reardon IM; Deibel MR Jr.; Leach KL, Tissue distribution and cellular localization of hsp56, an FK506-binding protein. Characterization using a highly specific polyclonal antibody. The Journal of biological chemistry 1992, 267 (30), 21285–8. [PubMed: 1383222]
- [94]. Czar MJ; Owens-Grillo JK; Dittmar KD; Hutchison KA; Zacharek AM; Leach KL; Deibel MR Jr.; Pratt WB, Characterization of the protein-protein interactions determining the heat shock protein (hsp90.hsp70.hsp56) heterocomplex. The Journal of biological chemistry 1994, 269 (15), 11155–61. [PubMed: 8157642]
- [95]. Peattie DA; Harding MW; Fleming MA; DeCenzo MT; Lippke JA; Livingston DJ; Benasutti M, 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 of the United States of America 1992, 89 (22), 10974–8. [PubMed: 1279700]
- [96]. Riggs DL; Roberts PJ; Chirillo SC; Cheung-Flynn J; Prapapanich V; Ratajczak T; Gaber R; Picard D; Smith DF, The Hsp90-binding peptidylprolyl isomerase FKBP52 potentiates glucocorticoid signaling *in vivo*. The EMBO journal 2003, 22 (5), 1158–67. [PubMed: 12606580]
- [97]. Silverstein AM; Galigniana MD; Kanelakis KC; Radanyi C; Renoir JM; Pratt WB, Different regions of the immunophilin FKBP52 determine its association with the glucocorticoid receptor, hsp90, and cytoplasmic dynein. The Journal of biological chemistry 1999, 274 (52), 36980–6. [PubMed: 10601253]
- [98]. Galigniana MD; Radanyi C; Renoir JM; Housley PR; Pratt WB, 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. The Journal of biological chemistry 2001, 276 (18), 14884–9. [PubMed: 11278753]
- [99]. Chambraud B; Rouviere-Fourmy N; Radanyi C; Hsiao K; Peattie DA; Livingston DJ; Baulieu EE, Overexpression of p59-HBI (FKBP59), full length and domains, and characterization of PPlase activity. Biochemical and biophysical research communications 1993, 196 (1), 160–6. [PubMed: 8216288]
- [100]. Callebaut I; Renoir JM; Lebeau MC; Massol N; Burny A; Baulieu EE; Mornon JP, 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 of the United States of America 1992, 89 (14), 6270–4. [PubMed: 1631118]
- [101]. Le Bihan S; Renoir JM; Radanyi C; Chambraud B; Joulin V; Catelli MG; Baulieu EE, The mammalian heat shock protein binding immunophilin (p59/HBI) is an ATP and GTP binding protein. Biochemical and biophysical research communications 1993, 195 (2), 600–7. [PubMed: 8373400]
- [102]. Miyata Y; Chambraud B; Radanyi C; Leclerc J; Lebeau MC; Renoir JM; Shirai R; Catelli MG; Yahara I; Baulieu EE, 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 of the United States of America 1997, 94 (26), 14500–5. [PubMed: 9405642]

- [103]. Radanyi C; Chambraud B; Baulieu EE, 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 of the United States of America* 1994, 91 (23), 11197–201. [PubMed: 7526392]
- [104]. Massol N; Lebeau MC; Renoir JM; Faber LE; Baulieu EE, Rabbit FKBP59-heat shock protein binding immunophilin (HBI) is a calmodulin binding protein. *Biochemical and biophysical research communications* 1992, 187 (3), 1330–5. [PubMed: 1384470]
- [105]. Cheung-Flynn J; Roberts PJ; Riggs DL; Smith DF, C-terminal sequences outside the tetratricopeptide repeat domain of FKBP51 and FKBP52 cause differential binding to Hsp90. *The Journal of biological chemistry* 2003, 278 (19), 17388–94. [PubMed: 12611898]
- [106]. Tranguch S; Cheung-Flynn J; Daikoku T; Prapapanich V; Cox MB; Xie H; Wang H; Das SK; Smith DF; Dey SK, Cochaperone immunophilin FKBP52 is critical to uterine receptivity for embryo implantation. *Proceedings of the National Academy of Sciences of the United States of America* 2005, 102 (40), 14326–31. [PubMed: 16176985]
- [107]. Cheung-Flynn J; Prapapanich V; Cox MB; Riggs DL; Suarez-Quian C; Smith DF, Physiological role for the cochaperone FKBP52 in androgen receptor signaling. *Molecular endocrinology* (Baltimore, Md.) 2005, 19 (6), 1654–66.
- [108]. Wang MH; Baskin LS, Endocrine disruptors, genital development, and hypospadias. *Journal of andrology* 2008, 29 (5), 499–505. [PubMed: 18497336]
- [109]. Baskin LS, Hypospadias. *Advances in experimental medicine and biology* 2004, 545, 3–22. [PubMed: 15086017]
- [110]. Yong W; Yang Z; Periyasamy S; Chen H; Yucel S; Li W; Lin LY; Wolf IM; Cohn MJ; Baskin LS; Sanchez ER; Shou W, Essential role for Co-chaperone Fkbp52 but not Fkbp51 in androgen receptor-mediated signaling and physiology. *The Journal of biological chemistry* 2007, 282 (7), 5026–36. [PubMed: 17142810]
- [111]. Chen H; Yong W; Hinds TD Jr.; Yang Z; Zhou Y; Sanchez ER; Shou W, Fkbp52 regulates androgen receptor transactivation activity and male urethra morphogenesis. *The Journal of biological chemistry* 2010, 285 (36), 27776–84. [PubMed: 20605780]
- [112]. Yang Z; Wolf IM; Chen H; Periyasamy S; Chen Z; Yong W; Shi S; Zhao W; Xu J; Srivastava A; Sanchez ER; Shou W, FK506-binding protein 52 is essential to uterine reproductive physiology controlled by the progesterone receptor A isoform. *Molecular endocrinology* (Baltimore, Md.) 2006, 20 (11), 2682–94.
- [113]. Hirota Y; Tranguch S; Daikoku T; Hasegawa A; Osuga Y; Taketani Y; Dey SK, Deficiency of immunophilin FKBP52 promotes endometriosis. *The American journal of pathology* 2008, 173 (6), 1747–57. [PubMed: 18988805]
- [114]. Hirota Y; Acar N; Tranguch S; Burnum KE; Xie H; Kodama A; Osuga Y; Ustunel I; Friedman DB; Caprioli RM; Daikoku T; Dey SK, Uterine FK506-binding protein 52 (FKBP52)-peroxiredoxin-6 (PRDX6) signaling protects pregnancy from overt oxidative stress. *Proceedings of the National Academy of Sciences of the United States of America* 2010, 107 (35), 15577–82. [PubMed: 20713718]
- [115]. Wolf IM; Periyasamy S; Hinds T Jr.; Yong W; Shou W; Sanchez ER, Targeted ablation reveals a novel role of FKBP52 in gene-specific regulation of glucocorticoid receptor transcriptional activity. *The Journal of steroid biochemistry and molecular biology* 2009, 113 (1–2), 36–45. [PubMed: 19073255]
- [116]. Sinars CR; Cheung-Flynn J; Rimerman RA; Scammell JG; Smith DF; Clardy J, Structure of the large FK506-binding protein FKBP51, an Hsp90-binding protein and a component of steroid receptor complexes. *Proceedings of the National Academy of Sciences of the United States of America* 2003, 100 (3), 868–73. [PubMed: 12538866]
- [117]. Baughman G; Wiederrecht GJ; Campbell NF; Martin MM; Bourgeois S, FKBP51, a novel T-cell-specific immunophilin capable of calcineurin inhibition. *Molecular and cellular biology* 1995, 15 (8), 4395–402. [PubMed: 7542743]

- [118]. Barent RL; Nair SC; Carr DC; Ruan Y; Rimerman RA; Fulton J; Zhang Y; Smith DF, Analysis of FKBP51/FKBP52 chimeras and mutants for Hsp90 binding and association with progesterone receptor complexes. *Molecular endocrinology* (Baltimore, Md.) 1998, 12 (3), 342–54.
- [119]. Smith DF; Baggenstoss BA; Marion TN; Rimerman RA, Two FKBP-related proteins are associated with progesterone receptor complexes. *The Journal of biological chemistry* 1993, 268 (24), 18365–71. [PubMed: 7688746]
- [120]. Davies TH; Ning YM; Sanchez ER, A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. *The Journal of biological chemistry* 2002, 277 (7), 4597–600. [PubMed: 11751894]
- [121]. Riggs DL; Cox MB; Tardif HL; Hessling M; Buchner J; Smith DF, Noncatalytic role of the FKBP52 peptidyl-prolyl isomerase domain in the regulation of steroid hormone signaling. *Molecular and cellular biology* 2007, 27 (24), 8658–69. [PubMed: 17938211]
- [122]. Reynolds PD; Ruan Y; Smith DF; Scammell JG, Glucocorticoid resistance in the squirrel monkey is associated with overexpression of the immunophilin FKBP51. *The Journal of clinical endocrinology and metabolism* 1999, 84 (2), 663–9. [PubMed: 10022435]
- [123]. Febbo PG; Lowenberg M; Thorner AR; Brown M; Loda M; Golub TR, Androgen mediated regulation and functional implications of fkb51 expression in prostate cancer. *The Journal of urology* 2005, 173 (5), 1772–7. [PubMed: 15821585]
- [124]. Amler LC; Agus DB; LeDuc C; Sapinoso ML; Fox WD; Kern S; Lee D; Wang V; Leysens M; Higgins B; Martin J; Gerald W; Dracopoli N; Cordon-Cardo C; Scher HI; Hampton GM, Dysregulated expression of androgen-responsive and nonresponsive genes in the androgen-independent prostate cancer xenograft model CWR22-R1. *Cancer research* 2000, 60 (21), 6134–41. [PubMed: 11085537]
- [125]. Magee JA; Chang LW; Stormo GD; Milbrandt J, Direct, androgen receptor-mediated regulation of the FKBP5 gene via a distal enhancer element. *Endocrinology* 2006, 147 (1), 590–8. [PubMed: 16210365]
- [126]. Hinz M; Scheidereit C, The IkappaB kinase complex in NF-kappaB regulation and beyond. *EMBO reports* 2014, 15 (1), 46–61. [PubMed: 24375677]
- [127]. Romano MF; Avellino R; Petrella A; Bisogni R; Romano S; Venuta S, Rapamycin inhibits doxorubicin-induced NF-kappaB/Rel nuclear activity and enhances the apoptosis of melanoma cells. *European journal of cancer* (Oxford, England : 1990) 2004, 40 (18), 2829–36.
- [128]. Gao T; Furnari F; Newton AC, PHLPP: a phosphatase that directly dephosphorylates Akt, promotes apoptosis, and suppresses tumor growth. *Molecular cell* 2005, 18 (1), 13–24. [PubMed: 15808505]
- [129]. Pei H; Li L; Fridley BL; Jenkins GD; Kalari KR; Lingle W; Petersen G; Lou Z; Wang L, FKBP51 affects cancer cell response to chemotherapy by negatively regulating Akt. *Cancer cell* 2009, 16 (3), 259–66. [PubMed: 19732725]
- [130]. Gallo LI; Lagadari M; Piwien-Pilipuk G; Galigniana MD, The 90-kDa heat-shock protein (Hsp90)-binding immunophilin FKBP51 is a mitochondrial protein that translocates to the nucleus to protect cells against oxidative stress. *The Journal of biological chemistry* 2011, 286 (34), 30152–60. [PubMed: 21730050]
- [131]. Toneatto J; Guber S; Charo NL; Susperreguy S; Schwartz J; Galigniana MD; Piwien-Pilipuk G, Dynamic mitochondrial-nuclear redistribution of the immunophilin FKBP51 is regulated by the PKA signaling pathway to control gene expression during adipocyte differentiation. *Journal of cell science* 2013, 126 (Pt 23), 5357–68. [PubMed: 24101724]
- [132]. Meng X; Lu X; Morris CA; Keating MT, A novel human gene FKBP6 is deleted in Williams syndrome. *Genomics* 1998, 52 (2), 130–7. [PubMed: 9782077]
- [133]. Fraune J; Schramm S; Alsheimer M; Benavente R, The mammalian synaptonemal complex: protein components, assembly and role in meiotic recombination. *Experimental cell research* 2012, 318 (12), 1340–6. [PubMed: 22394509]
- [134]. Crackower MA; Kolas NK; Noguchi J; Sarao R; Kikuchi K; Kaneko H; Kobayashi E; Kawai Y; Kozieradzki I; Landers R; Mo R; Hui CC; Nieves E; Cohen PE; Osborne LR; Wada T; Kunieda T; Moens PB; Penninger JM, Essential role of Fkbp6 in male fertility and homologous chromosome pairing in meiosis. *Science* (New York, N.Y.) 2003, 300 (5623), 1291–5.

- [135]. Jarczowski F; Fischer G; Edlich F, FKBP36 forms complexes with clathrin and Hsp72 in spermatocytes. *Biochemistry* 2008, 47 (26), 6946–52. [PubMed: 18529014]
- [136]. Jarczowski F; Jahreis G; Erdmann F; Schierhorn A; Fischer G; Edlich F, FKBP36 is an inherent multifunctional glyceralde-hyde-3-phosphate dehydrogenase inhibitor. *The Journal of biological chemistry* 2009, 284 (2), 766–73. [PubMed: 19001379]
- [137]. Linnert M; Lin YJ; Manns A; Haupt K; Paschke AK; Fischer G; Weiwad M; Lucke C, The FKBP-type domain of the human aryl hydrocarbon receptor-interacting protein reveals an unusual Hsp90 interaction. *Biochemistry* 2013, 52 (12), 2097–107. [PubMed: 23418784]
- [138]. Jin YJ; Albers MW; Lane WS; Bierer BE; Schreiber SL; Burakoff SJ, Molecular cloning of a membrane-associated human FK506- and rapamycin-binding protein, FKBP-13. *Proceedings of the National Academy of Sciences of the United States of America* 1991, 88 (15), 6677–81. [PubMed: 1713687]
- [139]. Futer O; DeCenzo MT; Aldape RA; Livingston DJ, FK506 binding protein mutational analysis. Defining the surface residue contributions to stability of the calcineurin co-complex. *The Journal of biological chemistry* 1995, 270 (32), 18935–40. [PubMed: 7642551]
- [140]. Partaledis JA; Berlin V, The FKB2 gene of *Saccharomyces cerevisiae*, encoding the immunosuppressant-binding protein FKBP-13, is regulated in response to accumulation of unfolded proteins in the endoplasmic reticulum. *Proceedings of the National Academy of Sciences of the United States of America* 1993, 90 (12), 5450–4. [PubMed: 7685904]
- [141]. Pacheco-Rodriguez G; Moss J; Vaughan M, BIG1 and BIG2: brefeldin A-inhibited guanine nucleotide-exchange proteins for ADP-ribosylation factors. *Methods in enzymology* 2002, 345, 397–404. [PubMed: 11665623]
- [142]. Padilla PI; Chang MJ; Pacheco-Rodriguez G; Adamik R; Moss J; Vaughan M, Interaction of FK506-binding protein 13 with brefeldin A-inhibited guanine nucleotide-exchange protein 1 (BIG1): effects of FK506. *Proceedings of the National Academy of Sciences of the United States of America* 2003, 100 (5), 2322–7. [PubMed: 12606707]
- [143]. Walensky LD; Gascard P; Fields ME; Blackshaw S; Conboy JG; Mohandas N; Snyder SH, The 13-kD FK506 binding protein, FKBP13, interacts with a novel homologue of the erythrocyte membrane cytoskeletal protein 4.1. *The Journal of cell biology* 1998, 141 (1), 143–53. [PubMed: 9531554]
- [144]. Lin IY; Yen CH; Liao YJ; Lin SE; Ma HP; Chan YJ; Chen YM, Identification of FKBP11 as a biomarker for hepato-cellular carcinoma. *Anticancer research* 2013, 33 (6), 2763–9. [PubMed: 23749938]
- [145]. Boudko SP; Ishikawa Y; Nix J; Chapman MS; Bachinger HP, Structure of human peptidyl-prolyl cis-trans isomerase FKBP22 containing two EF-hand motifs. *Protein science : a publication of the Protein Society* 2014, 23 (1), 67–75. [PubMed: 24272907]
- [146]. Solscheid B; Tropschug M, A novel type of FKBP in the secretory pathway of *Neurospora crassa*. *FEBS letters* 2000, 480 (2–3), 118–22. [PubMed: 11034311]
- [147]. Zhang X; Wang Y; Li H; Zhang W; Wu D; Mi H, The mouse FKBP23 binds to BiP in ER and the binding of C-terminal domain is interrelated with Ca²⁺ concentration. *FEBS letters* 2004, 559 (1–3), 57–60. [PubMed: 14960307]
- [148]. Shadidy M; Caubit X; Olsen R; Seternes OM; Moens U; Krauss S, Biochemical analysis of mouse FKBP60, a novel member of the FKBP family. *Biochimica et biophysica acta* 1999, 1446 (3), 295–307. [PubMed: 10524204]
- [149]. Davis EC; Broekelmann TJ; Ozawa Y; Mecham RP, Identification of tropoelastin as a ligand for the 65-kD FK506-binding protein, FKBP65, in the secretory pathway. *The Journal of cell biology* 1998, 140 (2), 295–303. [PubMed: 9442105]
- [150]. Murphy LA; Ramirez EA; Trinh VT; Herman AM; Anderson VC; Brewster JL, Endoplasmic reticulum stress or mutation of an EF-hand Ca(2+)-binding domain directs the FKBP65 rotamase to an ERAD-based proteolysis. *Cell stress & chaperones* 2011, 16 (6), 607–19. [PubMed: 21761186]
- [151]. Galat A; Lane WS; Standaert RF; Schreiber SL, A rapamycin-selective 25-kDa immunophilin. *Biochemistry* 1992, 31 (8), 2427–34. [PubMed: 1371698]

- [152]. Riviere S; Menez A; Galat A, On the localization of FKBP25 in T-lymphocytes. *FEBS letters* 1993, 315 (3), 247–51. [PubMed: 8422914]
- [153]. Yang WM; Yao YL; Seto E, The FK506-binding protein 25 functionally associates with histone deacetylases and with transcription factor YY1. *The EMBO journal* 2001, 20 (17), 4814–25. [PubMed: 11532945]
- [154]. Ahn J; Murphy M; Kratowicz S; Wang A; Levine AJ; George DL, Down-regulation of the stathmin/Op18 and FKBP25 genes following p53 induction. *Oncogene* 1999, 18 (43), 5954–8. [PubMed: 10557083]
- [155]. Ochocka AM; Kampanis P; Nicol S; Allende-Vega N; Cox M; Marcar L; Milne D; Fuller-Pace F; Meek D, FKBP25, a novel regulator of the p53 pathway, induces the degradation of MDM2 and activation of p53. *FEBS letters* 2009, 583 (4), 621–6. [PubMed: 19166840]
- [156]. Nakajima O; Nakamura F; Yamashita N; Tomita Y; Suto F; Okada T; Iwamatsu A; Kondo E; Fujisawa H; Takei K; Goshima Y, FKBP133: a novel mouse FK506-binding protein homolog alters growth cone morphology. *Biochemical and biophysical research communications* 2006, 346 (1), 140–9. [PubMed: 16756961]
- [157]. Viklund IM; Aspenstrom P; Meas-Yedid V; Zhang B; Kopec J; Agren D; Schneider G; D'Amato M; Olivo-Marin JC; Sansonetti P; Van Nhieu GT; Pettersson S, WAFL, a new protein involved in regulation of early endocytic transport at the intersection of actin and microtubule dynamics. *Experimental cell research* 2009, 315 (6), 1040–52. [PubMed: 19121306]
- [158]. Charters AR; Kobayashi M; Butcher SP, Immunochemical analysis of FK506 binding proteins in neuronal cell lines and rat brain. *Biochemical Society transactions* 1994, 22 (4), 411S. [PubMed: 7535258]
- [159]. Steiner JP; Dawson TM; Fotuhi M; Glatt CE; Snowman AM; Cohen N; Snyder SH, High brain densities of the immunophilin FKBP colocalized with calcineurin. *Nature* 1992, 358 (6387), 584–7. [PubMed: 1380130]
- [160]. Chattopadhyaya S; Harikishore A; Yoon HS, Role of FK506 binding proteins in neurodegenerative disorders. *Current medicinal chemistry* 2011, 18 (35), 5380–97. [PubMed: 22087831]
- [161]. Pallen CJ; Wang JH, A multifunctional calmodulin-stimulated phosphatase. *Archives of biochemistry and biophysics* 1985, 237 (2), 281–91. [PubMed: 2983609]
- [162]. Lyons WE; George EB; Dawson TM; Steiner JP; Snyder SH, Immunosuppressant FK506 promotes neurite outgrowth in cultures of PC12 cells and sensory ganglia. *Proceedings of the National Academy of Sciences of the United States of America* 1994, 91 (8), 3191–5. [PubMed: 7512727]
- [163]. Gold BG; Storm-Dickerson T; Austin DR, The immunosuppressant FK506 increases functional recovery and nerve regeneration following peripheral nerve injury. *Restorative neurology and neuroscience* 1994, 6 (4), 287–96. [PubMed: 21551759]
- [164]. Sharkey J; Butcher SP, Immunophilins mediate the neuroprotective effects of FK506 in focal cerebral ischaemia. *Nature* 1994, 371 (6495), 336–9. [PubMed: 7522303]
- [165]. Gold BG; Zeleny-Pooley M; Wang MS; Chaturvedi P; Armistead DM, A nonimmunosuppressant FKBP-12 ligand increases nerve regeneration. *Experimental neurology* 1997, 147 (2), 269–78. [PubMed: 9344552]
- [166]. Steiner JP; Connolly MA; Valentine HL; Hamilton GS; Dawson TM; Hester L; Snyder SH, Neurotrophic actions of nonimmunosuppressive analogues of immunosuppressive drugs FK506, rapamycin and cyclosporin A. *Nature medicine* 1997, 3 (4), 421–8.
- [167]. Steiner JP; Hamilton GS; Ross DT; Valentine HL; Guo H; Connolly MA; Liang S; Ramsey C; Li JH; Huang W; Howorth P; Soni R; Fuller M; Sauer H; Nowotnik AC; Suzdak PD, Neurotrophic immunophilin ligands stimulate structural and functional recovery in neurodegenerative animal models. *Proceedings of the National Academy of Sciences of the United States of America* 1997, 94 (5), 2019–24. [PubMed: 9050897]
- [168]. Guo X; Dawson VL; Dawson TM, Neuroimmunophilin ligands exert neuroregeneration and neuroprotection in midbrain dopaminergic neurons. *The European journal of neuroscience* 2001, 13 (9), 1683–93. [PubMed: 11359520]

- [169]. Costantini LC; Cole D; Chaturvedi P; Isacson O, Immunophilin ligands can prevent progressive dopaminergic degeneration in animal models of Parkinson's disease. The European journal of neuroscience 2001, 13 (6), 1085–92. [PubMed: 11285005]
- [170]. Edlich F; Weiwad M; Wildemann D; Jarczowski F; Kilka S; Moutty MC; Jahreis G; Lucke C; Schmidt W; Striggow F; Fischer G, The specific FKBP38 inhibitor N-(N',N'-dimethylcarboxamidomethyl)cycloheximide has potent neuroprotective and neurotrophic properties in brain ischemia. The Journal of biological chemistry 2006, 281 (21), 14961–70. [PubMed: 16547004]
- [171]. Price RD; Yamaji T; Yamamoto H; Higashi Y; Hanaoka K; Yamazaki S; Ishiye M; Aramori I; Matsuoka N; Mutoh S; Yanagihara T; Gold BG, FK1706, a novel nonimmunosuppressive immunophilin: neurotrophic activity and mechanism of action. European journal of pharmacology 2005, 509 (1), 11–9. [PubMed: 15713424]
- [172]. Gaali S; Kirschner A; Cuboni S; Hartmann J; Kozany C; Balsevich G; Namendorf C; Fernandez-Vizarra P; Sippel C; Zannas AS; Draenert R; Binder EB; Almeida OF; Ruhter G; Uhr M; Schmidt MV; Touma C; Bracher A; Hausch F, Selective inhibitors of the FK506-binding protein 51 by induced fit. Nature chemical biology 2015, 11 (1), 33–7. [PubMed: 25436518]
- [173]. Hausch F, FKBP5 and their role in neuronal signaling. Biochimica et biophysica acta 2015.
- [174]. O'Leary JC 3rd; Zhang B; Koren J 3rd; Blair L; Dickey CA, The role of FKBP5 in mood disorders: action of FKBP5 on steroid hormone receptors leads to questions about its evolutionary importance. CNS & neurological disorders drug targets 2013, 12 (8), 1157–62. [PubMed: 24040820]
- [175]. Bendor JT; Logan TP; Edwards RH, The function of alpha-synuclein. Neuron 2013, 79 (6), 1044–66. [PubMed: 24050397]
- [176]. Gerard M; Debyser Z; Desender L; Kahle PJ; Baert J; Baekelandt V; Engelborghs Y, The aggregation of alpha-synuclein is stimulated by FK506 binding proteins as shown by fluorescence correlation spectroscopy. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2006, 20 (3), 524–6. [PubMed: 16410343]
- [177]. Gerard M; Deleersnijder A; Daniels V; Schreurs S; Munck S; Reumers V; Pottel H; Engelborghs Y; Van den Haute C; Taymans JM; Debyser Z; Baekelandt V, Inhibition of FK506 binding proteins reduces alpha-synuclein aggregation and Parkinson's disease-like pathology. The Journal of neuroscience : the official journal of the Society for Neuroscience 2010, 30 (7), 2454–63. [PubMed: 20164329]
- [178]. Mandelkow EM; Mandelkow E, Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harbor perspectives in medicine 2012, 2 (7), a006247. [PubMed: 22762014]
- [179]. Hernandez F; Avila J, Tauopathies. Cellular and molecular life sciences : CMLS 2007, 64 (17), 2219–33. [PubMed: 17604998]
- [180]. Chambraud B; Sardin E; Giustiniani J; Dounane O; Schumacher M; Goedert M; Baulieu EE, A role for FKBP52 in Tau protein function. Proceedings of the National Academy of Sciences of the United States of America 2010, 107 (6), 2658–63. [PubMed: 20133804]
- [181]. Giustiniani J; Chambraud B; Sardin E; Dounane O; Guillemeau K; Nakatani H; Paquet D; Kamah A; Landrieu I; Lippens G; Baulieu EE; Tawk M, Immunophilin FKBP52 induces Tau-P301L filamentous assembly *in vitro* and modulates its activity in a model of tauopathy. Proceedings of the National Academy of Sciences of the United States of America 2014, 111 (12), 4584–89. [PubMed: 24623856]
- [182]. Jinwal UK; Koren J 3rd; Borysov SI; Schmid AB; Abisambra JF; Blair LJ; Johnson AG; Jones JR; Shults CL; O'Leary JC 3rd; Jin Y; Buchner J; Cox MB; Dickey CA, The Hsp90 cochaperone, FKBP51, increases Tau stability and polymerizes microtubules. The Journal of neuroscience : the official journal of the Society for Neuroscience 2010, 30 (2), 591–9. [PubMed: 20071522]
- [183]. Staibano S; Mascolo M; Ilardi G; Siano M; De Rosa G, Immunohistochemical analysis of FKBP51 in human cancers. Current opinion in pharmacology 2011, 11 (4), 338–47. [PubMed: 21530399]
- [184]. Romano S; Sorrentino A; Di Pace AL; Nappo G; Mercogliano C; Romano MF, The emerging role of large immunophilin FK506 binding protein 51 in cancer. Current medicinal chemistry 2011, 18 (35), 5424–9. [PubMed: 22087835]

- [185]. Romano S; D'Angelillo A; Romano MF, Pleiotropic roles in cancer biology for multifaceted proteins FKBP5. *Biochimica et biophysica acta* 2015.
- [186]. Velasco AM; Gillis KA; Li Y; Brown EL; Sadler TM; Achilleos M; Greenberger LM; Frost P; Bai W; Zhang Y, Identification and validation of novel androgen-regulated genes in prostate cancer. *Endocrinology* 2004, 145 (8), 3913–24. [PubMed: 15131019]
- [187]. Ni L; Yang CS; Gioeli D; Frierson H; Toft DO; Paschal BM, FKBP51 promotes assembly of the Hsp90 chaperone complex and regulates androgen receptor signaling in prostate cancer cells. *Molecular and cellular biology* 2010, 30 (5), 1243–53. [PubMed: 20048054]
- [188]. Periyasamy S; Hinds T Jr.; Shemshedini L; Shou W; Sanchez ER, FKBP51 and Cyp40 are positive regulators of androgen-dependent prostate cancer cell growth and the targets of FK506 and cyclosporin A. *Oncogene* 2010, 29 (11), 1691–701. [PubMed: 20023700]
- [189]. Romano S; D'Angelillo A; Pacelli R; Staibano S; De Luna E; Bisogni R; Eskelinen EL; Mascolo M; Cali G; Arra C; Romano MF, Role of FK506-binding protein 51 in the control of apoptosis of irradiated melanoma cells. *Cell death and differentiation* 2010, 17 (1), 145–57. [PubMed: 19696786]
- [190]. Romano S; Mallardo M; Romano MF, FKBP51 and the NF-kappaB regulatory pathway in cancer. *Current opinion in pharmacology* 2011, 11 (4), 288–93. [PubMed: 21565553]
- [191]. Romano S; D'Angelillo A; D'Arrigo P; Staibano S; Greco A; Brunetti A; Scalvenzi M; Bisogni R; Scala I; Romano MF, FKBP51 increases the tumour-promoter potential of TGF-beta. *Clinical and translational medicine* 2014, 3 (1), 1. [PubMed: 24460977]
- [192]. Romano S; Staibano S; Greco A; Brunetti A; Nappo G; Iardi G; Martinelli R; Sorrentino A; Di Pace A; Mascolo M; Bisogni R; Scalvenzi M; Alfano B; Romano MF, FK506 binding protein 51 positively regulates melanoma stemness and metastatic potential. *Cell death & disease* 2013, 4, e578. [PubMed: 23559012]
- [193]. Hou J; Wang L, FKBP5 as a selection biomarker for gemcitabine and Akt inhibitors in treatment of pancreatic cancer. *PloS one* 2012, 7 (5), e36252. [PubMed: 22590527]
- [194]. Li L; Lou Z; Wang L, The role of FKBP5 in cancer aetiology and chemoresistance. *British journal of cancer* 2011, 104 (1), 19–23. [PubMed: 21119664]
- [195]. Mousses S; Wagner U; Chen Y; Kim JW; Bubendorf L; Bittner M; Pretlow T; Elkahoul AG; Trepel JB; Kallioniemi OP, Failure of hormone therapy in prostate cancer involves systematic restoration of androgen responsive genes and activation of rapamycin sensitive signaling. *Oncogene* 2001, 20 (46), 6718–23. [PubMed: 11709706]
- [196]. Bai X; Jiang Y, Key factors in mTOR regulation. *Cellular and molecular life sciences : CMLS* 2010, 67 (2), 239–53. [PubMed: 19823764]
- [197]. Schiene-Fischer C, Multidomain peptidyl prolyl cis/trans Isomerases. *Biochimica et biophysica acta* 2014.
- [198]. Polydefkis M; Sirdofsky M; Hauer P; Petty BG; Murinson B; McArthur JC, Factors influencing nerve regeneration in a trial of timcodar dimesylate. *Neurology* 2006, 66 (2), 259–61. [PubMed: 16434669]
- [199]. Marshall VL; Grosset DG, GPI-1485 (Guilford). *Curr Opin Investig Drugs* 2004, 5 (1), 107–12.

Fig. (1). A schematic presentation of the domain structures of the human FKBP family. The information is from UniProt database.

Fig. (2). The action mechanism of FK506 and rapamycin in T lymphocyte activation.

FK506 binds to cytosolic FKBP12 to form the FKBP12-FK506 complex. The complex inhibits CaN-dependent dephosphorylation of NFATs in the cytoplasm and prevents their nuclear translocation and transcription of T-cell activation genes. Rapamycin also form a complex with FKBP12. However, this rapamycin-FKBP12 targets mTOR and inhibits its function in cell growth, blocking cell cycle progression.

Fig. (3). FKBP12 and FKBP12.6 stabilize and modulate intercellular Ca^{2+} release channels. FKBP12 and FKBP12.6 physically associate with Ca^{2+} release channels on the sarcoplasmic reticulum and endoplasmic reticulum. One molecule of FKBP12 or FKBP12.6 binds to one receptor within a tetramer. FKBP12 selectively binds to RyR1 and IP₃R, whereas within FKBP12.6 preferentially associates with RyR2. CaN is anchored to IP₃R through FKBP12 and modulates the phosphorylation of IP₃R.

Fig. (4). The signaling mechanisms of FKBP38 in regulation of mTOR and apoptosis. FKBP38, acting in a way similar to that of the rapamycin-FKBP12 complex, binds and inhibits mTORC1 function. This inhibitory action of FKBP38 is antagonized by the Ras-like small GTPase Rheb in response to growth factor and amino acid stimulation. Rheb binds directly FKBP38 and releases mTORC1 for activation. In apoptosis regulation, FKBP38 is responsible for recruiting Bcl-2 and Bcl-X_L to mitochondria. Rheb is believed to disassociate the two antiapoptotic proteins from FKBP38 on mitochondria and facilitates their interaction with pro-apoptotic proteins, Bak and Bax.

Fig. (5). A general mechanism for the role of FKBP51 and FKBP52 in regulation of steroid receptors.

In the absence of ligand binding steroid receptors (SR) associate with Hsp90 through their interaction with FKBP51 and are sequestered in the cytoplasm. Upon ligand binding, the receptors exchange the binding with FKBP51 for FKBP52. FKBP52 then targets the receptor-Hsp90 complexes to dynein motor protein, leading to redistribution of the receptors into the nucleus through the nuclear pore complex (NPC), where they regulate transcription. FK506 disrupts the receptor complex by binding to the PPIase domain of FKBP52.

Fig. (6). The action mechanisms of FKBP51 in regulating the AKT and NF- κ B pathways. FKBP51 functions as a scaffolding protein that bridges the association of PHLPP with AKT. The association promotes PHLPP-mediated dephosphorylation of AKT at position 473, resulting in downregulation of AKT activity. In the NF- κ B pathway FKBP51 regulates NF- κ B activity by modulating the phosphorylation state of inhibitor of I κ B. FKBP51 binds to IKK α and stimulates IKK α -directed phosphorylation of I κ B. FKBP51 also interacts with CaN and inhibits CaN-dependent dephosphorylation of I κ B. Therefore, FKBP51 promotes aberrant NF- κ B activation and the expression of antiapoptotic proteins.(3) FKBP51 facilitates the activation of NF- κ B pathway through the interaction with IKK0 α and enhancing the IKK kinase activity. Rapamycin prevents the action of FKBP51 in the NK- κ B pathway by inhibits the PPIase activity of FKBP51.