Review

FKBP51 and FKBP52 in signaling and disease

Cheryl L. Storer[1], Chad A. Dickey[2], Mario D. Galigniana[3], Theo Rein[4] and Marc B. Cox[1]

[1] The Border Biomedical Research Center and Department of Biological Sciences, University of Texas at El Paso, El Paso, TX 79968, USA
[2] Departments of Molecular Medicine & Psychiatry, University of South Florida Alzheimer's Institute, Tampa, FL 33613, USA
[3] Instituto de Biología y Medicina Experimental (IBYME)-CONICET (1428ADN) Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales (C1428EGA) Universidad de Buenos Aires, Buenos Aires, Argentina
[4] Max Planck Institute of Psychiatry, 80804 Munich, Germany

FKBP51 and FKBP52 are diverse regulators of steroid hormone receptor signaling, including receptor maturation, hormone binding and nuclear translocation. Although structurally similar, they are functionally divergent, which is largely attributed to differences in the FK1 domain and the proline-rich loop. FKBP51 and FKBP52 have emerged as likely contributors to a variety of hormone-dependent diseases, including stress-related diseases, immune function, reproductive functions and a variety of cancers. In addition, recent studies have implicated FKBP51 and FKBP52 in Alzheimer's disease and other protein aggregation disorders. This review summarizes our current understanding of FKBP51 and FKBP52 interactions within the receptor–chaperone complex, their contributions to health and disease, and their potential as therapeutic targets for the treatment of these diseases.

FKBP51 and FKBP52 structure and function

It has been 20 years since the 51 and 52-kDa FK506-binding proteins FKBP51 and FKBP52 were first identified in complex with the steroid hormone receptors [1,2]. Since then, much progress has been made in understanding the mechanisms by which they regulate steroid hormone receptor signaling and the resulting roles they play in endocrine-related physiological processes. Over the years, FKBP51 and FKBP52 have emerged as potential therapeutic targets for a wide variety of endocrine-related diseases, including prostate cancer, breast cancer, male and female contraception, stress-related diseases and metabolic diseases. As a result, researchers in academia and industry are increasingly focused on the identification and development of novel drugs that target FKBP51 and FKBP52.

FKBP51 and FKBP52 are HSP90 co-chaperones that modify steroid hormone receptor (SHR) activity. FKBP51 and FKBP52 share 70% similarity and contain an active peptidyl prolyl isomerase (PPIase) domain, bind the 90-kDa heat shock protein (HSP90) through a C-terminal tetratricopeptide repeat (TPR) domain [3], and adopt similar conformations (Figure 1) [4]. FKBP52 is a positive regulator of the glucocorticoid receptor (GR) [5],

Glossary

AKT: serine/threonine protein kinase that regulates apoptosis, cell migration, transcription, proliferation and glucose metabolism.
Antineoplastic therapy: chemotherapy that targets all actively dividing cells.
β-Importin: during nuclear import, β-importin tethers incoming proteins to the nuclear pore complex.
FKBP51: 51-kDa FK506 binding protein that binds the immunosuppressive drug FK506 without initiating immunosuppression.
FKBP52: 52-kDa FK506 binding protein that binds the immunosppressive drug FK506 without initiating immunosuppression.
FK1 domain: FKBP12-like domain 1 of FKBP51 and FKPB52, responsible for binding to FK506, for PPIase activity and for steroid hormone receptor regulation.
FK2 domain: FKBP12-like domain 2, present in FKBP51 and FKBP52; differs slightly from the FK1 and lacks PPIase and FK506 binding ability.
FK506: also called tacrolimus, a macrolide drug that complexes with FKBP12 and inhibits calcineurin phosphatase activity. This leads to immunosuppression by blocking T-cell signal transduction cascades and interleukin-2 transcription.
Geldanamycin: benzoquinone ansamycin antibiotic that directly binds HSP90 and inhibits its function.
HSP90: the 90-kDa heat shock protein is a molecular chaperone involved in protein folding, tumor repression and cell signaling. Steroid hormone receptors require association with HSP90 to fold to a conformation capable of binding to a ligand.
Hypothalamus pituitary adrenal (HPA) axis: interactions between the hypothalamus, the pituitary gland and the adrenal glands are crucial parts of the neuroendocrine system. This pathway is responsible for the regulation of stress reactions, energy storage and output, emotion and affect, sexuality, digestion and the immune system.
MHC II: major histocompatibility complex class II molecules are located on subclasses of antigen-presenting cells and display extracellular protein fragments to $CD4^+$ helper T cells to determine the immune response.
NF-κB: nuclear factor κ light-chain enhancer of activated B cells is a transcription factor complex found in most animal cells that regulates cellular responses to infections and stress.
Nup62: nucleoporin 62 is a complex of proteins that associates with the importin αβ complex of the nuclear pore to assist in the import of proteins with nuclear localization signals.
PPIase activity: peptidyl prolyl isomerase activity catalyzes *cis–trans* isomerization reactions of peptide bonds involving the amino acid proline. PPIase activity is required for the proper folding of several, but not all, proteins.
Protein aggregation disorders: agglomeration of proteins occurs in diseases such as Alzheimer's disease, bovine spongiform encephalopathy (mad cow disease) and Huntington's disease.
Radicicol: also known as monorden, radicicol is a macrolactone antibiotic that binds HSP90 and alters its function. It also inhibits tyrosine kinase and is anti-angiogenic.
Reticulosyte lysate assembly system: cell-free assembly system that contains all the eukaryotic cofactors necessary for steroid hormone receptor folding and allows for reconstitution of the receptors with chaperone complexes *in vitro*.
Tau: tau proteins are found primarily in neurons of the central nervous system and normally help in microtubule stabilization. Defective folding of tau and the resultant agglomeration are associated with neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.
TPR domain: the tetratricopeptide repeat is a structural motif used in protein–protein interactions. The TPR domains on FKBP51 and FKBP52 bind specifically to the extreme C terminus of HSP90.

Corresponding author: Cox, M.B. (mbcox@utep.edu)

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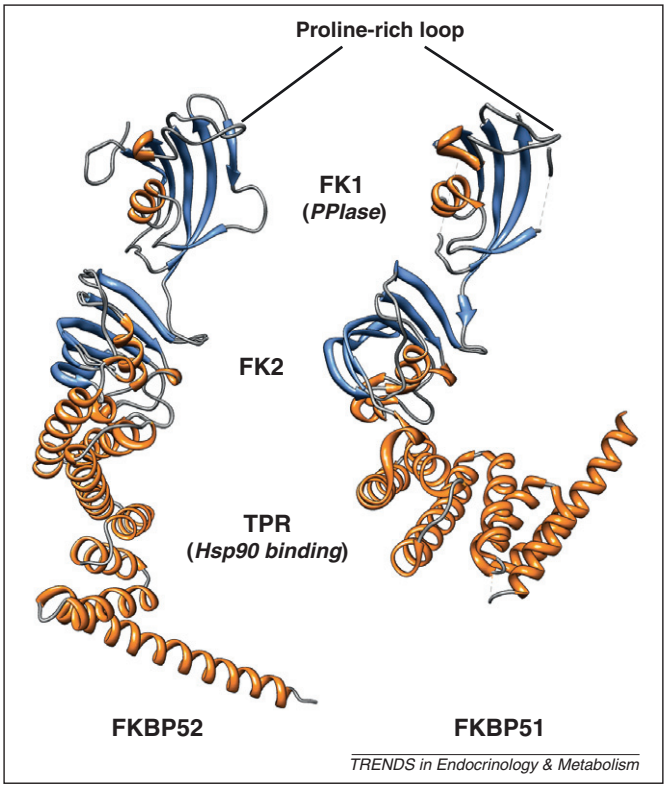

Figure 1. FKBP51 and FKBP52 X-ray crystallographic structures. The three-dimensional structure of human FKBP51 (PDB number 1KT0) and a composite of two partial structures for human FKBP52 (PDB numbers 1Q1C and 1P5Q) are shown in ribbon format colored based on secondary structure. The important functional domains and regions are illustrated. The C-terminal TPR domain mediates binding to HSP90. FKBP12-like domains 1 and 2 are also shown. FK2 is similar to FK1, but lacks PPIase activity and does not bind the immunosuppressive ligand FK506. The FK1 domain contains a functional PPIase active site and binds FK506. Although PPIase activity is not required for receptor regulation, the FK1 domain is crucial for FKBP function. In particular, the proline-rich loop overhanging the PPIase pocket is crucial for receptor regulation, is largely responsible for the divergent functions of FKBP51 and FKBP52, and may serve as a functionally important interaction surface. The figure, including the overlay of the two partial FKBP52 structures, was created using UCSF Chimera version 1.5.

progesterone receptor (PR) [6], and androgen receptor (AR) [7], but not the estrogen receptor (ER) or mineralocorticoid receptor (MR) [5]. FKBP51 is a negative regulator of SHR activity in most studies reported [8]. The FKBPs compete for binding to the SHR complex and, as a result, overexpression of FKBP51 decreases receptor regulation by FKBP52 [5] and in the case of AR, hormone binding affinity is increased fivefold in the presence of FKBP52 versus FKBP51 [9].

The major FKBP functional domains include FKBP12-like domains 1 and 2 (FK1 and FK2) and the tetratricopeptide repeat (TPR) domain (Figure 1) [10]. The FK1 domain facilitates binding to the immunosuppressive drug FK506, confers PPIase activity [3], and is the primary regulatory domain for SHRs [5]. The FK1 domains of FKBP51 and FKBP52 exhibit comparable PPIase enzyme activity towards small peptide substrates. The FK1 domain is deemed crucial for receptor potentiation by FKBP52 [5], but its enzyme activity is not required for this potentiation. Domain integrity in and around the PPIase pocket is essential [9]. Although residues crucial for PPIase activity are conserved in FKBP52 and FKBP51, residues of the proline-rich loop suspended above the PPIase pocket differ, and thus significantly affect protein interactions with larger peptide substrates [3,10]. These differences are also probably responsible for the divergent functions of the FKBPs, because a randomly identified FKBP51 mutant containing two point mutations (A116 V and L119P) in the FKBP51 proline-rich loop showed full FKBP52-like activity towards AR [9].

Seven to nine amino acids of the FK linker connect the FK1 and FK2 domains in FKBP51 and FKBP52. In FKBP52, this linker is crowned by the casein kinase 2 (CK2) phosphorylation sequence TEEED. CK2 phosphorylation at T143 could decrease binding to HSP90 [11], but this finding was not replicated in an *in vitro* study in which HSP90 binding was compared between wild-type FKBP52 and the phosphomimetic mutant FKBP52-T143E [12]. Phosphorylation of T143 completely abrogates FKBP52 regulation of receptor function and is predicted to reorient the conformation of the FK1 domain. In FKBP51, this loop is crowned by the sequence FED, so phosphorylation of this site is not achieved. However, this difference does not account for the lack of receptor potentiation ability of FKBP51.

The FK2 domain is still enigmatic; although structurally similar to FK1, it lacks PPIase activity and does not bind the drug FK506. Deletion of three amino acids in the FKBP51 FK2 domain (D195, H196 and D197) does not disrupt HSP90 binding, but the mutant does not integrate normally into PR complexes. [10]. It is possible that this mutation decreases interaction with other components of the receptor complex, and possibly even the receptor itself.

The TPR domain confers HSP90 binding ability to the FKBPs through interaction with the EEVD motif in the extreme C terminus of HSP90. The TPR domain is characteristic of all FKBPs that interact with SHR complexes. Isothermal titration calorimetry suggests that the PPIase domain of FKBP51 binds a HSP90 dimer with only 25–33% of the affinity of the PPIase domain of FKBP52 [3]. However, the FKBP affinities for HSP90 do not accurately predict the FKBP abundance in HSP90-mediated receptor complexes. In a reticulocyte lysate assembly system, PR complexes showed a preference for FKBP51, GR complexes preferred FKBP51 and protein phosphatase 5, and ER complexes preferred cyclophilin 40 [13]. The phenomenon of client specificity supports the possibility that the FKBPs could potentiate receptors through direct association or through unique, receptor-specific adapter proteins. Indeed, HSP90-independent interactions have been reported between GR and the FK1 domain of FKBP52 [14].

In this article we propose a model in which holds the FKBP52 FK1 domain, and the proline-rich loop in particular, is not only responsible for the divergent functions of the FKBPs, but also serves as an interaction surface. The receptor specificity displayed by the FKBPs suggests that they directly contact the receptors within the receptor–chaperone complex. The fact that FKBP52 regulation has been localized to the receptor ligand binding domain (LBD) [5,15] suggests that the FK1 interaction partner is the receptor LBD. We propose that interaction with HSP90-receptor complex, which is stabilized by the p23 co-chaperone, brings the FKBP FK1 domain into contact with the receptor LBD and directly affects the hormone

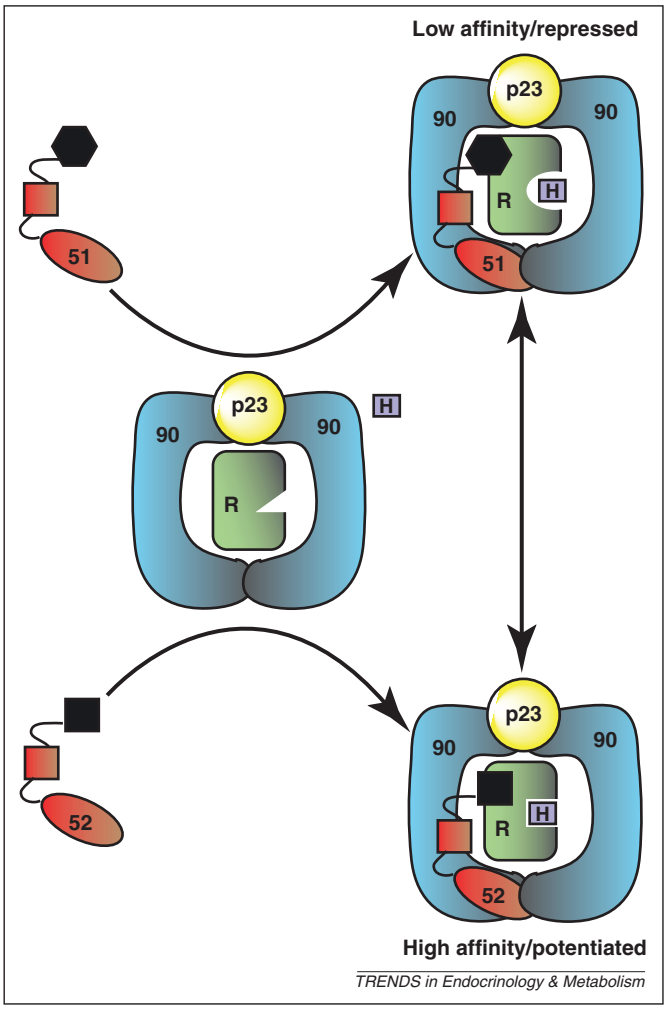

Figure 2. Model of FKBP regulation of receptor maturation and hormone binding. The FK1 domain, and the proline-rich loop in particular, is responsible for the divergent functions of the FKBPs and probably serves as an interaction surface. The difference in shape of the FKBP FK1 domains shown here illustrates the structural differences in the proline-rich loop between these two proteins. According to the current model, association of the FKBPs with the closed state of the HSP90 dimer, which is stabilized by the p23 cochaperone, brings the FK1 domain into contact with the receptor LBD to directly influence hormone binding affinity. As a result of differences in the FK1 domain, hormone binding is repressed in the presence of FKBP51 and potentiated in the presence of FKBP52.

Box 1. FKBP52: a diverse regulator of steroid hormone receptor signaling

Studies aimed at characterizing FKBP52 as a regulator of receptor maturation and hormone binding and those characterizing FKBP52 as a regulator of receptor subcellular localization have traditionally progressed independent of each other. This review presents both ideas with equal coverage. Based on the evidence, it is likely that FKBP52 is a regulator of both receptor hormone binding and receptor localization. The only area in which the two models do not agree is the timing for FKBP52 association with the receptor–chaperone complex and whether or not FKBP51 has a direct role in this process. First, when hormone is added to *in vitro* PR complexes with chemically suspended HSP90 dissociation ability, FKBP51 quickly dissociates, yet FKBP52 remains bound [88,89]. Second, in an *in vivo* study in which the HSP90 complex was suspended on ice to decrease the dissociation rate of HSP90, addition of hormone caused FKBP51 to be replaced with FKBP52 in complexes with GR [19]. Thus, evidence exists to support the hormone-induced switching of FKBP51 for FKBP52, as depicted in Figure 3. However, the fact that FKBP52 promotes increased receptor hormone binding affinity [9] suggests that FKBP52 is present in receptor–chaperone complexes before hormone binding and somehow primes the receptor for hormone binding. Indeed, complexes containing FKBP52 in the absence of hormone are observed. The FKBP52 FK1 domain is important for receptor regulation and recent studies suggest that the FK1 domain serves as an interaction surface that may directly contact the receptor LBD within the complex to promote increased hormone binding, as depicted in Figure 2 [9]. Recent evidence suggests the simultaneous binding of multiple TPR proteins to HSP90, although these studies were performed in the absence of HSP90 client protein [90,91]. Thus, the mutually exclusive model for TPR proteins may be more complicated than is currently thought. It is also important to point out that most studies have been performed using purified proteins in the absence of receptor and, more importantly, in different cell types. These differences in experimental conditions and systems could account, at least in part, for the differences discussed above. It is likely that FKBP52 plays an important role in the hormone binding step and continues to be crucial for receptor localization, and possibly even plays a role in receptor regulation in the nucleus. Further studies are needed to resolve these discrepancies and to bring the two models together.

binding affinity of the receptor (Figure 2; Box 1). The FKBP interaction surface on the receptor and the molecular mechanism by which this occurs are currently under investigation (Box 3).

Roles for FKBP51 and FKBP52 in receptor localization

In the absence of ligand, some SHRs reside primarily in the cytoplasm, whereas others are nuclear. Regardless of their primary localization, these receptors are not confined to any particular cell compartment and shuttle continuously between the cytoplasm and nucleus [16,17]. It has always been assumed that simple diffusion is the driving force for movement of these signaling molecules. However, the observation that proteins of the dynein–dynactin complex co-immunoprecipitate with the HSP90–FKBP52 complex and with GR [18–20] and MR [21–23] suggests that these motor proteins could power retrograde movement of these steroid receptors. Several observations agree with this hypothesis. The steroid-dependent nuclear accumulation of primarily cytoplasmic steroid receptors is rapid ($t_{0.5}$ = 4–5 min), but treatment of cells with HSP90-disrupting agents such as geldanamycin lowers the rate of translocation by an order of magnitude ($t_{0.5}$ = 40–60 min), during which the HSP90–FKBP52 complex is inactivated [18,21]. The rapid HSP90–FKBP-dependent movement of steroid receptors requires cytoskeletal tracts, with tubulin being physically linked to the receptor–HSP90–FKBP52–motor protein complex [17,24]. Coimmunoprecipitation of dynein and subunit components of dynactin with FKBP52 demonstrated that the motor protein complex binds the N Diff id="147">[147_TD$DIFF] terminus of FKBP52 in a manner that seems to be independent of the PPIase activity of FKBP52 [23,25]. Rather, the PPIase domain acts as a protein–protein interaction domain and the association of dynein–dynactin with FKBP52 is not affected by FK506.

Because the FKBPs and HSP90 are part of the same functional complex, it can be envisaged that disruption of the interaction between the FKBPs and motor proteins should yield similar levels of inhibition of SHR retrotransport as that measured in the presence of HSP90 inhibitors. This was demonstrated when the receptor was disconnected

from the transport machinery by overexpression of the PPIase peptide (interferes with dynein binding to FKBP52) [18–20], the TPR peptide (blocks FKBP52 binding to HSP90) [23] or the p50 (dynactin2) subunit of dynactin [18,20]. However, nuclear translocation of GR is delayed by FKBP51, which correlates with the poor interaction of FKBP51 with dynein [20].

In all these cases, nuclear localization of the cargo was not fully inhibited but was simply impaired, which suggests the existence of two types of transport, the rapid HSP90–FKBP52–dynein–dynactin-dependent mechanism ($t_{0.5}$ = 4–5 min) and an alternative, heterocomplex-independent and less efficient mechanism ($t_{0.5}$ = 40–60 min), which could be due to simple diffusion. Importantly, when the nuclear translocation rate of these receptors was impaired, they became highly sensitive to proteasomal degradation [26]. The same heterocomplex described for steroid receptors is also responsible for cytoplasmic retrotransport of the proapototic factor p53 [27], which suggests that the HSP90-based complex may play a general role in the retrotransport of a number of HSP90-associated factors towards the nuclear surface.

Inasmuch as the chaperone molecular bridge provides the traction chain for transport of the nuclear factor throughout the cytoplasm via microtubule tracks, dissociation of the HSP90-based complex from SHRs should not occur directly after ligand binding because the HSP90–FKBP52 complex is required for the normal retrotransport mechanism [17]. This is a major modification of the model postulated decades ago for SHR activation, which hypothesized that HSP90 anchors SHRs in the cytoplasmic compartment and only cytoplasmic dissociation of the chaperone permits nuclear translocation of the receptor (Figure 3; Box 1) [28,29]. The new model for SHR retrotransport implies that the chaperone machinery should remain associated with the receptor. It also implies that it could interact with structures of the nuclear pore complex during the nuclear translocation process. It was recently demonstrated that the chaperone complex binds the integral nuclear pore glycoprotein NUP62 and β-importin [30]. This facilitates passage of the untransformed receptor through the channel of the nuclear pore. It is possible that the chaperone complex associated with importins, nucleoporins and the cargo itself can act as a cooperative system to prevent the aggregation of cargoes when their hydrophobic domains are exposed in the channel during the translocation step. The association of TPR proteins such as FKBP52 to NAP62 is HSP90-dependent, as shown by the dissociation of FKBP52 from NUP62 with radicicol. Nonetheless, indirect immunofluorescence assays performed in intact cells treated with radicicol still show the presence of FKBP52 in the perinuclear ring [30], which suggests that this TPR protein may also bind to other perinuclear structures (e.g. other nucleoporins) in a HSP90-independent manner. Competition experiments with overexpression of the TPR domain showed that the

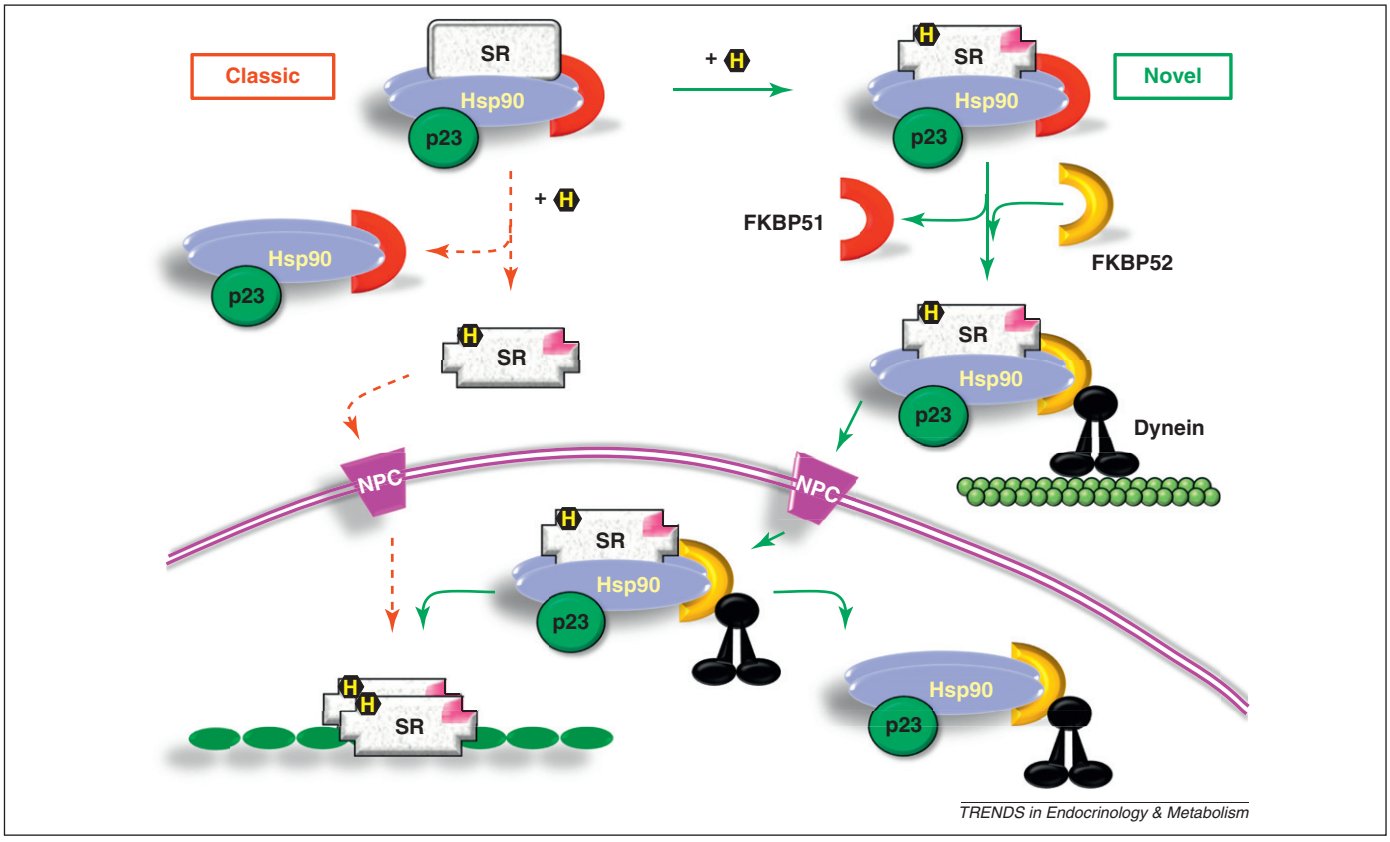

Figure 3. Models for steroid hormone receptor translocation. According to the classic model (dashed lines), the chaperone complex dissociates in the cytoplasm from the steroid receptor (SR) on hormone (H) binding. This transformed receptor passes through the nuclear pore complex (NPC) to reach its nuclear sites of action. The novel model is depicted with continuous lines. On steroid binding, the SR heterocomplex exchanges FKBP51 (brown crescent) for FKBP52 (dashed crescent), which is able to interact with dynein (black). The chaperone complex serves as a traction chain for the receptor, for which retrotransport occurs on cytoskeletal tracts. The nuclear localization signal (NL1; pink) protrudes on steroid binding and the whole SR–chaperone complex translocates through the NPC. The heterocomplex interacts with structural proteins of the pore, which are also chaperoned. Receptor transformation is nucleoplasmic and facilitates binding of the steroid-activated receptor to promoter sites.

Box 2. Role for the FKBPs in protein folding and aggregation disorders

A novel role for HSP90 and associated co-chaperones in protein folding and aggregation disorders such as Alzheimer's has emerged in recent years. Direct modulation of HSP90 may be clinically relevant for protein folding and aggregation disorders [92–95]. HSP90 cooperates with many co-chaperones to act on specific protein subclasses, such as transmembrane receptors and tau and other disordered proteins. Recent data suggest that one or more of these co-chaperones could be more specific drug targets with fewer adverse consequences [38,92]. For example, in a *Caenorhabditis elegans* model of tauopathy, tau levels increased and the pathological phenotype worsened when the ubiquitin ligase CHIP, which is also an HSP90 cochaperone, and FKBP52 were silenced [96]. However, the involvement of FKBP51 in tau pathogenesis was not described in this study, because *C. elegans* lacks an *FKBP51* gene. It was recently shown that FKBP51 preserves tau levels, but reduces its phosphorylation, perhaps by cooperating with a set of phosphatases [38]. FKBP51 also interacts with tau in human Alzheimer's disease brain tissue. More recently it was shown that increased levels of FKBP52 correspond with decreased tau stability [37,97]. Thus, these two proteins may have opposing roles for tau, despite similar structural features.

The roles of the PPIase activity of both FKBP51 and FKBP52 could be critical for the regulation of intrinsically disordered proteins such as tau, since a high percentage of proline residues is common among this family [98]. More than 20% of the residues between I151 and Q244 of tau are proline. Most of the known functions of tau are mediated through MT binding domains distal to this proline-rich region. However, many disease-associated phosphorylation events that seed tau tangle formation occur at proline-directed serine (S) and threonine (T) residues in this proline-rich region. This strongly suggests that important structural changes in the proline-rich region of tau regulate tangle formation. In particular, *cis–trans* isomerization around these prolines modulates protein phosphatase binding and activity at specific S/T sites. It is well established that peptidyl-prolyl isomerase 1 (PIN1) regulates tau phosphorylation in concert with protein phosphatase 2A (PP2A), specifically at T231 and T212 [99]. FKBP51 and FKBP52 probably have similar activity; however, unlike PIN1, the FKBPs probably coordinate with HSP90 to isomerize tau [49]. Thus, FKBP51 and FKBP52 may improve our understanding of tau biology and may be targets for drug development efforts in tauopathies.

perinuclear signal of FKBP52 was totally abolished, which indicates that the TPR domain is required for most, if not all, associations of FKBP52 with any structure of the nuclear envelope [30].

FKBP51 and FKBP52 in health and disease

Reproductive development and success

A role for FKBP52 in mammalian reproductive development and success emerged from the development and study of two independently derived *fkbp52*-deficient (52KO) mouse lines. The phenotypes observed in these mice directly correlate with observations previously obtained in biochemical and cellular studies. Male 52KO mice display phenotypes consistent with partial androgen insensitivity, including dysgenic prostate and seminal vesicles, ambiguous external genitalia including hypospadias, and retention of nipples into adulthood [7,31]. Despite the androgen insensitivity, the testes of 52KO mice develop normally. It is currently unclear whether some factor within the testis can complement for the loss of FKBP52 or androgen levels produced locally within the testis are enough to compensate for reduced AR activity. 52KO male mice do have reduced epididymal sperm counts and the sperm display abnormal morphology. It has also been reported that FKBP52 is present in epididymal sperm flagella and 52KO animals display reduced sperm motility [32]. The androgen insensitivity observed in 52KO mice does not account for reduced sperm motility, because this is an androgen-independent process. As discussed above, FKBP52 does interact with dynein motor proteins, which suggests a possible role for FKBP52 in the regulation of flagella movement. The available evidence suggests that FKBP52 may serve as an attractive target for male contraceptives; however, further studies of the role of FKBP52 in the testis and in sperm maturation and motility are needed (Box 3).

Female 52KO mice seem to be morphologically normal and display normal ovulation and fertilization, yet they are infertile. This infertility is the result of embryonic implantation and decidualization failure due to progesterone insensitivity and uterine defects [6,33,34]. Implantation failure may be due to increased uterine oxidative stress, because 52KO animals are sensitive to paraquat-induced oxidative stress and have reduced levels of the antioxidant peroxiredoxin-6 (PRDX6), and addition of exogenous antioxidant rescued implantation [33,35]. Finally, FKBP52 may promote endometriosis, because women with endometriosis show reduced FKBP52 expression, and the progesterone resistance observed in 52KO mice results in increased cell proliferation, inflammation and angiogenesis, which lead to endometriotic lesions [36]. Thus, evidence suggests a crucial role for FKBP52 in female reproduction and uterine signaling.

Mice deficient in *fkbp51* (51KO) display no overt morphological phenotypes. However, loss of both FKBP51 and FKBP52 (51/52KO) proteins results in embryonic lethality, although the cause of this phenotype has not been investigated (Box 3). Thus, FKBP51 and FKBP52 have some redundant role(s) in embryonic development. Whether or not this is an endocrine-related role is unknown and it could result from one or several of the non-endocrine related functions that have recently been characterized for the FKBP proteins. One of the more recent discoveries demonstrates a role of the FKBP proteins in microtubule assembly and tau pathogenesis (Box 2) [37,38]. This is of particular interest because it is the first example of a PPIase-dependent function for FKBP51 and FKBP52.

Cell proliferation and cancer

Research on FKBP51 in cancer etiology and response to antineoplastic therapy has intensified recently. It was initially reported that FKBP51 is an androgen-regulated gene in prostate cancer and a modulator of AR activity [39]. The protein is also upregulated in prostatic hyperplasia [40]. In prostate cancer cell lines, increased levels of FKBP51 and FKBP52 were observed, as well as an inhibitory effect of FK506 on androgen-stimulated cell growth [41]. Whereas gene knockout strategies revealed FKBP52, but not FKBP51, as an important facilitator of physiological AR activity [7,31], FKBP51 was also identified as a positive regulator of AR and androgen-dependent cell growth, and as a target of FK506 in prostate cancer cells

Box 3. Open questions for future investigation

- Do the FKBPs interact directly with the receptors within the HSP90 chaperone complex in the cytoplasm or do they influence the receptors indirectly through binding to HSP90?
- What are the FKBP interaction and/or regulatory sites on the receptors? Studies suggest that FKBP52 regulation is localized to the receptor LBD, but can this be narrowed to a specific surface and or surface residues within the LBD?
- The exchange of FKBP51 for FKBP52 on hormone binding is not entirely due to conformational changes in the receptor–chaperone complex, because FKBP52 can be found in association with the complex before hormone binding. What facilitates this exchange and what role does this exchange play in the receptor signaling pathways given that FKBP52 can still regulate receptor in experimental systems where FKBP51 is absent?
- Can the FKBPs interact directly with the receptors in an HSP90-independent manner in the nucleus and thus have HSP90-independent functional roles in the receptor signaling pathways?
- Why do 52KO mice develop normal testes despite significant developmental defects in other androgen-dependent tissues?
- The embryonic lethality phenotype in the double 51/52KO mice has not been characterized. At what stage do the embryos die and what causes this lethality?
- What is unique within prostate cancer cells that allows FKBP51 to act as a positive regulator of androgen receptor signaling? In line with this question, evidence suggests a more cell- and/or tissue-specific role for FKBP51. Besides prostate cancer cells, in what cell and or tissue types and under what conditions can FKBP51?
- What is the functional single nucleotide polymorphism of FKBP51 in stress-related disease and what is the mechanism by which it contributes to the disease state?
- Is *FKBP51* gene expression programmed (permanently altered) by stressful life experiences?
- What is the role of HSP90 in FKBP regulation of tau pathogenesis and what phosphatases and kinases are involved?
- Can FKBP-specific drugs be designed that distinguish between FKBP51 and FKBP52?

[42,43]. Potentiation of AR by FKBP51 was not found in other studies and may be cell-type-dependent [9,44]. Box 3

In colorectal adenocarcinoma, FKBP51 suppresses proliferation, which was ascribed to its action on GR [45]. GR action has also been invoked in myeloma cells, in which dexamethasone-induced expression of FKBP51 has been interpreted as an adaptive process before death [46]. In leukemia, inhibition of FKBP51 by rapamycin abolished doxorubicin-induced activation of NF-κB and thus enhanced drug-induced apoptosis [47]. A recent study described FKBP51 as a marker of melanocyte malignancy [48]. Irradiation caused apoptosis in cells with silenced FKBP51 and promoted autophagy in control cells. Inhibition of apoptosis in control cells involved FKBP51-dependent induction of NF-κB on irradiation.

A major advance in mechanistic understanding was the discovery that FKBP51 negatively regulates the activity of the cell growth regulator AKT by serving as a scaffolding protein to recruit the phosphatase PHLPP [49]. FKBP51 expression is decreased in several cancer cell lines and in pancreatic cancer tissue, and may correlate with increased AKT phosphorylation and reduced cell sensitivity to chemotherapeutic agents.

Overall, it seems that, depending on cell and cancer type, promotion or reduction of FKBP51 activity can produce a beneficial effect in the actions against cancer cell proliferation. This is most probably because of the multitude of molecular functions of FKBP51, and this should be carefully considered when developing FKBP51-targeting drugs for cancer therapy [48]. It is most likely that FKBP51 uses at least partially different surfaces for its divergent actions, which could eventually be exploited for specific drug development.

Given that FKBP51 expression is hormone-regulated [8], altered FKBP51 expression has been associated with a wide variety of cancers. By contrast, FKBP52 is ubiquitously expressed at high levels and is slightly upregulated under stress conditions [1]. Thus, less is known about the role of FKBP52 in cancer. Given the androgen, progesterone and glucocorticoid insensitivity phenotypes observed in *fkbp52*-deficient mice [6,7,31,34,50], FKBP52 is likely to have an important role and to serve as a therapeutic target in a variety of diseases that are dependent on these hormone signaling pathways.

The prostate dysgenesis observed in 52KO mice established FKBP52 as a crucially important regulator of prostate development [7], and enhanced FKBP52 levels have been observed in prostate needle biopsies from human patients [51]. In addition, a series of compounds that specifically inhibit FKBP52 regulation of AR function effectively block androgen-dependent gene expression and cell proliferation in prostate cancer cells [52]. Although FKBP52 is not a functional regulator of ER in cellular studies, FKBP52 expression is upregulated in breast tumors, and recent studies revealed *FKBP52* gene methylation in ER-negative but not in ER-positive breast cancer cells [53]. Thus, FKBP52 may also have a role in breast cancer tumorigenesis and/or progression.

Stress-related diseases and phenotypes

The search for molecular parameters in psychiatric disorders identified a correlation of an imbalanced stress hormone system, the hypothalamus pituitary adrenal (HPA) axis, with the risk for and course of diseases such as major depression, bipolar disorder, post-traumatic stress disorder (PTSD), schizophrenia and anxiety disorders [54,55]. The HPA axis is a hormone cascade comprising corticotropin-releasing hormone (CRH) secretion on stress, which triggers synthesis and release of corticotropin and results in the secretion of cortisol, which acts on various tissues (Figure 4). A crucial characteristic of the HPA axis is the negative feedback exerted by cortisol via the GR, which keeps the stress reaction in balance. The altered set-point of the HPA axis hormones observed in stress-related diseases is accompanied by altered reactivity of the HPA axis, and is interpreted as the body's inability to adequately terminate stress response, which increases the risk of disease development [54]. The corticosteroid receptor hypothesis stipulates that GR malfunction is causal for the inappropriate reaction of the HPA axis to stress [55]. Thus, researchers explored the molecular mechanisms that operate to calibrate GR activity with the aim of gaining a better understanding of stress-related diseases.

The discovery of divergent actions of FKBP51 and FKBP52 on GR [5,20], along with the correlation of FKBP51 with altered set-points of the HPA axis in squirrel monkeys, led to their inclusion as candidates in an association study in major depression [56]. This study was the

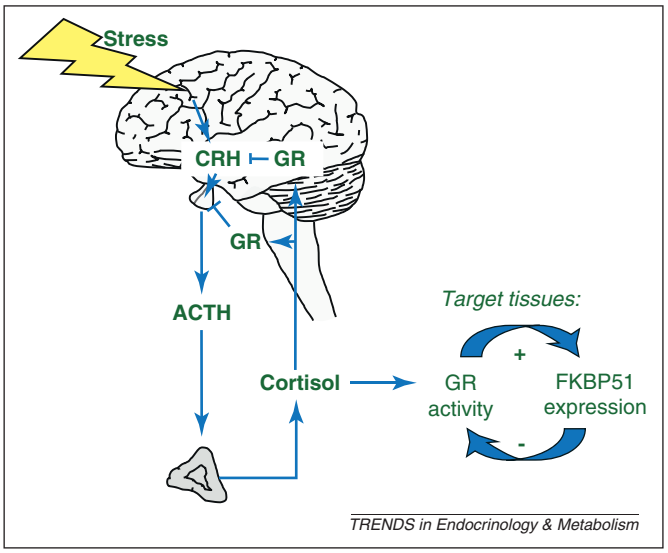

Figure 4. FKBP51 is linked to the HPA axis. On perception of stress, CRH is released from the hypothalamus, which promotes synthesis and release of ACTH from the pituitary. ACTH in turn increases release of cortisol from the adrenal glands. The inhibitory action of cortisol-activated GR on CRH and ACTH terminates the hormonal stress response and keeps the HPA axis in balance. FKBP51 expression is increased by GR and feeds back on GR in an inhibitory manner. This ultrashort feedback loop provides a mechanism by which FKBP51 regulates HPA axis activity, affects the impact of cortisol in target tissues, and links stress to its other molecular and physiological functions.

first to identify a correlation between *FKBP51* gene variants and response to antidepressant treatment, and with the reactivity of the HPA axis in the dexamethasone CRH test. *FKBP51* genetic polymorphisms and their relationship to antidepressant responses were confirmed in several large and small patient samples [57–60]. An association between *FKBP51* genotype and depression disease status was also discovered and in one study a gender-specific effect of this association was observed [59,61–63]. In addition, *FKBP51* polymorphisms were linked to suicide in several samples [62,64–66] and a gender-specific *FKBP51* genotype association with the personality traits of harm avoidance and cooperativeness has been reported [67]. Moreover, polymorphisms of *FKBP51* influenced recovery from psychosocial stress in healthy individuals [68].

FKBP51 gene variants are also associated with peritraumatic dissociation [69], an established risk factor for the development of posttraumatic stress disorder (PTSD) [70]. Several studies link FKBP51 to PTSD and lower FKBP51 expression was found in PTSD, consistent with the observation of enhanced GR responsiveness [71]. Intriguingly, recent studies suggest that *FKBP51* polymorphisms modify the effects of early life trauma in PTSD [72–74] and major depression [75].

Reports on FKBP51 and PTSD in particular suggest a function of FKBP51 as a modulator of the response to stressful life events and as a mediator of gene–environment interactions. Thus, the risk of disease development crucially depends on the *FKBP51* gene status. Even though it is very likely that FKBP51 operates in stress physiology through its action in GR and the HPA axis function, the exact mechanism of the gene–environment interaction remains to be elucidated, and no associating polymorphism has been reported so far. However, a recent study revealed decreased DNA methylation and increased expression of FKBP51 in mice after chronic exposure to corticosterone [76]. Thus, it is possible that *FKBP51* gene expression is programmed by stressful life events in a genotype-dependent fashion, and results from research into this issue are eagerly awaited.

Immune function

Several studies have revealed a role of FKBP51 in immune-related diseases and inflammation. Expression of FKBP51 was enhanced in bone marrow cells from patients suffering from rheumatoid arthritis [77]. Evidence has also been provided of modulation of NF-κB-dependent gene expression by FKBP51, with possible implications for various pathways [78,79]. This possibly links FKBP51 to NF-κB and its regulation in cell proliferation and survival, inflammation, immune regulation, metabolic diseases and hematopoiesis [80,81]. Another study revealed FKBP51 and NF-κB upregulation in bone-marrow-derived mononuclear cells from patients with rheumatoid arthritis [82]. Treatment of chronic obstructive pulmonary disease goes along with increased expression of FKBP51 [83]. FKBP51 has also been reported to mediate the effect of the immunosuppressant FK506 in inhibiting endogenous MHC class II-restricted antigen presentation [84]. Since GR is an established modulator of immune function, FKBP51 mediated regulation of GR activity per se could provide the basis for a role of FKBP51 in immune processes. Additional FKBP51 effects, such as its impact on NF-κB, are also operative. Mechanistically, evidence from glioma cells suggests that FKBP51 impacts on the stability of IκB and on phosphorylation of NF-κB, and enhances DNA binding of NF-κB [78].

FKBP51 is also able to mediate inhibition of the phosphatase calcineurin, which activates nuclear factor of activated T cells, by FK506 [85,86]. This function, however, is not unique to FKBP51, because the smaller FKBPs also mediate this effect, some of them even more efficiently [86]. Moreover, it has been reported by some that FKBP51 interacts with calcineurin in the absence of FK506 [87], but not by others [86].

Concluding remarks

It is becoming increasingly clear that FKBP52 associates with SHR–chaperone complexes to regulate hormone binding and plays a crucial role in receptor translocation to the nucleus, and possibly even regulates the receptors in the nucleus. Although FKBP51 is generally considered as a negative regulator of receptor function, evidence suggests that it displays tissue- and/or cell-type-specific effects on receptor signaling. As a result, both FKBP51 and FKBP52 are implicated in a variety of diseases and could serve as therapeutic targets for the treatment of these diseases. Efforts to therapeutically target the FKBP proteins are currently under way and these efforts would be enhanced by studies aimed at improving our understanding of FKBP interactions within the receptor–chaperone complex in both the cytoplasm and the nucleus.

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