Published in final edited form as:

Curr Opin Pharmacol. 2011 August ; 11(4): 332–337. doi:10.1016/j.coph.2011.04.012.

FKBP51 – a selective modulator of glucocorticoid and androgen sensitivity

Lance A. Stechschulte and Edwin R. Sanchez*

Center for Diabetes and Endocrine Research, Department of Physiology & Pharmacology, University of Toledo College of Medicine, 3035 Arlington Avenue, Toledo, OH 43614, USA

Abstract

FK506-binding protein 51 (FKBP51) is gaining increased recognition for its essential roles in cell biology. Originally discovered as a component of steroid receptor complexes, it is now known to regulate a diverse set of transcription factors, enzymes and structural proteins. Its cellular properties suggest numerous possible functions for FKBP51 in physiology, and the best clue to its potential importance may be the following: FKBP51 is a glucocorticoid-induced negative regulator of the glucocorticoid receptor. Thus, FKBP51 is intricately involved in regulation of the most pleiotropic hormone known to biology. In contrast to glucocorticoid receptor, FKBP51 is a positive regulator of the androgen receptor, suggesting that it functions as a reciprocal modulator of glucocorticoid- and androgen-mediated physiology. In this work, we evaluate this hypothesis by examining recent cellular and physiological evidence.

Introduction

As a member of the immunophilin family of proteins [1, 2], the FK506-binding protein 51 (FKBP51) is rapidly emerging as an important regulator of immunity, steroidal physiology, and basic cellular processes of protein folding and trafficking. Considerable interest has also arisen on the contribution of FKBP51 to neurological control of behavior and FKBP actions in neuroprotection and regeneration. The latter topics, however, have been covered by several recent reviews [1, 3-7], and will not be addressed here. Instead, this short review will focus on the FKBP51 interaction with glucocorticoid (GR) and androgen receptors (AR) and physiological effects of the protein on immunology, steroid sensitivity and prostate cancer. We apologize to those authors whose original studies were not cited due to conceptual and space constraints.

Activity & functional domains

Like all immunophilins [1], FKBP51 exhibits peptidyl-prolyl *cis-trans* isomerase (PPIase) activity (also known as rotamase activity) that catalyzes the interconversion of prolyl-peptide bonds between the *trans* and *cis* states, with the *trans* state being energetically preferred in protein folding [8]. Based on crystal structure analysis [9], FKBP51 is composed of several functional domains (Figure 1). The N-terminal FK1 domain

© 2011 Elsevier Ltd. All rights reserved.

*Corresponding author: Edwin R. Sanchez, (419) 383-4182, FAX (419) 383-2871, edwin.sanchez@utoledo.edu.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

encompasses the PPIase function which is inhibited by the direct binding of FK506 [10]. The FK1 domain shares 48% homology with FKBP12 and has comparable PPIase activity [9, 11]. The PPIase-like FK2 domain shares 26% homology with the FK domain of FKBP12 but lacks measurable PPIase activity [9] and cannot bind FK506 [12]. Although FKBP51 is approximately 60% identical to FKBP52 and shares a similar structural organization, functional and structural distinctions do occur. FKBP52 is phosphorylated in the hinge region at threonine 143 by casein kinase-2 which prevents binding to Hsp90 [13]. The hinge region of FKBP51 lacks this phosphorylation site, which may explain why FKBP51 is competitively preferred over FKBP52 in some nuclear receptor complexes [10, 14]. The C-terminal region contains a three-unit domain of tetratricopeptide repeat (TPR) motifs involved in protein-protein interactions [15]. A similar TPR domain is shared by FKBP52 and other large immunophilins and serves as the site of interaction with the C-terminal EEVD sequence of Hsp90 [12, 15, 16].

FKBP51 interactions with steroid receptors

Like FKBP52 [17], FKBP51 was originally discovered as a member of the progesterone receptor complex [18]. Since then it has been found to interact with glucocorticoid, androgen, estrogen and mineralocorticoid receptors [19-21]. With the exception of AR, FKBP51 has the overall effect of reducing receptor transcriptional activity. Using GR as prototype, the inhibitory effect of FKBP51 occurs by mechanisms that include sequestering of receptor to the cytoplasm, and reduction of hormone-binding affinity [19, 22, 23]. Though less studied, it appears that FKBP51 is required for optimal AR transcriptional activity [20, 24, 25]. Interestingly, with respect to hormone-binding function FKBP51 serves to increase this AR function, suggesting that FKBP51 can directly or indirectly target the ligand-binding domains of GR and AR, with opposing results. The exact molecular events that govern this effect remain unclear. In the case of GR, the PPIase activities of both FKBP51 and FKBP52 are not required for their modulatory functions [26]. In contrast to FKBP51, the better-studied FKBP52 serves to promote the molecular activities of both GR and AR [23, 27, 28]. Indeed, several investigations using FKBP52-deficient mice have shown that FKBP52 is essential for progesterone receptor action in uterine implantation [29, 30], for androgen receptor regulation of penile and prostate gland development [31, 32], and for GR control of hepatic gluconeogenesis [33]. Taken together, these facts suggest a model in which FKBP51 and FKBP52 act as selective pathway-specific modulators of GR and AR endocrine physiology (Figure 2).

Immunology & immunosuppression

The discovery that FKBP51 was structurally and functionally similar to FKBP12 led to early speculation that it contributed to the immunosuppressive actions of FK506, perhaps by inhibiting the calcineurin-NFAT pathway of T-lymphocytes, as documented for FKBP12 [34]. High level expression of FKBP51 in T-cells fostered this idea [35]. Interestingly, although FKBP51 can inhibit calcineurin in the presence and absence of FK506, it has little to no effect on NFAT transcriptional activity in cell-based assays [36-38]. A more rigorous test in T-cells derived from mice deficient in FKBP12 or FKBP12.6 demonstrated no contribution by FKBP51 to the anti-proliferative actions of FK506 [39]. Thus, FKBP51, like FKBP52 [40], is not an important factor in FK506-mediated immunosuppression at T-lymphocytes. Yet, it seems likely that FK506 binding to FKBP51 in lymphoid cells will have important consequences. One unexplored possibility is the ability of FK506 to potentiate the activity of the glucocorticoid receptor [41], which occurs by dissociating inhibitory FKBP51 from the GR complex [23]. Thus, the immunosuppressive actions of FK506 may be partly due to increased lymphoid cell sensitivity to endogenously circulating

glucocorticoids (GCs) or potent GC analogs that are often administered along with FK506 during immunosuppressive therapies.

Glucocorticoid resistance

Glucocorticoids are potent and pleiotropic hormones [42] that induce diverse down-regulatory mechanisms to protect against over-stimulation [43]. Upregulation of FKBP51 expression in GC target cells may represent just such a mechanism. Indeed, it is now clear that hormone-activated GR directly increases FKBP51 expression as an auto-regulatory process that decreases GC sensitivity [44-46]. Not surprisingly, reports exist that elevated FKBP51 expression promotes states of GC resistance. The first such evidence came from studies of New World primates, which have highly-elevated levels of circulating GCs to compensate for glucocorticoid insensitivity at target cells, especially lymphocytes [47, 48]. FKBP51 levels can be up to 13-fold higher in lymphocytes of the Bolivian squirrel monkey compared to humans, leading to GR heterocomplexes where FKBP51 is the predominant TPR component and receptor with reduced affinity for GC ligands. In humans, evidence for FKBP51-mediated GC resistance can now be found. High levels of FKBP51 correlate with resistance to GC therapies for asthma [49] and chronic obstructive pulmonary disease [50], and diagnostic assays are being developed using FKBP51 as markers of GC sensitivity [51].

Androgen sensitivity & prostate cancer

In contrast to GR, FKBP51 appears to be a positive regulator of androgen receptor activity [20, 24, 25]. Moreover, both natural androgens (dihydrotestosterone) and synthetic analogs (R1881) cause upregulation of FKBP51 expression [20, 52-56] by a direct binding of AR to enhancer elements in the FKBP51 (*fkbp5*) gene [57, 58], suggesting an auto-regulatory pathway designed to increase androgen sensitivity. These facts have identified FKBP51 as an interesting and potentially important candidate in the etiology of prostate cancer. The latest studies appear to support this hypothesis. Elevated levels of FKBP51 have been reported in human prostate cancer samples compared to non-cancerous tissues [25, 53, 56]. In studies employing xenograph animal models, androgen-independent tumors (CWR22-R) that arose from androgen-dependent tumors (CWR22) had higher levels of FKBP51 [56]. More informative, were studies in which expression of FKBP51 decreased in the CWR22-R tumors of mice following androgen-ablation, only for levels to return to normal over time, and to elevate even higher in mice treated with androgens [52]. Such a pattern is highly suggestive of a direct role by FKBP51 in prostate cancer growth and, perhaps, progression to the highly-invasive androgen-independent state.

Direct tests of the role played by FKBP51 in prostate cells responses have taken several approaches. First, results in a variety of prostate cancer cells lines have shown that FKBP51 promotes hormone-activated AR transcriptional activity [20, 24] and, in one report, androgen-independent activity [25]. More importantly, the two most recent findings demonstrate that FKBP51 is nearly essential for androgen-induced growth of two different prostate cancer cell lines [24, 25]. Thus, the case is being made that targeting FKBP51 expression or activity may be an effective way to treat prostate cancers. Because the FKBP51/AR interaction is mediated by Hsp90, one treatment approach is the use of Hsp90 inhibitors, such as geldanamycin, some of which are undergoing clinical trials for various cancers [59]. Two recent reports showed that treatment of LNCaP prostate cancer cells with geldanamycin, or its derivative 17-AAG, reduced AR protein stability, hormone-binding function and transcriptional activity [24, 54]. A more specific pharmacologic approach has employed FK506. Although treatment of cells with FK506 increases GR activity [23], the opposite is true of AR. In LNCaP cells, treatment with FK506 inhibited the ligand-induced activity of AR at both reporter and endogenous genes by a mechanism that appears to reduce

the intrinsic hormone-binding function of the receptor [24, 25]. Although evidence was found that FK506 blocks the FKBP51/Hsp90 interaction [24], a direct demonstration that FK506 blocks FKBP51 interaction with AR, or the role of the FKBP51 PPIase function have yet to be determined. Molecular issues aside, it is clear that FK506 is also an effective inhibitor of androgen-induced growth of prostate cancer cells. In a study that compared AR-positive LNCaP cells to two AR-negative prostate cancer cell lines (DU145 and PC-3), an inhibitory effect of FK506 on growth was only found in the LNCaP cells treated with androgen [60], suggesting that FK506 acts by inhibiting the growth-promoting properties of AR. Since then, studies have shown that the FK506 anti-proliferative effect is mediated by FKBP51, rather than FKBP52 [24, 25]. The latter result is particularly intriguing, as elevated expression of FKBP51, but not FKBP52, has been found in human malignant prostate cancer samples [25].

Taken as a whole, these observations point to elevated expression or increased activity on the part of FKBP51 as a prime factor in the etiology of androgen-dependent prostate cancer. Thus, an important advance would be the development of FK506 analogs that specifically target FKBP51. Although the FK506 anti-proliferative effect on AR occurs through FKBP51, the activities of many FKBP5s, such as FKBP52 and FKBP12, are undoubtedly affected by the drug. Clearly, immunosuppression is not a side-effect that can be readily tolerated when using FK506 in cancer chemotherapy. Progress on this front has already occurred with the development of several FK506 derivatives with neuroregenerative properties that do not bind FKBP12 or that do not have the calcineurin-inhibition function necessary for immunosuppression [61]. At least one of these compounds has been found to specifically target FKBP52 in the process of neuroregeneration [62]. Although the specificities of these compounds for FKBP51 have yet to be determined, such efforts are likely to be fruitful, and may form the basis for further rational drug design in the treatment of prostate cancer.

Discussion

The works presented here are a partial showcase of the emerging importance of FKBP51 in steroidal control of physiology. Going forward, many under-investigated issues remain. What are the roles of FKBP51 outside of steroid receptors? Are all actions of FKBP51 mediated by an interaction with Hsp90? To what extent does FKBP51 duplicate the actions of FKBP52? On the latter point, it can be speculated that the reciprocal effects of FKBP51 and FKBP52 on GR hormone-binding function may be a way in which to regulate the local response of a tissue to uniform concentrations of circulating GCs. Yet, most of the emerging *in vivo* data suggest a more complex model in which the FKBP5s selectively control steroidal sensitivity, not only across but within receptor types. For example, the FKBP52-deficient male mouse exhibits hypospadias and prostate dysgenesis, while the FKBP51-deficient mouse does not [32], even though both proteins promote androgen sensitivity. Indeed, no physiological defect, androgen-mediated or otherwise, has yet been reported for the mutant FKBP51 mouse. The works reviewed here suggest that resistance to onset or severity of prostate cancer may be one such outcome. These and other issues await further experimentation.

Acknowledgments

This work was supported in part by National Institutes of Health grant DK70127.

References

1. Kang CB, Hong Y, Dhe-Paganon S, Yoon HS. FKBP family proteins: immunophilins with versatile biological functions. *Neurosignals*. 2008; 16:318–325. [PubMed: 18635947]
2. Romano S, Di Pace A, Sorrentino A, Bisogni R, Sivero L, Romano MF. FK506 binding proteins as targets in anticancer therapy. *Anticancer Agents Med Chem*. 2010; 10:651–656. [PubMed: 21182472]
3. Gold BG, Udina E, Bourdette D, Navarro X. Neuroregenerative and neuroprotective actions of neuroimmunophilin compounds in traumatic and inflammatory neuropathies. *Neurol Res*. 2004; 26:371–380. [PubMed: 15198862]
4. Quinta HR, Maschi D, Gomez-Sanchez C, Piwien-Pilipuk G, Galigniana MD. Subcellular rearrangement of hsp90-binding immunophilins accompanies neuronal differentiation and neurite outgrowth. *J Neurochem*. 2010; 115:716–734. [PubMed: 20796173]
5. Drago A, De Ronchi D, Serretti A. Pharmacogenetics of antidepressant response: an update. *Hum Genomics*. 2009; 3:257–274. [PubMed: 19403460]
6. Hunsberger JG, Austin DR, Chen G, Manji HK. Cellular mechanisms underlying affective resiliency: the role of glucocorticoid receptor- and mitochondrially-mediated plasticity. *Brain Res*. 2009; 1293:76–84. [PubMed: 19595676]
7. Salminen A, Ojala J, Kaarniranta K, Hiltunen M, Soininen H. Hsp90 regulates tau pathology through co-chaperone complexes in Alzheimer's disease. *Prog Neurobiol*. 2010
8. Schiene C, Fischer G. Enzymes that catalyse the restructuring of proteins. *Curr Opin Struct Biol*. 2000; 10(1):40–45. [PubMed: 10679456]
9. 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. *Proc Natl Acad Sci U S A*. 2003; 100:868–873. [PubMed: 12538866]
10. Nair SC, Rimerman RA, Toran EJ, Chen S, Prapapanich V, Butts RN, Smith DF. Molecular cloning of human FKBP51 and comparisons of immunophilin interactions with Hsp90 and progesterone receptor. *Mol Cell Biol*. 1997; 17:594–603. [PubMed: 9001212]
11. Pirkil F, Buchner J. Functional analysis of the Hsp90-associated human peptidyl prolyl cis/trans isomerases FKBP51, FKBP52 and Cyp40. *J Mol Biol*. 2001; 308:795–806. [PubMed: 11350175]
12. 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. *Mol Endocrinol*. 1998; 12:342–354. [PubMed: 9514152]
13. 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. *Proc Natl Acad Sci U S A*. 1997; 94:14500–14505. [PubMed: 9405642]
14. Banerjee A, Periyasamy S, Wolf IM, Hinds TDJ, 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; 47:10471–10480. [PubMed: 18771283]
15. Russell LC, Whitt SR, Chen MS, Chinkers M. Identification of conserved residues required for the binding of a tetratricopeptide repeat domain to heat shock protein 90. *J Biol Chem*. 1999; 274:20060–20063. [PubMed: 10400612]
16. Scheufler C, Brinker A, Bourenkov G, Pegoraro S, Moroder L, Bartunik H, Hartl FU, Moarefi I. Structure of TPR domain-peptide complexes: critical elements in the assembly of the Hsp70-Hsp90 multichaperone machine. *Cell*. 2000; 101:199–210. [PubMed: 10786835]
17. Tai PK, Maeda Y, Nakao K, Wakim NG, Duhring JL, Faber LE. A 59-kilodalton protein associated with progestin, estrogen, androgen, and glucocorticoid receptors. *Biochemistry*. 1986; 25:5269–5275. [PubMed: 3768347]
18. Smith DF, Baggenstoss BA, Marion TN, Rimerman RA. Two FKBP-related proteins are associated with progesterone receptor complexes. *J Biol Chem*. 1993; 268:18365–18371. First publication to describe FKBP51. [PubMed: 7688746]

19. Davies TH, Ning YM, Sanchez ER. A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. *J Biol Chem.* 2002; 277:4597–4600. [PubMed: 11751894]
20. Febbo PG, Lowenberg M, Thorner AR, Brown M, Loda M, Golub TR. Androgen mediated regulation and functional implications of fkbp51 expression in prostate cancer. *J Urol.* 2005; 173:1772–1777. [PubMed: 15821585]
21. Gallo LI, Ghini AA, Pilipuk GP, Galigniana MD. Differential Recruitment of Tetratricopeptide Repeat Domain Immunophilins to the Mineralocorticoid Receptor Influences both Heat-Shock Protein 90-Dependent Retrotransport and Hormone-Dependent Transcriptional Activity. *Biochemistry.* 2007; 46:14044–14057. [PubMed: 18001136]
22. Reynolds PD, Ruan Y, Smith DF, Scammell JG. Glucocorticoid resistance in the squirrel monkey is associated with overexpression of the immunophilin FKBP51. *J Clin Endocrinol Metab.* 1999; 84:663–669. First evidence that FKBP51 promotes glucocorticoid resistance. [PubMed: 10022435]
23. Davies TH, Ning YM, Sanchez ER. Differential Control of Glucocorticoid Receptor Hormone-Binding Function by Tetratricopeptide Repeat (TPR) Proteins and the Immunosuppressive Ligand FK506. *Biochemistry.* 2005; 44:2030–2038. [PubMed: 15697228]
24. 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. *Mol Cell Biol.* 2010; 30:1243–1253. Authors provide evidence for elevated FKBP51 expression in LAPC-4 prostate cancer cells grown in castrated mice and that FKBP51 positively regulates androgen receptor transcriptional activity. [PubMed: 20048054]
25. Periyasamy S, Hinds TJ, 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; 29:1691–1701. Authors demonstrate a direct role for FKBP51 in androgen-induced growth of LNCaP prostate cancer cells and that the growth inhibitory effect of FK506 is mediated by FKBP51. [PubMed: 20023700]
26. 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. *Mol Cell Biol.* 2007; 27:8658–8669. [PubMed: 17938211]
27. 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. *EMBO J.* 2003; 22:1158–1167. [PubMed: 12606580]
28. Wochnik GM, Ruegg J, Abel GA, Schmidt U, Holsboer F, Rein T. FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *J Biol Chem.* 2005; 280:4609–4616. [PubMed: 15591061]
29. 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. *Proc Natl Acad Sci U S A.* 2005; 102:14326–14331. [PubMed: 16176985]
30. Yang Z, Wolf IM, Chen H, Periyasamy S, Chen Z, Yong W, Shi S, Zhao W, Xu J, Srivastava A, et al. FK506-binding protein 52 is essential to uterine reproductive physiology controlled by the progesterone receptor a isoform. *Mol Endocrinol.* 2006; 20:2682–2694. [PubMed: 16873445]
31. Cheung-Flynn J, Prapapanich V, Cox MB, Riggs DL, Suarez-Quian C, Smith DF. Physiological role for the cochaperone FKBP52 in androgen receptor signaling. *Mol Endocrinol.* 2005; 19:1654–1666. [PubMed: 15831525]
32. Yong W, Yang Z, Periyasamy S, Chen H, Yucel S, Li W, Lin LY, Wolf IM, Cohn MJ, Baskin LS, et al. Essential role for Co-chaperone Fkbp52 but not Fkbp51 in androgen receptor-mediated signaling and physiology. *J Biol Chem.* 2007; 282:5026–5036. First description of an FKBP51 genetically modified mouse. In comparison to FKBP52-KO mouse, the FKBP51-KO mouse did not demonstrate penile or prostate developmental defects, suggesting that any effect of FKBP51 on androgen physiology is likely to be manifest in adult animals. [PubMed: 17142810]
33. Warriar M, Hinds TDJ, Ledford KJ, Cash HA, Patel PR, Bowman TA, Stechschulte LA, Yong W, Shou W, Najjar SM, Sanchez ER. Susceptibility to diet-induced hepatic steatosis and glucocorticoid resistance in FK506-binding protein 52-deficient mice. *Endocrinology.* 2010; 151:3225–3236. [PubMed: 20427484]

34. Schreiber SL. Chemistry and biology of the immunophilins and their immunosuppressive ligands. *Science*. 1991; 251:283–287. [PubMed: 1702904]
35. Baughman G, Wiederrecht GJ, Chang F, Martin MM, Bourgeois S. Tissue distribution and abundance of human FKBP51, and FK506-binding protein that can mediate calcineurin inhibition. *Biochem Biophys Res Commun*. 1997; 232:437–443. [PubMed: 9125197]
36. Baughman G, Wiederrecht GJ, Campbell NF, Martin MM, Bourgeois S. FKBP51, a novel T-cell-specific immunophilin capable of calcineurin inhibition. *Mol Cell Biol*. 1995; 15:4395–4402. [PubMed: 7542743]
37. Li TK, Baksh S, Cristillo AD, Bierer BE. Calcium- and FK506-independent interaction between the immunophilin FKBP51 and calcineurin. *J Cell Biochem*. 2002; 84:460–471. [PubMed: 11813252]
38. Weiwad M, Edlich F, Kilka S, Erdmann F, Jarczowski F, Dorn M, Moutty MC, Fischer G. Comparative analysis of calcineurin inhibition by complexes of immunosuppressive drugs with human FK506 binding proteins. *Biochemistry*. 2006; 45:15776–15784. [PubMed: 17176100]
- 39•. Xu X, Su B, Barndt RJ, Chen H, Xin H, Yan G, Chen L, Cheng D, Heitman J, Zhuang Y, et al. FKBP12 is the only FK506 binding protein mediating T-cell inhibition by the immunosuppressant FK506. *Transplantation*. 2002; 73:1835–1838. The authors provide genetic proof that FKBP51 does not contribute to the immunosuppressive actions of FK506, suggesting that specific drug targeting of FKBP51 should be free of immunosuppressive side effects. [PubMed: 12085010]
40. Wiederrecht G, Hung S, Chan HK, Marcy A, Martin M, Calaycay J, Boulton D, Sigal N, Kincaid RL, Siekierka JJ. Characterization of high molecular weight FK-506 binding activities reveals a novel FK-506-binding protein as well as a protein complex. *J Biol Chem*. 1992; 267:21753–21760. [PubMed: 1383226]
41. Ning YM, Sanchez ER. Potentiation of glucocorticoid receptor-mediated gene expression by the immunophilin ligands FK506 and rapamycin. *J Biol Chem*. 1993; 268:6073–6076. [PubMed: 7681058]
42. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med*. 2005; 353:1711–1723. [PubMed: 16236742]
43. Schaaf MJ, Cidlowski JA. Molecular mechanisms of glucocorticoid action and resistance. *J Steroid Biochem Mol Biol*. 2002; 83(1-5):37–48. [PubMed: 12650700]
44. Hubler TR, Scammell JG. Intronic hormone response elements mediate regulation of FKBP5 by progestins and glucocorticoids. *Cell Stress Chaperones*. 2004; 9:243–252. [PubMed: 15544162]
45. U M, Shen L, Oshida T, Miyauchi J, Yamada M, Miyashita T. Identification of novel direct transcriptional targets of glucocorticoid receptor. *Leukemia*. 2004; 18:1850–1856. [PubMed: 15385927]
46. Paakinaho V, Makkonen H, Jaaskelainen T, Palvimo JJ. Glucocorticoid receptor activates poised FKBP51 locus through long-distance interactions. *Mol Endocrinol*. 2010; 24:511–525. [PubMed: 20093418]
47. Denny WB, Valentine DL, Reynolds PD, Smith DF, Scammell JG. Squirrel monkey immunophilin FKBP51 is a potent inhibitor of glucocorticoid receptor binding. *Endocrinology*. 2000; 141:4107–4113. [PubMed: 11089542]
48. Westberry JM, Sadosky PW, Hubler TR, Gross KL, Scammell JG. Glucocorticoid resistance in squirrel monkeys results from a combination of a transcriptionally incompetent glucocorticoid receptor and overexpression of the glucocorticoid receptor co-chaperone FKBP51. *J Steroid Biochem Mol Biol*. 2006; 100:34–41. [PubMed: 16723223]
49. Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci U S A*. 2007; 104:15858–15863. [PubMed: 17898169]
50. Holownia A, Mroz RM, Kolodziejczyk A, Chyczewska E, Braszko JJ. Increased FKBP51 in induced sputum cells of chronic obstructive pulmonary disease patients after therapy. *Eur J Med Res*. 2009; 14 4:108–111. [PubMed: 20156738]

51. Vermeer H, Hendriks-Stegeman BI, van der Burg B, van Buul-Offers SC, Jansen M. Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: a potential marker for glucocorticoid sensitivity, potency, and bioavailability. *J Clin Endocrinol Metab.* 2003; 88:277–284. [PubMed: 12519866]
- 52•. Amler LC, Agus DB, LeDuc C, Sapinoso ML, Fox WD, Kern S, Lee D, Wang V, Leysens M, Higgins B, et al. Dysregulated expression of androgen-responsive and nonresponsive genes in the androgen-independent prostate cancer xenograft model CWR22-R1. *Cancer Res.* 2000; 60:6134–6141. Using the highly relevant xenograph model in mice, the authors show that FKBP51 is androgen regulated in prostate cancer cells *in vivo*, and that its expression is even higher in cells that have transitioned to androgen-independence. [PubMed: 11085537]
53. Zhu W, Zhang JS, Young CY. Silymarin inhibits function of the androgen receptor by reducing nuclear localization of the receptor in the human prostate cancer cell line LNCaP. *Carcinogenesis.* 2001; 22:1399–1403. [PubMed: 11532861]
54. Vanaja DK, Mitchell SH, Toft DO, Young CY. Effect of geldanamycin on androgen receptor function and stability. *Cell Stress Chaperones.* 2002; 7:55–64. [PubMed: 11894840]
55. Clegg N, Eroglu B, Ferguson C, Arnold H, Moorman A, Nelson PS. Digital expression profiles of the prostate androgen-response program. *J Steroid Biochem Mol Biol.* 2002; 80:13–23. [PubMed: 11867260]
56. 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; 145:3913–3924. [PubMed: 15131019]
57. Magee JA, Chang LW, Stormo GD, Milbrandt J. Direct, androgen receptor-mediated regulation of the FKBP5 gene via a distal enhancer element. *Endocrinology.* 2006; 147:590–598. [PubMed: 16210365]
58. Makkonen H, Kauhanen M, Paakinaho V, Jaaskelainen T, Palvimäki JJ. Long-range activation of FKBP51 transcription by the androgen receptor via distal intronic enhancers. *Nucleic Acids Res.* 2009; 37:4135–4148. [PubMed: 19433513]
59. Miyata Y. Hsp90 inhibitor geldanamycin and its derivatives as novel cancer chemotherapeutic agents. *Curr Pharm Des.* 2005; 11:1131–1138. [PubMed: 15853661]
- 60•. Periyasamy S, Warriar M, Tillekeratne MP, Shou W, Sanchez ER. The immunophilin ligands cyclosporin A and FK506 suppress prostate cancer cell growth by androgen receptor-dependent and -independent mechanisms. *Endocrinology.* 2007; 148:4716–4726. First evidence that FK506 can effectively inhibit androgen-induced growth of prostate cancer cells *in vitro*. [PubMed: 17615153]
61. Gold BG, Armistead DM, Wang MS. Non-FK506-binding protein-12 neuroimmunophilin ligands increase neurite elongation and accelerate nerve regeneration. *J Neurosci Res.* 2005; 80:56–65. [PubMed: 15732051]
62. Price RD, Yamaji T, Yamamoto H, Higashi Y, Hanaoka K, Yamazaki S, Ishiye M, Aramori I, Matsuoka N, Mutoh S, et al. FK1706, a novel non-immunosuppressive immunophilin: neurotrophic activity and mechanism of action. *Eur J Pharmacol.* 2005; 509:11–19. [PubMed: 15713424]

Highlights

- FKBP51 is a cochaperone to steroid receptors, including glucocorticoid (GR) and androgen receptors (AR).
- FKBP51 modulates molecular properties of GR and AR, including hormone-binding function.
- Interestingly, FKBP51 exerts negative regulation on GR, but positive regulation of AR.
- The reciprocal modulation of GR and AR by FKBP51 is evaluated based on the most recent *in vivo* data.

Figure 1.
Domain maps of human FKBP51 and FKBP52. PPIase, peptidyl-prolyl *cis-trans* isomerase; TPR, tetratricopeptide repeat. See text for discussion.

Figure 2. FKBP51 and FKBP52 are pathway-specific modulators of glucocorticoid- and androgen-mediated responses. Although molecular data originally suggested global effects of FKBP51 and FKBP52 on steroid sensitivity, the emerging *in vivo* evidence suggests more complex roles for the proteins as modulators of specific physiologic responses. COPD, chronic obstructive pulmonary disease. See text for discussion.