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# Impact of FKBP52 on cell proliferation and hormone-dependent cancers

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## Abstract

FK506 binding protein 52 (FKBP52) (gene name *FKBP4*) is a 52 kDa protein that belongs to the FKBP family; it binds to the immunosuppressant FK506 and has proline isomerase activity. In addition to its FK domain-containing peptidylprolyl isomerase activity, FKBP52 also acts as a cochaperone through the tetratricopeptide repeat domain that mediates binding to heat shock protein 90. Previous studies have reported that FKBP52 is associated with hormone-dependent, stress-related, and neurodegenerative diseases, revealing its diverse functions. In particular, the effects of FKBP52 on cancer have attracted considerable attention. FKBP52 promotes the growth of hormone-dependent cancers by activating steroid hormone receptors. Recent studies have shown that the expression of FKBP52 is increased not only in steroid hormone-dependent cancer cells but also in colorectal, lung, and liver cancers, revealing its diverse functions that contribute to cancer growth. This review summarizes reports related to hormone-dependent cancer and cell proliferation in terms of the structure of FKBP52 and its function on interacting molecules.

**KEYWORDS**
cancer, FKBP52, HSP90, proline isomerase, steroid hormone receptor

## 1 | DOMAIN STRUCTURE AND ROLE

The FKBP family is a group of genes with an FK506 binding domain (FK domain, also known as the PPIase domain); 18 different genes have been identified in this family.[1] The domains of 16 genes are shown in Figure 1A, excluding FKBPL and FKBP1C.[2] Recent studies have reported that FKBP1C is a long noncoding RNA.[3] The FKBP family is characterized by the presence of pairs of genes with similar structures (e.g., FKBP12 and FKBP12.6). FKBP12 was the first gene discovered in the FKBP family,[4] and the other FKBPs were discovered based on their similarities with FKBP12. FKBP12 is the primary target of two well-known drugs, FK506 and rapamycin; when FKBP12 binds to FK506 or rapamycin, it inhibits calcineurin and rapamycin complex 1 (TORC1), respectively. High-molecular-weight FKBPs (large FKBPs) have a more complex structure than FKBP12, and some have multiple PPIase domains; FKBP51 and FKBP52 have

**Abbreviations:** AR, androgen receptor; AR-V7, androgen receptor splice variant 7; BRCA1, breast cancer susceptibility gene 1; CaM, calmodulin; CRPC, castration-resistant prostate cancer; DHT, dihydrotestosterone; ERα, estrogen receptor α; FKBP, FK506 binding protein; GR, glucocorticoid receptor; HSP90, heat shock protein 90; hTERT, human telomerase reverse transcriptase; IKK, IκB kinase; IκBα, inhibitor of NF-κBα; KD, knockdown; LBD, ligand binding domain; MR, mineralocorticoid receptor; NF-κB, nuclear factor-κB; NSCLC, non-small-cell lung cancer; PPIase, peptidylprolyl isomerase; PR, progesterone receptor; SHR, steroid hormone receptor; Tau, tubulin-associated unit; TPR, tetratricopeptide repeat; TRPC1/3, transient receptor potential cation channel, subfamily C, member 1/3; TRPV5, transient receptor potential cation channel, subfamily V, member 5.

two, whereas FKBP60 and FKBP65 have four PPIase domains. However, not all PPIase domains are enzymatically active and bind FK506.[5] In addition to the PPIase domain, there is a TPR domain in the FKBP family that mediates HSP90 binding.[6] The function of each FKBP is described in the following review[5]: FKBP52 is one of the best-known large FKBPs. FKBP52 pairs with FKBP51 and has an FK1 domain, an FK linker connecting FK1 and FK2, an FK2 domain, a TPR domain, and a putative CaM-binding domain. As FKBP51 and FKBP52 have opposing roles in the SHRs, except for the AR, the roles of the FK1 and FK2 domains will be discussed by comparing FKBP51 and FKBP52. Figure 1B shows the FKBP52 domain and interacting molecules that bind through the domains. Interacting molecules include those that act in the plasma membrane, cytoplasm, and nucleus. As FKBP52 is abundant in the cytoplasm,[7] the cytoplasm could be the primary site of action of FKBP52. Although the FK1 domain has PPIase activity, its enzymatic activity does not affect the regulation of AR and GR activities.[8] This suggests that the structure of the FK1 domain is important for its function through interactions with several proteins. This hypothesis is supported by studies that have focused on the differences in the FK1 domain of FKBP52 and FKBP51. It has been reported that FKBP51 suppresses the transcriptional activity of the GR, whereas FKBP52 activates it.[9] To explore the reason for this difference, Riggs et al.[8] focused on differences in the amino acid residues in the proline-rich loop of the FK1 domain. The 119th amino acid in FKBP52 is proline, whereas the corresponding amino acid residue in FKBP51 is leucine. The FKBP51-L119P mutant, in which the leucine of FKBP51 was mutated to proline to mimic FKBP52, increased the transcriptional activity of the GR and

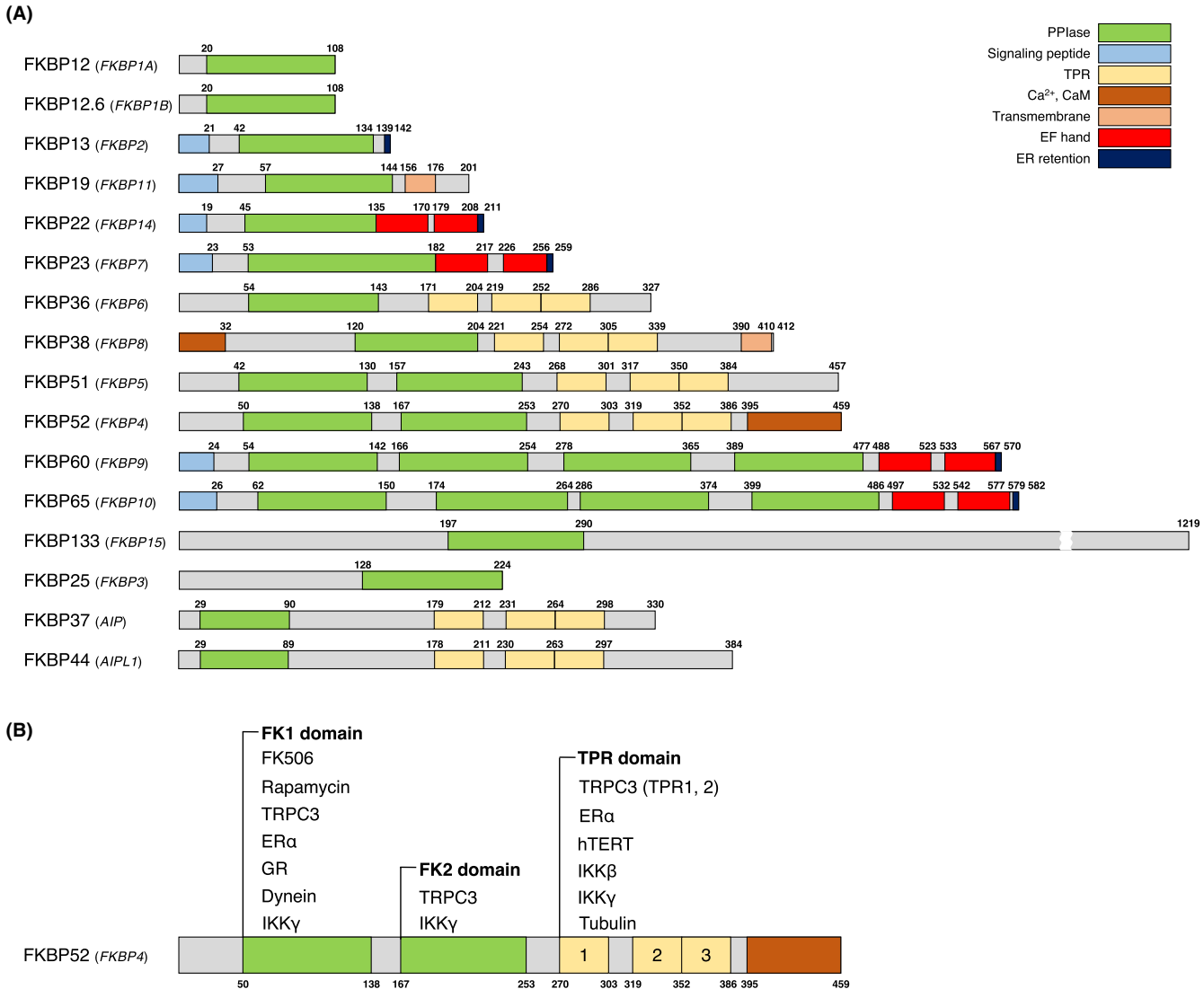


FIGURE 1 Domain structure of the human FK506 binding protein (FKBP) family. (A) The domain structure of the FKBP family is shown with protein and gene names on the left. The numbers in the upper part of the figure indicate the amino acids bordering the domain structure, and the numbers on the far right indicate the number of amino acids of each protein. (B) The domain structure of FKBP52 along with the binding molecules and drugs are shown. The binding molecules and drugs are listed in the domain column to which they bind. Tetratricopeptide repeat (TPR) domain is divided into 1–3. Binding domains not determined are: androgen receptor, progesterone receptor, mineralocorticoid receptor, RelA, TRPC1, TRPV5, and tau. CaM, calmodulin; ER, endoplasmic reticulum; PPIase, peptidylprolyl isomerase.

its affinity for glucocorticoids. These results indicate that the structure of the FK1 domain, particularly FKBP52-P119, is important for the activation of SHRs. The FK1 domain of FKBP52 is required for binding to dynein, which is involved in intracellular trafficking,[10,11] whereas FKBP51 does not bind to dynein.[12] This difference could also be due to the differences in the structure of the FK1 domain. Ligand binding domain replacement experiments have shown that the LBD is important for transcriptional activation by FKBP52[9] and binding to FKBP52.[13] It has been shown that the LBD of ERα binds to the FK1 domain of FKBP52.[12] These results suggest that FKBP52 associates with the LBD through its FK1 domain and may contribute to the transcriptional activity of SHRs. The FK linker connects the FK1 and FK2 domains. FKBP52-T143 is a consensus sequence for CK2, suggesting that it is phosphorylated by CK2. The phosphorylation of T143 by CK2 inhibits the binding of HSP90 to FKBP52.[14] However, subsequent studies have reported that binding to HSP90 was retained in the phosphor-mimic FKBP52-T143E mutant.[15] The fact that the T143E mutant did not affect binding to HSP90, but failed to enhance the transcriptional activity of the SHRs, suggests that T143 is an important residue in the regulation of SHRs. The FK2 domain is similar to the FK1 domain but lacks PPIase activity.[16] The FKBP51-Δ3 mutant, which lacks D195, H196, and D197 of the FK2 domain, binds HSP90, but does not bind to the PR.[17] However, the loss of the corresponding residue in FKBP52 did not affect its binding to the PR or HSP90. This suggests that there is diversity in the functionally important residues of the FK2 domain. The TPR domain of FKBP52 is required for binding to HSP90.[18] FKBP52 lacking the TPR domain and below (i.e., only the FK1 and FK2 domains) did not enhance the transcriptional activity of the GR.[9] The FKBP52-TPR mutant, which cannot bind HSP90, does not enhance the transcriptional activity of the GRs.[9] These findings suggest that the binding of FKBP52 to HSP90 is important for FKBP52 function. FKBP52 contains a CaM-binding domain at its C-terminus. Given that the deletion of this domain has been shown to reduce the interaction between FKBP52 and HSP90, this domain is important for binding these proteins.[18]

## 2 | PHYSIOLOGICAL FUNCTIONS

Because FKBP52 binds to and enhances the activity of SHRs such as AR, ERα, and PR, FKBP52-deficient mice experience pronounced effects on their reproductive system. Male FKBP52-KO mice displayed phenotypes consistent with partial androgen insensitivity, including dysgenic prostate and seminal vesicles, ambiguous external genitalia, infertility including hypospadias, and retention of the nipples, in vivo.[19,20] The testes developed normally, but showed decreased sperm counts in the epididymis, abnormal sperm morphology, and decreased motility.[21] As the testes were approximately 80% smaller in AR-KO mice,[22] it can be concluded that the function of the AR is not completely deficient in FKBP52-KO mouse testes. This could be because the phenotype induced by FKBP52-KO is compensated by FKBP51.[23] It is known that the function of dynein is important for sperm motility, and given that FKBP52 binds to dynein, it is also considered that the loss of FKBP52 might have some effect on sperm motility through dynein.[24] FKBP52-KO female mice have partially impaired ovulation and mammary gland development.[25] In addition, FKBP52 loss results in reduced PR activity, making pregnancy impossible; however, administration of progesterone allows normal pregnancy.[26–28] The abnormalities in the reproductive organs in FKBP52-KO mice are considered to be primarily due to effects on SHRs such as ERα, PR, and AR. FKBP52-KO mice have also been shown to be sensitive to paraquat-induced oxidative stress. This is because of the decreased expression of the antioxidant PRDX6; the exogenous addition of antioxidants restores implantation.[25] Moreover, FKBP52 was downregulated in patients with endometriosis.[29] This was attributed to the increased expression of microRNA-29c, which targets *FKBP4*, and the decreased transcript levels of *FKBP4*.[30] As progesterone resistance increases cell proliferation, inflammation, and angiogenesis, leading to endometriosis, FKBP52 plays a role in suppressing endometriosis through PR activation. However, FKBP52 has other targets besides SHRs, such as the TRP family, NF-κB, and tau. It is not clear whether these molecules are involved in the development of the reproductive organs, and further scrutiny is needed to determine whether the FKBP52-KO phenotype to the reproductive organs is caused solely by SHRs. In addition, FKBP52 is involved in axon guidance during development,[31] inhibition of myocardial hypertrophy,[32] and $Ca^{2+}$ reabsorption in the kidney[33] through the regulation of the TRP family involved in $Ca^{2+}$ influx, but it is not clear how these functions relate to observed phenotype in FKBP52-KO mice.

## 3 | ACTIVATION MECHANISM OF INTERACTING MOLECULES

Steroid hormone receptors need to bind to ligands in the cytoplasm before they can regulate transcription on DNA.[34] FKBP52 enhances the affinity between SHRs and their ligands by binding to SHRs in the cytoplasm. Furthermore, it promotes the nuclear translocation and stability of SHRs. In the nucleus, the SHR is thought to dimerize after the dissociation of FKBP52 and the SHR.[24] Thus, FKBP52 controls the SHR in multiple steps. The specific regulation by FKBP52 depends on the type of nuclear receptor. Table 1 summarizes the targets of FKBP52, the points of action on the targets, and their binding domains.

### 3.1 | Steroid hormone receptors

#### 3.1.1 | Androgen receptor

FKBP52 has been reported to activate the AR.[20] In particular, it affects the DHT affinity of the AR, with a fivefold increase in DHT affinity in the presence of FKBP52.[8] It was reported that PPIase activity is required for the regulation of the AR activity in experiments using FKBP52-F67D/D68V mutants.[19] However, this mutation may not be appropriate because it may alter the conformation of the

**TABLE 1** Targets of FK506 binding protein 52 (FKBP52) and the role of FKBP52 on those targets

| Target | Function | Binding site | PPIase activity | HSP90 binding |
|---|---|---|---|---|
| AR | Increasing the affinity of AR for androgen,[8] dimer formation of AR[38] | No data | Unnecessary[38] | Necessary[19] |
| GR | Increasing the affinity of GR for glucocorticoids,[9] promoting GR nuclear translocation,[43] inhibiting GR nuclear translocation[44] | FK1 domain to LBD[13] | Unnecessary[8] | Necessary[9] |
| PR | Increasing the affinity of PR for progesterone[9] | No data | No data | No data |
| ERα | Increasing protein stability of ERα[46] | FK1 domain to LBD,[12] TPR domain[46] | Necessary[46] | Necessary[46] |
| MR | Increasing the affinity of MR for aldosterone,[50,51] promoting MR nuclear translocation[11] | No data | No data | Necessary[11] |
| RelA | Promoting RelA nuclear translocation[55] | No data | Necessary[55] | Unnecessary[55] |
| IKKβ | Promoting IKK complex formation[56] | TPR domain[56] | No data | Necessary[56] |
| IKKγ | | FK1, FK2, TPR domain[56] | | |
| hTERT | Promoting hTERT nuclear translocation,[61] increasing protein stability of hTERT[61] | TPR domain[61] | No data | Necessary[61] |
| TRPC1 | Upregulation of TRPC1 activity[31] | To N- and C-terminus[31] | Necessary[31] | No data |
| TRPC3 | Downregulation of TRPC3 activity[32] | FK1, FK2, TPR1,2 to C-terminus[32] | Necessary[32] | No data |
| TRPV5 | Downregulation of TRPV5 activity[33] | Not to N- or C-terminus[33] | Necessary[33] | No data |
| Tubulin | Preventing tubulin polymerization[66] | Below the TPR domain[66] | No data | No data |
| Tau | Inhibition of tubulin polymerization induced by tau[7] | No data | No data | No data |

*Note*: This table displays the targets whose functions are regulated by FKBP52 and shows the role of FKBP52 in these targets, the binding domain to FKBP52, and whether peptidylprolyl isomerase (PPIase) activity or heat shock protein 90 (HSP90) binding is required.

Abbreviations: AR, androgen receptor; ERα, estrogen receptor α; GR, glucocorticoid receptor; hTERT, human telomerase reverse transcriptase; IKK, IκB kinase; LBD, ligand binding domain; MR, mineralocorticoid receptor; PR, progesterone receptor; TPR, tetratricopeptide repeat; TRPC, transient receptor potential cation channel, subfamily C; TRPV, transient receptor potential cation channel, subfamily V.

PPIase domain and its surface interactions with nonsubstrate partners. Experiments using the FKBP52-F67Y mutation, which affects only PPIase activity, showed that PPIase activity did not affect the AR activity.[8] This suggested that the structure of the FK1 domain is important for AR regulation. As the LBD has been predicted to interact with FKBP52 in studies using other SHRs,[9,13] it is likely that the AR also binds through the LBD. The AR-V7 lacks the hinge region and the LBD, and thus cannot bind to dynein. Therefore, CRPC cells expressing AR-V7 are insensitive to the therapeutic microtubule inhibitor taxane.[35] In addition, MJC13, which inhibits the dissociation of FKBP52 and the AR, decreases the transcription of AR targets; however, MJC13 treatment did not affect the transcription of AR-V7 overexpressing cells.[36] This suggests that the LBD of the AR plays an important role in regulation by FKBP52. FK506 and the HSP90 inhibitor geldanamycin decreased the association between FKBP52 and the AR.[19] In addition, the FKBP52-TPR mutant, which cannot bind to HSP90, cannot enhance the transcriptional activity of the AR compared to FKBP52-WT.[19] Treatment of prostate cancer cells with FK506, which can inhibit FKBP52, inhibited the growth of the AR-positive prostate cancer cells.[37] Similarly, FKBP52-KD also inhibited the growth of prostate cancer cells.[38] Recently, our group reported that FKBP52 promotes AR dimerization without affecting its nuclear translocation or protein stability[38] (Figure 2A). As cytoplasmic localization of FKBP52 increases the binding of AR to DHT in the cytoplasm and AR dimerization occurs in the nucleus,[39] it is possible that binding of AR to FKBP52 in the cytoplasm regulates AR function, which may trigger AR dimerization later in the nucleus. Another possibility is that the small amount of FKBP52 present in the nucleus binds to AR and promotes its dimerization. Knockdown of FKBP52 or treatment with MJC13 suppresses dimer formation in the ARs. Consistent with the result that the FKBP52-PPIase mutant did not affect the transcriptional activity of the ARs,[8] the enzymatic activity mutant of FKBP52 did not affect AR dimerization.[38] These results indicate that the regulation of the ARs is distinct from the model in which FKBP52 promotes the nuclear translocation of the SHRs through dynein.

### 3.1.2 | Glucocorticoid receptor

FKBP52 enhances the transcriptional activity of the GR.[9] It has been reported that glucocorticoid treatment replaces FKBP51 bound to

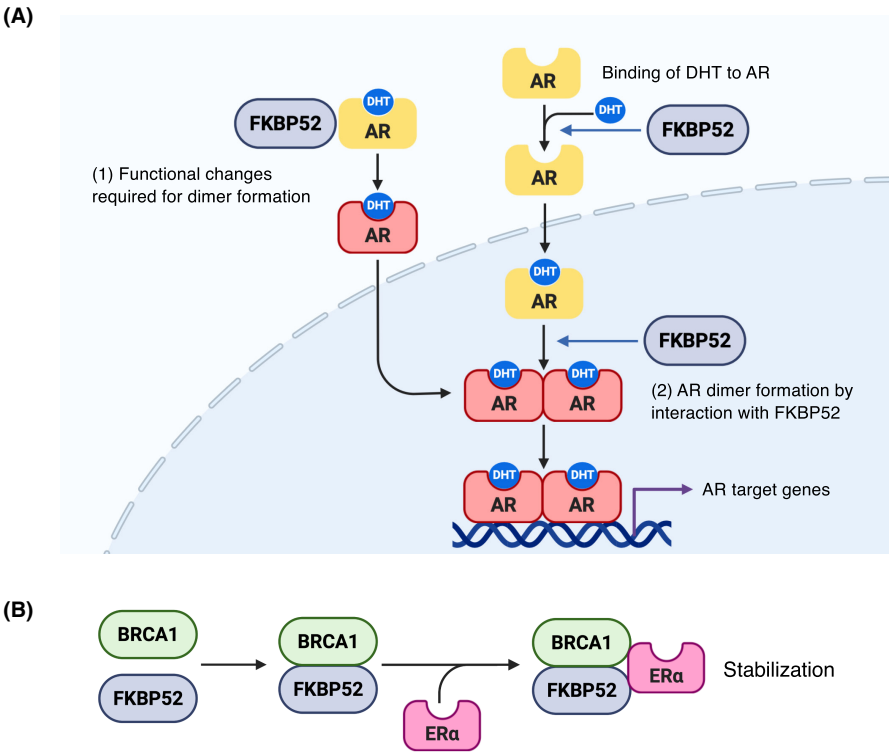


**FIGURE 2** Model of androgen receptor (AR) and estrogen receptor α (ERα) regulation by FK506 binding protein 52 (FKBP52). (A) After AR binds to dihydrotestosterone (DHT) in the cytoplasm, AR dimer formation occurs in the nucleus. Dimerized AR transcribes the AR target genes. FKBP52 upregulates the affinity of DHT for AR in the cytoplasm. The binding of FKBP52 to AR in the cytoplasm could induce functional changes of AR, which can trigger AR dimerization later in the nucleus. Another possibility is that the binding of FKBP52 to AR in the nucleus promotes its dimerization. (B) FKBP52 contributes to ERα stabilization by mediating the binding of ERα to breast cancer susceptibility gene 1 (BRCA1).

GR with FKBP52.[40] Glucocorticoid receptor can bind FKBP52 even in the absence of HSP90,[41] and the FK1 domain of FKBP52 binds to GR-LBD.[13] Thus, a model in which FKBP52 increases the glucocorticoid affinity of the GRs has been proposed.[24] Experiments using FKBP52-PPIase mutants showed that PPIase activity did not affect the transcriptional activity of the GRs.[8] As the GR is known to bind dynein,[10,40,42] the GR-HSP90-FKBP52 complex is considered to be nuclear-translocated through dynein.[40] Following nuclear translocation, the GR dissociates from FKBP52, resulting in GR dimer formation.[40] In experiments with neuroblast cells, nuclear translocation of the GR during cortisol treatment was inhibited by the knockdown of FKBP52.[43] However, in breast cancer cell lines, the relationship between FKBP52 and GR is reversed, FKBP52 binds to the GR and inhibits its nuclear translocation.[44] These results suggest that GR regulation by FKBP52 could differ among cell types.

### 3.1.3 | Progesterone receptor

FKBP52 has been reported to upregulate PRs. The transcriptional activity of PRs and the expression of PR target genes decreased in FKBP52-KO mice.[27,28] The affinity of the PR for progesterone was reduced in the ovaries of FKBP52-KO mice.[28] However, other reports indicate that the affinity of the PR for progesterone was not affected in FKBP52-KO mice.[27] The question remains as to whether FKBP52 affects the affinity between the PR and progesterone. Previous reports have shown that PR expression is not decreased in FKBP52-KO mice.[27,28] However, PR protein expression was decreased in an FKBP52-KD endometrial stromal cell model.[45] Based on these results, it is questionable whether FKBP52 affects the protein levels in the PR.

### 3.1.4 | Estrogen receptor α

Estradiol-induced transcriptional activation of the ERα is decreased in FKBP52-KO mice.[27] The crystal structure of the ERα and MRI revealed that the ERα binds to the FK1 domain of FKBP52.[12] In addition, FKBP52 binds to the ERα and contributes to ERα stabilization[46] (Figure 2B). Breast cancer susceptibility gene 1 mediates monoubiquitylation of the ERα, which inhibits polyubiquitination and protects it from proteasomal degradation.[47] Consistent with this report, the knockdown of BRCA1 promotes ERα degradation, suggesting that BRCA1 is essential for ERα stabilization.[46] FKBP52 mediates the binding of BRCA1 to the ERα, suggesting the possibility that FKBP52 promotes the BRCA1-mediated monoubiquitylation of ERα. The FKBP52-TPR mutant showed decreased binding to the ERα, suggesting that HSP90 plays an important role in the binding of FKBP52 to the ERα. Both HSP90 and FKBP52 are mainly present in the cytoplasm and HSP90 may be required for the binding of ERα and FKBP52. Considering these factors, it is possible that the association between FKBP52 and ERα may occur in the cytoplasm and this association may induce stabilization of ERα. Overexpression of FKBP52-WT increased ERα protein levels, but overexpression of PPIase or TPR domain mutants did not alter ERα protein levels, suggesting that PPIase activity and binding to HSP90 are essential for ERα stabilization. As FKBP52 expression increases in response to estrogen,[48] and it activates the transcriptional activity of the ERα,[46,49] it is assumed that the ERα and FKBP52 form positive

feedback. In a study using SK-N-MC cells, a human neuroblastoma cell line, overexpression of FKBP52 did not increase the transcriptional activity of the ERα.[46,49] These results suggested that the relationship between the ERα and FKBP52 could differ among cell types.

#### 3.1.5 | Mineralocorticoid receptor

Heat shock protein 90 binds to the MR and is required for its affinity to aldosterone.[50,51] It has also been shown that aldosterone increases the MR and HSP90 binding.[52] Geldanamycin inhibits the nuclear translocation of MRs.[52] Because geldanamycin inhibits the nuclear translocation of MRs, HSP90 is also important for the nuclear translocation of MRs.[11,52] The MR also binds to FKBP52 and dynein.[11] Aldosterone treatment promoted MR binding to FKBP52 and dynein.[11] Geldanamycin inhibited the binding of MRs to FKBP52 and dynein.[11] FKBP52-KO inhibits the nuclear translocation of MRs but does not affect their aldosterone affinity.[11] Given these results, HSP90 and FKBP52 are considered to play important roles in the nuclear translocation of MRs by dynein. However, FKBP52 overexpression did not alter the transcriptional activity of the MRs.[49,53]

### 3.2 | Other targets

#### 3.2.1 | Nuclear factor-κB

Although NF-κB, a transcription factor that regulates inflammation, is not classified as an SHR, it is known to be regulated by FKBP52. The transcription factors RelA and p50 and their inhibitor IκBα form a complex. Cytokines and other signals induce the phosphorylation of IκBα by the IKK complex, which in turn promotes the activation of RelA and p50.[54] FKBP52 promotes the nuclear translocation of RelA.[55] FKBP52 also promotes IKK complex formation and contributes to NF-κB activation.[56] RelA does not bind to HSP90;[55] PPIase activity is required for the enhancement of NF-κB transcriptional activity, based on experiments using FKBP52-PPIase mutants. In contrast, the FKBP52-TPR mutant does not bind to IKK.[56] Thus, it is feasible that the association between FKBP52 and IKK is dependent on HSP90. Similar to GR and MR, the nuclear translocation of NF-κB is dependent on dynein[57]; therefore, it is thought to bind dynein in the cytoplasm through FKBP52 and then translocate into the nucleus.

#### 3.2.2 | Human telomerase reverse transcriptase

Human telomerase reverse transcriptase is also regulated by FKBP52. Human telomerase reverse transcriptase binds to HSP90[58,59] and HSP90 contributes to the folding of the hTERT protein.[60] FKBP52 promotes the nuclear translocation of hTERT by linking hTERT to dynamitin, a member of the dynactin complex.[61] Therefore, FKBP52 is thought to act on hTERT in the cytoplasm. The FKBP52-TPR mutant did not bind to hTERT. This suggests that the interaction between FKBP52 and hTERT requires HSP90. In addition, geldanamycin inhibits the nuclear translocation of hTERT in the presence of proteasome inhibitors. Furthermore, the knockdown of FKBP52 or treatment with geldanamycin increased the ubiquitination of hTERT, suggesting that FKBP52 and HSP90 might also contribute to hTERT stability. As hTERT expression is upregulated in cancer cells,[62] FKBP52 could contribute to cancer cell malignancy by activating the hTERT function.

#### 3.2.3 | $Ca^{2+}$ channel

In neuronal cells, FKBP52 has been reported to activate TRPC1, and NMR analysis revealed that FKBP52 catalyzes the isomerization of N- and C-terminal proline in TRPC1.[31] TRPC1 is a channel involved in $Ca^{2+}$ influx that belongs to the TRP family. Its *Xenopus* homolog (xTRPC1) is involved in axon guidance.[31,63] The FKBP52-F67D/D68V mutant did not activate TRPC1, suggesting that PPIase activity of FKBP52 might be required for TRPC1 activation. Overexpression of FKBP52-F67D/D68V mutant, or FK506 treatment, causes defects in the guidance of the developing *Xenopus* spinal cord. This indicates that FKBP52 has an important role in TRPC1-mediated axon guidance. TRPC3 has been reported to be repressively regulated by FKBP52 in cardiomyocytes.[32] TRPC3 is known to promote myocardial hypertrophy and cardiomyocyte apoptosis in the heart.[64,65] FKBP52 interacts with the C-terminus of TRPC3 through several regions, including the FK1, FK2, and TPR (TPR1 and TPR2). Decreased expression of FKBP52 causes TRPC3-dependent hypertrophy of cardiomyocytes. This suggests that FKBP52 inhibits myocardial hypertrophy by suppressing TRPC3. TRPV5 is responsible for $Ca^{2+}$ reabsorption in renal epithelial cells, and its $Ca^{2+}$ uptake activity is inhibited by FKBP52.[33] Thus, FKBP52 plays an important role in $Ca^{2+}$ reabsorption in the kidney through TRPV5. Compared to the WT, overexpression of the FKBP52-F67D/D68V mutant did not inhibit $Ca^{2+}$ uptake, indicating that FKBP52-PPIase activity might be required for TRPV5 inhibition. It should be noted that the FKBP52-F67D/D68V mutants may have lost their interaction with TRPV5.[33] The domain in which FKBP52 interacts with TRPC1 and TRPV5 remains unclear. However, FK506 treatment did not alter the binding of FKBP52 to TRPV5, suggesting that binding could occur in regions other than the FK1 domain.[33]

#### 3.2.4 | Tubulin

FKBP52 has been shown to bind to tubulin and negatively regulate tubulin polymerization.[66] Binding to tubulin requires a domain below the TPR, whereas inhibition of polymerization requires a CaM-binding domain. Subsequent studies have revealed that FKBP52 binds to tau,[7] a polymerization-promoting factor of tubulin, and it is speculated that FKBP52 inhibits tubulin polymerization by binding to tau and blocking its activity. Tau plays an important role in

neurite outgrowth.[67] Overexpression of FKBP52 inhibits neurite outgrowth,[7] suggesting that FKBP52 suppresses neurite outgrowth by inhibiting tau.

## 4 | EXPRESSION LEVEL OF FKBP52 IN CANCER TISSUES AND ITS RELATIONSHIP WITH THEIR PROLIFERATION

FKBP52 activates SHRs and is involved in the proliferation of prostate and breast cancer cells.[23] Notably, FKBP52 expression is upregulated in several cancers in addition to SHR-related cancers, suggesting that the cancer-associated function of FKBP52 is not specific to SHRs (Table 2).

### 4.1 | Prostate cancer

Prostate cancer is most commonly studied for FKBP52. Increased FKBP52 expressions have been found in human prostate cancer and prostate cancer cell lines,[37,68] suggesting that FKBP52 is a potential biomarker for prostate cancer. Amplification of the copy number of FKBP52 has been found in CRPC.[69] A comprehensive clinical sample analysis has shown FKBP52 to be a biomarker for prostate-specific antigen recurrence in patients with prostate cancer.[38] Although the mechanism by which *FKBP4* expression increases in cancer cells is largely unknown, prostate cancer studies have revealed that *FKBP4* is transcribed by the oncogene c-Myc.[70] Androgen receptor binds to the promoter region of *FKBP4* in prostate cancer[71] and increased expression of *FKBP4* in response to DHT.[72] These results suggest that AR might regulate the transcription of *FKBP4*. As mentioned above, FKBP52 increases the affinity of AR for DHT and AR dimerization, and increases the transcriptional activity of AR. Thus, MJC13 inhibits the proliferation of prostate cancer cell lines.[73,74] The effect of MJC13 is enhanced in DHT-treated conditions; therefore, a higher efficacy can be expected in conditions where hormone therapy is effective. However, cells expressing AR-V7 are resistant to MJC13 and geldanamycin,[75] suggesting that targeting FKBP52 is not a universal approach for prostate cancer. Androgen receptor has an important role in prostate cancer development[76] and its activity is activated by FKBP52. It also activates proliferation in prostate cancer through its interaction with FKBP52. FKBP52 is upregulated in prostate cancer and its high expression is associated with poor prognosis. Given this information, the interaction of FKBP52 with AR and the activation of AR could contribute to the development of prostate cancer. However, tumorigenesis experiments using mutants that are deficient in binding ability have not yet been reported. Therefore, the extent to which the interaction between FKBP52 and AR affects tumorigenesis is not clear.

### 4.2 | Breast cancer

FKBP52 is highly expressed in breast cancer cell lines.[77] Estrogen increases *FKBP4* expression at the transcriptional level.[48] In addition, the *FKBP4* gene region was found to be unmethylated in ERα-positive cells but methylated in ERα-negative cells.[78] This suggests that *FKBP4* is a target of the ERα and could form a positive feedback loop by promoting *FKBP4* expression. Indeed, high FKBP52 expression is a poor prognostic factor in patients with ERα-positive breast cancer cells.[46,79] Furthermore, high expression of FKBP52 is a poor prognostic factor in ERα- and PR-negative breast cancers, and the knockdown of FKBP52 inhibits proliferation in ERα-negative breast cancer cell lines.[80] The fact that FKBP52 affects the proliferation of ERα-negative breast cancer cell lines suggests that FKBP52 might regulate signaling other than the ERα. Indeed, interactome analysis of FKBP52 revealed that FKBP52 interacts with PI3K.[80] Phosphorylation of AKT, a target of PI3K, was decreased in FKBP52-KD cells, indicating that FKBP52 activates AKT through PI3K. Both ERα and PR are involved in breast cancer development.[81,82] FKBP52 interacts with ERα through BRCA1 and plays a role in ERα stability. FKBP52 also interacts with PR and is involved in the activation of PR. FKBP52 is upregulated in breast cancer and its high expression is associated with poor prognosis. Given this information, the interaction of FKBP52 with ERα and PR may contribute to the development of breast cancer. However, experiments on tumorigenesis using mutants lacking the binding ability have not been reported. Therefore, the importance of the interaction of FKBP52 with ERα and PR in tumorigenesis is unclear.

**TABLE 2** Expression of FK506 binding protein 52 (FKBP52) in cancer cells

| Cancer type | FKBP52 expression | KD | Role of FKBP52 | |
|---|---|---|---|---|
| Prostate cancer | Upregulated[37,68] | Inhibition of proliferation[38] | Upregulates AR dimerization[38] | |
| Breast cancer ($ER\alpha^+$) | Upregulated[46,77] | Inhibition of proliferation[46] | Upregulates ERα stability[46] | |
| Breast cancer ($ER\alpha^-$) | Upregulated[77,80] | Inhibition of proliferation[80] | Upregulates PI3K/AKT pathway[80] | |
| Colon cancer | Upregulated[83,84] | No effect[83] | Resistance to 5-FU[83] | |
| Lung cancer | Upregulated[56,85] | Inhibition of proliferation[56,85] | Upregulates PI3K/AKT pathway[85] | Upregulates IKK/NF-κB pathway[56] |
| Liver cancer | Upregulated[86] | No data | No data | |

*Note*: Expression levels of FKBP52 in each cancer cell line are shown. The table also indicates the phenotype of the FKBP52 knockdown (KD) and the function of FKBP52 in cancer cells.

Abbreviations: AR, androgen receptor; ERα, estrogen receptor α; 5-FU, 5-fluorouracil; IKK, IκB kinase; NF-κB, nuclear factor-κB.

### 4.3 | Other cancers

Database analysis revealed that FKBP52 expression is increased in colorectal cancer.[83,84] Although the knockdown of FKBP52 did not affect the growth of colon adenocarcinoma cell lines, increased sensitivity to 5-fluorouracil was observed in FKBP52-KD cells.[83] Additionally, *FKBP4* was transcriptionally activated by E2F1.[84] The expression of FKBP52 is also increased in lung adenocarcinoma and is a poor prognostic factor for the disease.[56] Similarly, FKBP52 is overexpressed in NSCLC and is a poor prognostic factor.[85] FKBP52-KD in NSCLC decreases phosphorylation of AKT and mTOR, similar to that reported in breast cancer.[80] This indicates that FKBP52 contributes to proliferation through the PI3K/AKT/mTOR signaling pathway. Increased FKBP52 expression has also been observed in c-Myc-induced liver cancer (hepatocellular carcinoma), making FKBP52 a potential biomarker for liver cancer.[86] These results reinforce the activation of *FKBP4* transcription by c-Myc, as observed in prostate cancer.[70] Tumors of the hematopoietic system are induced to form tumors through NF-κB.[87] As described above, RelA is activated by FKBP52 through its interaction with FKBP52. FKBP52 also interacts with IKKβ and IKKγ, and promotes IKK complex formation. Based on this information, the interaction of FKBP52 with RelA and IKK could contribute to the development of tumors of the hematopoietic system. However, tumorigenesis experiments using mutants that are deficient in binding ability have not yet been reported. Therefore, the extent to which the interaction of FKBP52 with RelA and IKK affects tumorigenesis is not clear.

## 5 | CONCLUSION

The effects of FKBP52 on SHR-mediated cell proliferation are becoming clearer. FKBP52 enhances the transcriptional activity of SHR by promoting its nuclear translocation, stabilization, and dimer formation. Moreover, FKBP52 is also involved in signaling pathways unrelated to SHRs. As the expression of FKBP52 is increased in several cancers and overexpression of FKBP52 is associated with poor prognosis, FKBP52 is considered an effective therapeutic target for cancer. As FKBP52 has many functions as a PPIase and cochaperone, it is important to clearly distinguish its functions. In addition, it is also unclear how the activity of FKBP52 is regulated. It is necessary to identify molecules that function upstream of FKBP52 as well as the posttranslational modifications of FKBP52. Further studies will greatly advance our understanding of the regulation and functions of FKBP52.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

### ETHICS STATEMENTS

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