FK506 binding protein 51 (FKBP51, also called FKBP5) belongs to a family of immunophilins, FK506 binding proteins (FKBPs). Members of this family contain both FKBP domain(s) and tetratricopeptide repeat (TPR) domain(s) (Kang et al, 2008). The FKBP domain contains peptidylprolyl isomerase (PPIase) activity that catalyses the cis–trans conversion of peptidylprolyl bonds, a reaction that is important for protein folding (Fruman et al, 1994). The TPR domains at the C terminus are involved in protein–protein interactions (Scheufler et al, 2000). In general, TPR domains are all-helical structures consisting of 2–16 units of a consensus 34-aa motif. The domain is found in more than 800 different proteins from bacteria and humans. The first described and most well-known FKB family member is FKBP12, a small protein with a single FKBP domain and a molecular size of 12 kDa. FK506 binding protein 12 is a major binding partner for FK506 and rapamycin (Siekerka et al, 1989). Additional members of this family have been identified on the basis of their ability to bind FK506, including FKBP13, FKBP25, FKBP38, FKBP52, and FKBP51 (named to reflect their molecular weights), all of which contain the FKBP domain that is responsible for drug ligand binding and PPIase activity (Kang et al, 2008).

Human FKBP5 was first cloned from a HeLa cell cDNA library in 1995 (Baughman et al, 1995). It mediates FK506 inhibition of calcineurin in vitro and is highly expressed in murine T lymphocytes (Baughman et al, 1997). FK506 binding protein 5 contains two consecutive FKBP domains and a three-unit repeat of the TPR domain (Figure 1). The first FKBP domain (FK1) of FKBP5 shares 48% sequence identity to the FK domain of FKBP12 and has measurable PPIase activity, with a binding pocket for FK506 and rapamycin (Sinars et al, 2003). FK2 is also structurally similar to the FKBP domain of FKBP12, despite having only 26% sequence identity. However, FK2 lacks measurable PPIase activity. Presumably, FK2 resulted from an FK domain duplication event, but subsequently lost its PPIase activity, while it appeared to have gained protein interaction ability (Sinars et al, 2003). The FKBP5 structure study provides important initial insights into the relative orientations of the FK1, FK2, and TPR domains that are important for protein interaction and/or drug ligand binding (Sinars et al, 2003).

One of the major functions of FKBP5 is its involvement in the modulation of steroid receptor function, including progesterone, androgen and glucocorticoid receptors (GR), by forming a complex with the heat shock proteins Hsp90/Hsp70. Both FKBP5 and its family member FKBP4 (also called FKBP52) are involved in steroid receptor signalling, and their interchange served as the earliest known event in steroid receptor activation. Davies et al (2002) have used both in vitro and in vivo models to show the hormone-induced loss of FKBP5 and gain of FKBP4, providing evidence that the hormone-binding event causes an interchange of FKBP5 and FKBP4 immunophilins within the GR heterocomplex. The complex then dissociates, allowing the binding of GR to DNA-binding motifs in its target genes to regulate gene transcription (Figure 2A). Therefore, FKBP5 has been identified as a sensitive biomarker of corticosteroid responsiveness in vivo (Table 1) (Sinars et al, 2003; Rees-Unwin et al, 2007). In addition to a role in tumourigenesis (see below), numerous studies have also indicated that FKBP5 may have a role in psychiatric diseases such as depression and in response to the treatment of depression through modulation of hormone receptors (Schosser and Kasper, 2009). FK506 binding protein 5 and Hsp90 are also important for the clearance of tau, a microtubule-associated protein that accumulates in a group of neurodegenerative disorders such as Alzheimer’s disease (Jinwal et al, 2010).

Of equal or greater interest than these effects on steroid hormone signalling are recent studies that have indicated that FKBP5 could also be a biomarker for tumourigenesis and chemoresistance. Roles in those processes extend beyond its functions as a co-chaperone and a PPIase. Subsequent paragraphs will focus on the discovery of the role of FKBP5 in cancer aetiology and chemoresistance.
FK506 BINDING PROTEIN 51 EXPRESSION AND REGULATION IN CANCER

Human FKBP5 is highly expressed in multiple tissues, including kidney, skeletal muscle, liver, placenta, heart, and peripheral blood. However, its expression level is much lower in the pancreas, spleen, and stomach (Baughman et al., 1997). Although initial studies found no detectable FKBP5 in the brain, colon, or lung, subsequent studies have shown expression of FKBP5 in human brain tissues (Nair et al., 1997) and colon tissues (Mukaide et al., 2008). FK506 binding protein 5 expression can be induced through the activation of progesterone receptor, androgen receptor (AR), and GR (Ratajczak, 2008). FK506 binding protein 5 expression can also be induced by the GR in human lung cancer A549 cells, where FKBP5 mRNA are accumulated in response to dexamethasone exposure (Paakinaho et al., 2010). A major intrinsic enhancer within the FKBP5 locus was identified to bind to GR. There were also GREs identified in the proximal promoter of FKBP5. The GR is capable of activating FKBP5 transcription and also evoking changes in chromatin structure (Paakinaho et al., 2010). FK506 binding protein 5 can also function within an auto-regulatory negative feedback loop to modulate its own expression. Exogenous FKBP5 expression was able to downregulate the transcription of genomic FKBP5 in the presence of dexamethasone through this auto-regulation process (Park et al., 2007).

Both overexpression and downregulation of FKBP5 have been observed in human cancers. According to the Oncomine, FKBP5 is overexpressed in brain cancers, prostate cancer, lymphoma, head and neck cancer, and melanoma. On the other hand, FKBP5 has also been shown to be downregulated in pancreatic cancer (Pei et al., 2009), melanoma, colon cancer, and testicular cancer. Gene expression data for those studies are available through the Oncomine, and studies describing these observations are also

**Figure 1** Structure of FKBP5 with its major domains that are critical for its function as well as with the list of its interactive proteins by domain. AKT = a serine/threonine protein kinase, also called PKB; AR = androgen receptor; FK = FKBP-type domain; GR = glucocorticoid receptor; Hsp90 = heat shock protein 90; IkB = IkB kinase ; PHLPP = PH domain and leucine-rich repeat protein phosphatases; PR = progesterone receptor; TPR = tetratricopeptide repeat.

**Figure 2** Schematic model of FKBP5 functions involved in several different signalling pathways, including glucocorticoid receptor (GR) signalling pathways (A), as well as NF-κB and AKT–mTORC1 pathways. (A) In the absence of dexamethasone, FKBP5 is the primary immunophilin of the FKBP–Hsp90–GR complex in an inactive stable state. Upon dexamethasone binding, FKBP5 is displaced by FKBP4, and the complex can enter the nucleus. The complex then dissociates, allowing binding of GR to DNA-binding motifs of target genes, leading to apoptosis. (B) In the presence of doxorubicin or damage from radiation, FKBP5 might involve in the control of IKK activity, which can induce IkB degradation via its phosphorylation, nuclear translocation, and activation of NF-κB, and the expression of its target genes, consequently triggering cell apoptosis. (C) FK506 binding protein 5 interacts with PHLPP and AKT, acting as a scaffolding protein that promotes the interaction between AKT and PHLPP, thereby enhancing the dephosphorylation of AKT and inactivating AKT, which results in the blockade of AKT signalling for cell survival and leads to cell apoptosis or death.
ROLE OF FKBP5 IN TUMOURIGENESIS AND RESPONSE TO ANTI NEOPLASTIC THERAPY

FK506 binding protein 5 has been shown to be involved in a variety of different signalling pathways, including steroid receptor signalling pathways, NF-κB, and Akt (a serine/threonine protein kinase, also called PKB). FKBP5 stimulates the NF-κB pathway (Avellino et al., 2005). They showed that treatment of melanoma or acute lymphoblastic leukaemia cell lines with anthracycline would downregulate of FKBP5 and increased the rapamycin inhibition of NF-κB activity. This effect was associated with FKBP5 activity, as downregulation of FKBP5 increased the rapamycin inhibition of NF-κB activity, and, in turn, increased apoptosis (Avellino et al., 2005). In addition, the same group also found that higher expression of FKBP5 might influence radiosensitivity through the activation of NF-κB in melanoma cells (Romano et al., 2010). They also found that FKBP5 was overexpressed in melanoma samples compared with normal skin tissue, and pretreatment of mice xenograft tumours with FKBP5-siRNA provoked massive apoptosis after irradiation (Romano et al., 2010). These experiments provided evidence that, both in vitro and in vivo, FKBP5 might be a promising target for radiosensitising agents against malignant melanoma.

FK506 binding protein 5 is a negative regulator of Akt activation in tumourigenesis and chemoresistance

Regulation of NF-κB by FKBP5 emphasised the potential importance of FKBP5 in tumourigenesis and response to therapy. However, it was not until very recently that another important function of FKBP5 was identified. Studies from our laboratory first demonstrated, through the use of genome-wide screening, that levels of FKBP5 were associated with response to two cytidine analogues, gemcitabine and cytosine arabinoside (ArC) (Li et al., 2008). Higher levels of expression of FKBP5 were associated with sensitivity and lower levels of expression were associated with resistance to gemcitabine and ArR. Furthermore, downregulation of FKBP5 desensitised pancreatic and breast cancer cell lines to several different classes of chemotherapeutic agents, including not only cytidine analogues but also taxanes, irinotecan, and etoposide (Li et al., 2008; Pei et al., 2009). In this case, the actions of FKBP5 on NF-κB activation or hormone induction could not explain the increased chemoresistance in cells with decreased FKBP5 expression, suggesting the existence of other mechanisms by which FKBP5 regulates cell survival.

FK506 binding protein 5 is a key regulatory component of the androgen receptor complex

Although FKBP5 knockout mice show normal androgen signalling (Yong et al., 2007), it has been linked to AR signalling and prostate cancer. As discussed above, FKBP5 itself is a target gene of AR. FK506 binding protein 5 can form a complex with AR to enhance AR transcriptional activity in prostate cancer (Febbo et al., 2004). Recent studies by Bouwmeester et al. (2004) first identified a physical interaction between FKBP5 and nuclear factor κB kinase 2 (IKK2) during a proteomics study. In their study, FKBP5 was copurified with IKK2 as well as IKKα, TGF beta activated kinase 1, and MAP kinase/ERK kinase kinase 1 (Bouwmeester et al., 2004). The interaction with IKK2 was confirmed by co-immunoprecipitation. These results indicated that FKBP5 might have a role in NF-κB signalling.

Several studies by Romano et al. have demonstrated that the downregulation of FKBP5 can sensitize cells to irradiation and anthracyclines through the regulation of NF-κB (Avellino et al., 2005). They showed that treatment of melanoma or acute lymphoblastic leukaemia cell lines with anthracycline would induce NF-κB activity. However, treatment with rapamycin significantly sensitised the cells to anthracycline by inhibition of the NF-κB activity. This effect was associated with FKBP5 activity, as downregulation of FKBP5 increased the rapamycin inhibition of NF-κB activity, and, in turn, increased apoptosis (Avellino et al., 2005). In addition, the same group also found that higher expression of FKBP5 might influence radiosensitivity through the activation of NF-κB in melanoma cells (Romano et al., 2010). They also found that FKBP5 was overexpressed in melanoma samples compared with normal skin tissue, and pretreatment of mice xenograft tumours with FKBP5-siRNA provoked massive apoptosis after irradiation (Romano et al., 2010). These experiments provided evidence that, both in vitro and in vivo, FKBP5 might be a promising target for radiosensitising agents against malignant melanoma.

The alterations of antineoplastic activity and drug susceptibility in cancer cells were also associated with the levels of FKBP5 (Table 1).

| Antineoplastic agent | Signalling pathway involved | Type of cancer | Change in FKBP5 expression | Alteration of drug susceptibility | Reference |
|----------------------|-----------------------------|----------------|-----------------------------|---------------------------------|-----------|
| FK506, rapamycin     | PR, GR                      | Breast cancer  | Upregulated                 | Resistance                      | Le Bihan, Marsaud et al (1998) |
| FK506                | AR                          | Prostate cancer| Upregulated                 | Resistance                      | Ni et al (2010)                  |
| Dexamethasone        | GR                          | Myeloma        | Upregulated                 | Resistance                      | Rees-Lewin et al (2007)          |
| Rapamycin            | NF-κB                       | ALL, melanoma  | Upregulated                 | Resistance                      | Romano et al (2004); Avellino et al (2005) |
| Radiation            | NF-κB                       | Melanoma       | Upregulated                 | Resistance                      | Romano et al (2010)              |
| Gemcitabine          | AKT                         | Pancreatic cancer | Downregulated              | Resistance                      | Li et al (2008); Pei et al (2009) |

Table 1: Table of relationship between FKBP5 levels in cancer and drug activity of antineoplastic agents

Abbreviations: AKT = a serine/threonine protein kinase, also called protein kinase B; AR = androgen receptor; FKBP5 = FK506 binding protein 5; CR = glucocorticoid receptor; NF-κB = nuclear factor-κB; PR = progesterone receptor.
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dephosphorylate Ser473 (Brognard and Newton, 2008). Therefore, the balance between kinases and phosphatases determines AKT activity. We found that FKBP5 functions as a scaffolding protein that enhances the PHLP–AKT interaction and facilitates PHLP-mediated dephosphorylation of AKT-Ser473. Downregulation of FKBP5 results in decreased PHLP–AKT interaction and increased AKT phosphorylation. Therefore, FKBP5 might also function as a tumour suppressor in the AKT signalling pathway, similar to phosphatase and tensin homologue (PTEN). Indeed, we found that FKBP5 levels were low or absent in pancreatic cancer cell lines and tissue samples from patients with pancreatic cancer, correlating with increased AKT Ser473 phosphorylation. We also observed downregulation of FKBP5 in breast cancer cell lines. High levels of FKBP5 led to decreased AKT phosphorylation and increased chemosensitivity, whereas low levels of FKBP5 resulted in increased AKT phosphorylation and decreased chemosensitivity. These observations make FKBP5 a potentially important biomarker for sensitivity to chemotherapy, and variation in FKBP5 levels might determine patient responses to chemotherapy (Figure 2C and Table 1) (Pei et al, 2009). In addition, determination of levels of FKBP5 might provide insights that could help to select patients for different combination therapies with inhibitors targeting the AKT pathway (Pei et al, 2009).

CONCLUSIONS

In summary, FKBP5 has altered expression levels in many different tumours. Through its influence on steroid receptor maturation, as well as NF-xB and AKT signalling pathways, FKBP5 plays an important role in tumorigenesis and response to anti-neoplastic therapy (Figure 2 and Table 1). All of these observations raise the possibility that FKBP5 might be a biomarker for chemoradiosensitivity. On the basis of studies using lymphoblastoid cell lines from 300 individuals, we have observed large variations in FKBP5 expression that correlate with cellular sensitivity to gemcitabine and AraC (Li et al, 2008). Future studies will be needed to confirm the role of FKBP5 in predicting chemosensitivity in clinical samples. In addition, it would be important to investigate factors that are responsible for variation in FKBP5 expression in individuals. Common single-nucleotide polymorphisms (SNPs) in the FKBP5 gene might contribute to variation in FKBP5 protein expression. Therefore, genotyping these SNPs and determining how they affect FKBP5 expression and, thus, drug sensitivity or tumourigenesis might be important next steps for this line of investigation. Additionally, the role of FKBP5 in tumourigenesis remains controversial. Whether FKBP5 functions as an oncogene or a tumour suppressor might depend on the tissue type and differences among pathways expressed in those tumours. For example, FKBP5 is found to be downregulated in pancreatic tumour tissue, while it is overexpressed in melanoma. These discrepancies need to be further clarified in the future using animal models.

Because of the role of FKBP5 in the regulation of multiple important biological pathways as discussed in this review, variation in FKBP5 could be of significance in many diseases beyond cancer, and in diseases such as diabetes (Tian, 2005). All of these possibilities will need to be investigated. Future studies will also be required to address questions such as how FKBP5 is regulated, and whether there are other pathways in which FKBP5 might be involved.

In summary, FKBP5 has multiple roles in the regulation of a variety of signalling pathways. Therefore, understanding the mechanisms underlying its regulation and its role in the development of cancer and in response to anti-neoplastic therapy could help make it possible to better individualise the treatment of human disease.

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