FKBP immunophilins and Alzheimer's disease: A chaperoned affair

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The FK506-binding protein (FKBP) family of immunophilins consists of proteins with a variety of protein–protein interaction domains and versatile cellular functions. Analysis of the functions of immunophilins has been the focus of studies in recent years and has led to the identification of various molecular pathways in which FKBPs play an active role. All FKBPs contain a domain with prolyl *cis*/*trans* isomerase (PPIase) activity. Binding of the immunosuppressant molecule FK506 to this domain inhibits their PPIase activity while mediating immune suppression through inhibition of calcineurin. The larger members, FKBP51 and FKBP52, interact with Hsp90 and exhibit chaperone activity that is shown to regulate steroid hormone signalling. From these studies it is clear that FKBP proteins are expressed ubiquitously but show relatively high levels of expression in the nervous system. Consistent with this expression, FKBPs have been implicated with both neuroprotection and neurodegeneration. This review will focus on recent studies involving FKBP immunophilins in Alzheimer's-disease-related pathways.

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1. Overview of immunophilins

In general, immunophilins are proteins with a cytoplasmic localization and their physiological function is that of a chaperone with peptidyl-prolyl *cis*/*trans* isomerase (PPIase) activity (Barik 2006). Interestingly, the name 'immunophilin' reflects the discovery of these proteins as binding partners of exogenous ligands with immunosuppressant properties, such as cyclosporine A, rapamycin and FK506. Both cyclosporine A, produced by the fungus *Beauveria nivea*, and rapamycin and FK506, produced by the bacteria *Streptomyces hygroscopicus* and *S. tsukubaensis*, respectively, are normally never encountered by mammalian cells. However, binding of these ligands to mammalian immunophilins has been shown to induce immunosuppression (Dawson *et al.* 1994), leading to a fantastic success for the transplantation field. Subsequent to the discovery of their immunosuppressive function, immunophilins were shown to be involved in various cellular signalling pathways, including calcium homeostasis, steroid receptor signalling and, recently, copper trafficking (reviewed in Avramut and Achim 2003; Sanokawa-Akakura *et al.* 2004).

The immunophilin family comprises the cyclophilins, which bind cyclosporine, FK506-binding proteins (FKBPs), which bind rapamycin and FK506, and the smaller-size parvulin (Barik 2006). All of these proteins exhibit prolyl-isomerase activity, in addition to other more subfamily-specific functions. The cyclosporins and FKBPs are the largest sub-families. According to the Panther classification (*http://www.pantherdb.org/*), humans express 7 major cyclophilins and 12 FKBPs. In this review, we will concentrate on the description of the FKBP family and will review demonstrated chaperone-related functions of members of this family in the nervous system.

2. FK506-binding protein family

Members of the FKBP family are distinguished by their molecular weight and their domain structure, which contains

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Abbreviations used: AD, Alzheimer's disease; AICD, amyloid intracellular domain; APP, amyloid precursor protein; FKBD, FK506-binding domain; FKBP, FK506-binding protein; FTDP, fronto-temporal dementia and Parkinsonism linked to chromosome 17; mTOR, mammalian target of rapamycin; TPR, tetratricopeptide

their common PPIase domain. When present, the immunosuppressant compound FK506 binds the PPIase domain of FKBPs, inhibiting its activity. This binding also results in inhibition of the phosphatase activity of calcineurin and ultimately in the suppression of IL-2 expression and T-cell activation (Dumont 2000). A second immunosuppressant molecule, rapamycin, also binds the PPIase domain and induces immunosuppression through interactions with the mammalian target of rapamycin (mTOR; reviewed in Rostaing and Kamar, 2010). Thus, the PPIase domain, also called FK506-binding domain (FKBD) serves two mutually exclusive functions: when bound to FK506 or rapamycin, it causes immunosuppression; when not bound to the immunophilin ligands, it interacts with cellular proteins and modifies signalling pathways by its isomerase activity (reviewed in Kang *et al.* 2008). These chaperone-related functions are common to all members of the FKBP family that contain an active PPIase/FKBD domain.

In general, FKBPs fall into three sizes, indicated by their name. The smaller-size immunophilins are represented by the mammalian FKBP12 protein (figure 1). FKBP12 comprises 108 amino acids, which primarily encode the PPIase/FKBD domain. To date, a number of cellular substrates of FKBP12 have been described, including calcineurin, the ryanodyne receptor (RyR) and TGFβ (reviewed in Kang *et al.* 2008). A second prototype protein of the FKBP family is FKBP38 (figure 1). FKBP38 does contain a PPIase/FKBD domain, but it is considered a non-canonical member of the family because its PPIase/FKBD domain does not bind immunophilin ligands and it does not exhibit immunosuppressant activity (Kang *et al.* 2008). It has been shown that FKBP38 interacts with presenilins and promotes apoptosis (Wang *et al.* 2005); however, various conflicting studies suggest that the function of this immunophilin is unique and several aspects of it remain to be elucidated. The third class of FKBP genes is represented by the larger-size proteins FKBP51 and FKBP52 (figure 1). The PPIase/FKBD domain is duplicated in these proteins and in addition they possess repeats of the tetratricopeptide

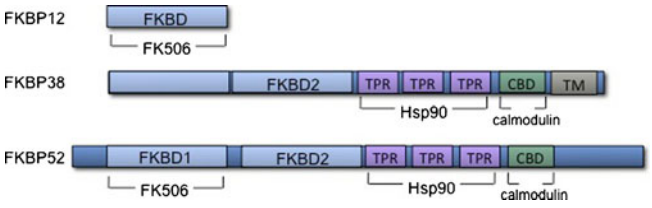

Figure 1. The FKBP family comprises proteins with three different molecular weights, ranging from 12 to 52 kDa. The three types of FKBPs have varying domain structures. Shown are the structural elements of each of these types of proteins. FKBD: FK506-binding domain, TPR: tricopeptide repeat, CBD: calmodulin-binding domain, TM: transmembrane domain.

(TPR) domain, which mediates protein–protein interactions, and a calmodulin-binding domain, located at the C′ end of the protein (reviewed in Davies and Sanchez 2005). The TPR and calmodulin-binding structural motifs confer additional functions to these proteins. A well-characterized function of the large immunophilins, which also led to their initial identification, is their participation in the Hsp90–steroid receptor complex. Indeed, FKBP51/52 have been shown to participate in signalling by the progesterone, androgen and glucocorticoid receptors (Pratt 1997).

3. Natural versus pharmacological role of FKBPs

Given their enormous significance in the transplantation field, the naturally occurring immunophilin ligands FK506 and cyclosporine have been studied extensively in recent years for their pharmacological properties. In addition, the involvement of rapamycin in TOR signalling has commanded great interest in the cancer field (Zhou *et al.* 2010). These studies have led to the development of immunophilin ligands as powerful drugs. In an interesting twist of evolution, higher organisms like humans, who normally would not encounter the naturally occurring immunophilin ligands, nevertheless express a wide repertoire of receptors for these ligands. Although the discovery of FKBPs and other immunophilins originally centered on their interactions with the FK506 and rapamycin ligands, FKBP immunophilins have been recently found to have complex and varied functions in their natural environment.

Apart from their proline isomerase activity, the chaperone function of the large immunophilins, FKBP51 and FKBP52, has been implicated in their interactions with steroid receptor complexes. Mice that carry knock-out mutations of the large immunophilins are viable but show reproductive abnormalities (Cheung-Flynn *et al.* 2005). Analysis of these abnormalities led to the discovery of the role of FKBPs in steroid receptor-mediated signalling and their association with both the androgen (Cheung-Flynn *et al.* 2005) and progesterone (Tranguch *et al.* 2005; Hong *et al.* 2007) receptors. Most recently, it was shown that FKBP52, in addition to regulating progesterone receptor signalling, also plays a protective role against oxidative stress in ovaries (Hirota *et al.* 2010). These studies have expanded the cellular pathways where immunophilin function is required. Showing mostly ubiquitous expression, FKBPs are very highly expressed in the nervous system (Steiner *et al.* 1992). In accordance with this pattern of expression, a lot of the functions of FKBPs are centered on the nervous system and encompass neuroprotective and neurodegenerative pathways (Pastorino *et al.* 2006; Liu *et al.* 2006; Jinwal *et al.* 2010). Recent literature covering the functions of FKBPs in Alzheimer-disease-related processes is presented below.

4. FKBPs affect the metabolism of tau protein

Recent studies have revealed a role for immunophilins in tau metabolism and function. Tau is a microtubule-binding protein that has been associated with a number of neurodegenerative tauopathies, including fronto-temporal dementia and Parkinsonism linked to chromosome 17 (FTDP), Alzheimer's and Pick's disease (reviewed in Dolan and Johnson 2010). Pathological hyperphosphorylation of tau causes its dissociation from microtubules, resulting in disorganization of the cytoskeleton. In addition, hyperphosphorylated tau clumps into aggregates called neurofibrillary tangles, which are found in all tauopathies and cause major disruptions of cellular functions. Different FKBP immunophilins were found to associate with tau. Sugata *et al.* (2009) report that the smaller FKBP12 co-localizes with neurofibrillary tangles in brains of Alzheimer patients. In these studies, Alzheimer's disease (AD) brains contained overall lower levels of FKBP12, relative to age-matched controls, but FKBP12 immunoreactivity was found in both tau tangles and dystrophic neurites while it was also associated with senile plaques. These results suggest that FKBP12 may be interacting with abnormal forms of tau, although it is not clear whether this association promotes, or is a consequence of, tau hyperphosphorylation.

Both the large immunophilins FKBP51 and FKBP52 are also involved in tau turnover. Jinwal *et al.* (2010) have shown that knock-down of FKBP51 by siRNA-reduced tau protein levels in HeLa cells. In a reciprocal experiment, FKBP51 overexpression increased levels of tau, confirming the siRNA observations. These results were indeed supported by previous observations showing that knock-down of the chaperone Hsp90, which interacts with FKBP51- and FKBP52-reduced levels of tau (Salminen *et al.* 2010). Based on these findings, Jinwal *et al.* (2010) proposed that FKBP51 promotes the association of tau with Hsp90, leading to de-phosphorylation and proper recycling. In sharp contrast to these findings, Chambraud *et al.* (2010) showed that the second canonical large immunophilin, FKBP52, had the opposite effects on tau. FKBP52 overexpression in PC12 cells downregulated tau protein levels. In order to test the effects of FKBP52 binding to tau in a functional assay, Chambraud *et al.* (2007) showed in earlier studies that FKBP52 knock-down caused neurite over-extension, presumably through increased tubulin polymerization. Suggesting that binding of FKBP52 to tau prevents its association with tubulin, the authors proposed that in the absence of FKBP52, tau binding to mictotubules was enhanced and resulted in longer projections (Chambraud *et al.* 2007).

Even though FKBP51 and FKBP52 have very similar structure and are both mostly ubiquitously expressed, the opposite effects that these proteins exert on tau complicate the understanding of their functions. The PPIase domain of FKBP51 was shown to be essential for promoting tau de-phosphorylation and tubulin polymerization. However, the PPIase domain of FKBP52 was not analysed for functionality. Both the functions of FKBP51 and FKBP52 were in agreement with involvement of the Hsp90 complex. Thus, it is possible that the PPIase domain and the Hsp90-associated TPR domain are exerting different effects on tau. Alternatively, Jinwal *et al.* (2010) proposed that FKBP51 and FKBP52 may facilitate the interaction of different co-factors for different Hsp90 substrates. Indeed, further studies will be required in order to test these hypotheses.

5. Association of FKBPs with both the Alzheimer's amyloid precursor protein and beta-amyloid peptides

In addition to its association with tau tangles, the small immunophilin FKBP12 was shown to bind to the intracellular domain (AICD) of the amyloid precursor protein (APP; Liu *et al.* 2006). The FKBD of FKBP12 was shown to be necessary for this interaction, a conclusion that was further supported by the dose-dependent inhibition of the binding by addition of FK506 (Liu *et al.* 2006). Although this study does not propose a function for the physical interaction between FKBP12 and APP, it has been hypothesized that the FKBP12/APP interaction may play a role in the amyloidogenic processing of APP, thus affecting levels of Aβ peptides. Such a role would parallel the function of Pin1, a peptidyl-prolyl isomerase that belongs to the parvulin family, on APP. As shown, Pin1 promotes the *cis* to *trans* isomerization of T668–P669 in the cytoplasmic C′-terminal domain of APP (AICD), thus affecting production of Aβ (Pastorino *et al.* 2006). Currently it is not clear whether the interaction of FKBP12 with APP-AICD has an effect on Aβ production or whether exposure to FK506 would have a beneficial or detrimental effect on this process.

Most recently, our work has pointed to a novel role of the large immunophilin FKBP52, in AD-related processes. FKBP52 is upregulated along with the smaller immunophilin FKBP12 in regenerating neurons, suggesting that it may play a protective or regenerative role following injury (Lyons *et al.* 1994, 1995; Brecht *et al.* 2003; Li *et al.* 2004a). Supported by the above observations, we examined a possible role for FKBP52 in AD. In these studies, we have used transgenic *Drosophila* (Finelli *et al.* 2004) and mammalian cell cultures as model systems. Flies express an orthologue of FKBP52, called dFKBP59, a gene that is highly conserved both in amino acid sequence and structure. The *Drosophila* orthologue dFKBP59 regulates calcium channel activity in neuronal photoreceptor cells, suggesting that the neuronal expression has been conserved in lower organisms (Goel *et al.* 2001). Using appropriate fly strains, we found that

mutations in the *Drosophila* orthologue dFKBP59 exacerbate levels and toxicity of Aβ in transgenic *Drosophila* over-expressing Aβ peptides (Sanokawa-Akakura *et al.* 2010). In particular, overexpression of dFKBP52 suppressed the Aβ-induced short lifespan and reduced levels of Aβ in *Drosophila* CNS. Confirming the Drosophila data, similar reduction of Aβ peptides was observed in HEK-APP cells overexpressing FKBP52 (Sanokawa-Akakura *et al.* 2010). Our studies strongly implied to us that FKBP52 may play a neuroprotective role in human AD as well. As with other polygenic diseases, AD most likely results from an imbalance in expression or function of many different proteins (Fukumoto *et al.* 2002; Li *et al.* 2004b; Yang *et al.* 2003; Nahalkova *et al.* 2010; Mi *et al.* 2009; Kågedal *et al.* 2010; Chiba *et al.* 2009). Disrupted expression has also been documented for the smaller immunophilin FKBP12, which shows reduced levels of FKBP12 in AD brains (Sugata *et al.* 2009). To examine whether FKBP52 levels are altered in disease tissue, we compared protein expression in brains from people who had died of AD (figure 2; AD1–AD4) with the brains from people who had died without disease (C1, C4) or of other non-AD neurological disease (C2, C3). Samples from the temporal lobe and the hippocampus of four AD and four control patients were analysed. The ages of the patients ranged from 71.3 to 86.9 years for the control and 71.9 to 88.9 years for the AD patients. Each control sample was matched for age with each AD. We observed that the AD samples had lower expression of FKBP52 as compared to controls, in both areas of the brain. As expected, inter-individual variability of expression in the control samples was observed (quantification of the Western blot analysis is shown in figure 3, bar graphs are means and SEMs). Consistent with our prediction, the AD samples had lower expression of FKBP52.

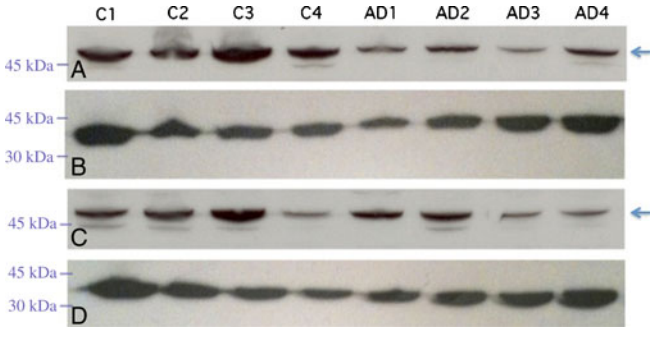

Figure 2. Western blot analysis of control (C1–C4) and Alzheimer's disease (AD1–AD4) brains. Protein extracts were prepared from the temporal cortex (**A**, **B**) and the hippocampus (**C**, **D**). The blots were probed with an anti-human FKBP52 antibody (**A**, **C**), then stripped and re-probed with an anti-actin antibody that also served as a loading control (**B**, **D**). The arrows point to FKBP52 (52 kDa).

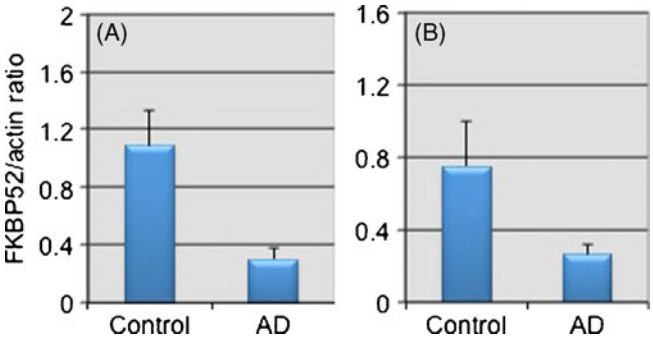

Figure 3. Quantification of FKBP52 protein (shown in figure 2), found in the temporal cortex (**A**) and the hippocampus (**B**) of control and Alzheimer's disease brains. The protein levels of FKBP52 were normalized against the corresponding levels of actin. Averages and standard deviation are shown ($P<0.05$).

Prompted by previous studies showing a direct physical interaction of the AICD domain of APP with the small immunophilin FKBP12, we also examined whether APP would associate with FKBP52. Indeed, we showed that endogenous APP could co-immunoprecipitate with FKBP52 in HEK cell lysates. This interaction could also be mediated by a truncated form of FKBP52 that carried the FKBD and could be competed by addition of FK506 (Sanokawa-Akakura *et al.* 2010). These data suggest that the PPIase domain of FKBP52 plays a direct role in the FKBP52–APP interaction. Binding of FKBP52 to APP may affect its amyloidogenic processing; however, the functional role of the FKBP52–APP interaction remains to be elucidated.

Metal homeostasis is instrumental in the pathology of AD and copper interactions with APP and Aβ, both of which contain copper-binding sites, have been widely documented and implicated in the disease (Atwood *et al.* 1998; Kong *et al.* 2007; Barnham and Bush 2008). It has been previously reported that FKBP52 is involved in regulation of intracellular copper through a direct interaction with the cytoplasmic copper transporter Atox1 (Sanokawa-Akakura *et al.* 2004). Following up this discovery, we examined whether manipulation of copper levels in flies mutant for FKBP52 might synergistically alter the toxicity of Aβ peptides. As we have shown in Sanokawa-Akakura *et al.* (2010), there is indeed evidence for a synergy between copper and FKBP52 on Aβ phenotypes. Our data suggest a model through which the effects of FKBP52 on Aβ may be mediated by changes in levels of intracellular copper.

6. Conclusions

Members of the FKBP immunophilin family have emerged as versatile proteins that participate in a variety of cellular pathways. Having a mostly cytoplasmic localization and wide pattern of expression, they contain domains that

mediate protein–protein interactions with various substrates, implicating their functions in diverse biochemical pathways. Most characterized is their binding to naturally occurring immunosuppressive ligands, a process that leads to immune suppression. Additional functions of FKBPs include chaperone activities that are mediated by binding to Hsp90–steroid receptors complexes, through which they help regulate signalling in reproductive tissues in mammals.

Although ubiquitously expressed, FKBPs have enriched expression in the nervous system and participate in neuronal differentiation and neuritic outgrowth (Quintá *et al.* 2010). In addition, it has been recently acknowledged that FKBPs play a role in neurodegeneration. Both the smaller FKBP12 as well as the large-molecular-weight immunophilins FKBP51 and FKBP52 have a role in microtubule polymerization by associating with the microtubule-binding protein tau. The smaller FKBP12 and the large FKBP52 show reduced expression in Alzheimer brains. Moreover, our recent work has implicated the larger FKBP52 in regulation of metabolism and toxicity of Alzheimer Aβ peptides. These findings suggest that the FKBP chaperones may form a new class of AD drug targets. Various non-immunosuppressive analogues that bind FKBPs have been developed and shown to bind FKBP52 intracellularly (Hamilton and Steiner 1998). These small molecules readily cross the blood–brain barrier and have been tested in spinal cord injury models and in neuropathy (Costantini *et al.* 2001). Thus, valuable tools for research as well as potential therapeutics exist to address FKBPs as potentially central therapeutic targets in the future.

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