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Hsp90 and FKBP51: complex regulators of psychiatric diseases

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Mood disorders affect nearly a quarter of the world's population. Therefore, understanding the molecular mechanisms underlying these conditions is of great importance. FK-506 binding protein 5 (*FKBP5*) encodes the FKBP51 protein, a heat shock protein 90 kDa (Hsp90) co-chaperone, and is a risk factor for several affective disorders. FKBP51, in coordination with Hsp90, regulates glucocorticoid receptor (GR) activity via a short negative feedback loop. This signalling pathway rapidly restores homeostasis in the hypothalamic–pituitary–adrenal (HPA) axis following stress. Expression of *FKBP5* increases with age through reduced DNA methylation. High levels of FKBP51 are linked to GR resistance and reduced stress coping behaviour. Moreover, common allelic variants in the *FKBP5* gene are associated with increased risk of developing affective disorders like anxiety, depression and post-traumatic stress disorder (PTSD). This review highlights the current understanding of the Hsp90 co-chaperone, FKBP5, in disease from both human and animal studies. In addition, *FKBP5* genetic implications in the clinic involving life stress exposure, gender differences and treatment outcomes are discussed.

This article is part of the theme issue 'Heat shock proteins as modulators and therapeutic targets of chronic disease: an integrated perspective'.

1. Introduction

Over the past two decades, scientific literature has greatly increased our understanding of how stressful situations affect our psychological and physical health. Considering that adverse life events and exposure to trauma are very common, there is great interest in understanding the impact that disruption of stress signalling homeostasis has on the development of central nervous system (CNS) diseases. The 90 kDa heat shock protein (Hsp90) is an integral component in the molecular chaperone machine that regulates hormone signalling and stress response. Hsp90 regulates glucocorticoid receptor (GR) activity through several signalling feedback loops able to restore hypothalamic–pituitary–adrenal (HPA) homeostasis after stressful situations [1]. The regulation of these feedback loops is primarily accomplished through interactions with two Hsp90 co-chaperones, FK-506 binding protein 51 (FKBP51) and 52 (FKBP52).

In addition to the glucocorticoid signalling, these molecular chaperones are known to participate in a variety of processes in the CNS. In the cytosol, these chaperones are responsible for regulating protein aggregation, protein trafficking and cellular metabolism. While Hsp90, FKBP51 and FKBP52 are primarily cytoplasmic residents, they have also been found to be released from the cell in exosomes [2,3]. Extracellular Hsp90 has been shown to regulate neuronal migration and extracellular protein aggregation [4,5], as well as a variety of other functions [6], but the function of extracellular FKBP51 and FKBP52 has not been well-characterized. On the cytoplasmic side of the plasma membrane, FKBP51 and FKBP52 have

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been shown to regulate synaptic plasticity and ion homeostasis by interacting with transmembrane channels such as the store-operated calcium (SOC) channels. In endothelial cells, overexpression of FKBP51 led to a decrease of calcium entry through SOC, while FKBP52 enhanced SOC entry [7]. Changes in calcium levels are known to disrupt essential cortical processes including neuronal excitability, neurotransmitter release and cell metabolism. In addition to FKBP51's participation in key cellular functions, genetic variants are common in patients with mental health disorders, suggesting FKBP51 may be a therapeutic target for the treatment of these disorders. This review will focus on the role of Hsp90/FKBP51 heterocomplexes in GR signalling and how dysregulation of this pathway has been associated with stress-related illnesses such as anxiety, depression and post-traumatic stress disorder (PTSD). Advances in using FKBP51 as a biomarker and potential therapeutics targeting this pathway will also be discussed.

2. Hsp90/FKBP51 heterocomplexes

(a) Hypothalamic–pituitary–adrenal axis regulation and glucocorticoid receptor signalling

Our central stress response system is the HPA axis. Upon stress, the paraventricular nucleus of the hypothalamus secretes corticotrophin-releasing hormone (CRH), which stimulates the release of the adrenocorticotropic hormone (ACTH) from the pituitary gland into the blood. ACTH activates the synthesis and secretion of glucocorticoids (like cortisol) from the adrenal glands, leading to higher cortisol levels in blood and tissues. The stress hormone, cortisol, targets two main receptors: mineralocorticoid receptor (MR) and GR. In particular, GR is highly expressed in key regions of the HPA axis, including the hippocampus, amygdala and hypothalamus [8]. As a negative feedback mechanism, cortisol binds to hypothalamic and pituitary GR. This interaction leads to the inhibition of secreted hormones ACTH and CRH, and restores basal cortisol levels [9]. The HPA stress response is essential for survival and enables triggering of the fight-or-flight response. However, an imbalance between activation and negative feedback in this system is often observed in psychiatric patients.

Following stress, cortisol diffuses into the cytosol where it binds to GR. Intracellularly, GR binds to a multimeric chaperone complex. These heterocomplexes are comprised of Hsp90, FKBP51 or FKBP52, Hsp70 and p23. Together, these complexes play a key role in modulating steroid receptor-associated activity, which regulates processes such as sexual reproduction, metabolism and stress adaptation [1,10,11]. Hsp90 serves as the centre point of this interaction through direct binding to GR and the FKBPs. In fact, inhibiting the ATPase activity of Hsp90 leads to reduced GR activity [12]. Both FKBP51 and FKBP52 bind directly to Hsp90 through their tetratricopeptide (TPR) domain [13]. Although FKBP51 and FKBP52 share high structural similarity and compete for binding [1,14], they are divergent in their regulatory role on GR activity. A complex of Hsp90 and FKBP51 slows GR translocation into the nucleus, reducing its activity [15]; inversely, FKBP52 enhances GR nuclear translocation and signalling [16]. Upon glucocorticoid binding to GR, FKBP51 dissociates from the Hsp90-heterocomplex and is replaced by FKBP52, leading to dynein-dependent GR nuclear translocation. Following nuclear translocation, GR homodimers bind to glucocorticoid response elements (GRE) to induce or inhibit the expression of various genes. One of the genes induced by this GR activity is the gene that encodes FKBP51, *FKBP5* [17]. High intracellular levels of FKBP51 lower the binding affinity of GR for glucocorticoids leading to GR resistance, as seen in squirrel monkeys and New World primates [14,18]. Therefore, the Hsp90/FKBP51 complex serves as a short, negative feedback regulator of GR signalling by diminishing GR ligand binding affinity (figure 1). This regulation is important to the understanding of several affective diseases, since these disorders have been associated with both increased and decreased GR sensitivity along with changes in basal and stimulated cortisol levels.

(b) FKBP51: stress, epigenetic and genetic regulation

Here we discuss how dysregulation of the Hsp90/FKBP51 heterocomplex may increase the susceptibility to developing psychiatric disorders. Variations in the function of this chaperone complex can be caused by changes in *FKBP5* levels due to genetic, epigenetic and environmental factors. In fact, several studies have demonstrated that the interaction of stress with *FKBP5* single nucleotide polymorphisms (SNP), such as rs1360780, increases the risk for developing PTSD (see [19] for review). Additionally, this allelic variant (rs1360780) has been shown to increase FKBP5 expression through decreased DNA methylation [20,21], which can also lead to GR resistance [22]. Similarly, other *FKBP5* allelic variations have been linked to several mental disorders such as anxiety, depression and schizophrenia [23–28] (figure 2). This suggests that, in addition to environmental factors such as stress, our genetic predisposition may alter our neurophysiology including biochemical processes, brain connectivity and gene expression (figure 3).

FKBP5 DNA methylation is a dynamic process. It is well-documented that stress exposure can induce epigenetic changes, such as alterations in DNA methylation. DNA methylation consists in transferring a methyl group onto a CpG site (or CG-rich region), which can affect gene transcription and expression [29]. Studies in tissue from human and mouse brains demonstrate that *FKBP5* DNA methylation is inversely correlated with FKBP51 expression [20,30–32]. Altered FKBP51 expression is significant since FKBP51 competes with other TPR-containing proteins for the same binding site on Hsp90. Since FKBP51 is one of the strongest-binding Hsp90 co-chaperones [33], imbalances in FKBP51 expression can lead to dramatic alterations in Hsp90 activity, client selection and the fate of client proteins that are dependent on Hsp90 interactions and regulation [32]. Taken together, epigenetic changes, in tandem with or in addition to functional genetic variants, can provide mechanisms to regulate *FKBP5* gene expression. This suggests that individual differences in basal or stress-induced *FKBP5* expression could affect one's resiliency to stress-related psychiatric disorders [34–37]. Understanding the interplay between genetic predisposition and environmental factors in the development of stress-related disorders may facilitate individualized treatment for these patients.

3. Risk for psychiatric disorders

(a) Depression

Depression is a polysymptomatic disorder, with presentations varying by individual but often including nervousness,

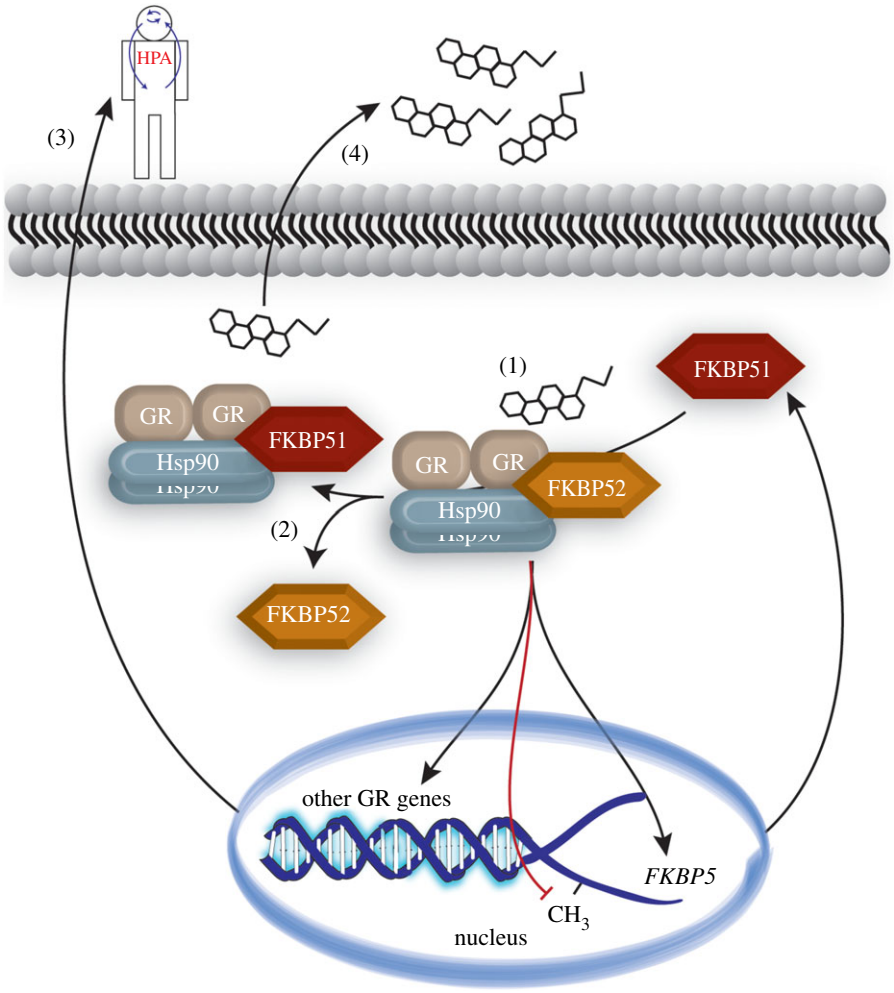

Figure 1. Overall regulation of *FKBP5* expression by GR following stress. (1) Stress produces CORT, which binds to GR, activating the GR/Hsp90/FKBP52 heterocomplex. GR forms a homodimer and translocates to the nucleus where it binds the GRE in the promoter region. This leads to reduced *FKBP5* methylation and increased FKBP51 production. (2) Increased FKBP51 outcompetes FKBP52 and decreases affinity of GR/Hsp90 for CORT and prevents GR translocation. (3) Impaired feedback inhibition of HPA axis. (4) Decreased CORT use by GR/Hsp90 leads to higher circulating CORT levels (hypercortisolemia). CORT = cortisol or corticosterone; FKBP51 = FK506 binding protein 51; FKBP52 = FK506 binding protein 52; GR = glucocorticoid receptor; Hsp90 = 90 kDa heat shock protein; HPA = hypothalamic–pituitary–adrenal axis; CH_3 = methyl group. (Online version in colour.)

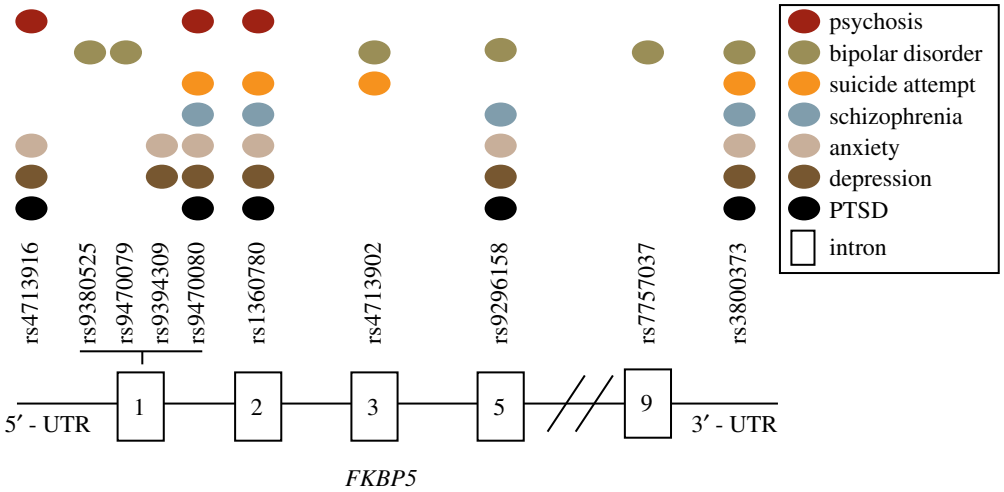

Figure 2. Schematic overview of the *FKBP5* single nucleotide polymorphisms (SNPs) and their association with mental health disorders. As represented, there is a genetic overlap between mental health disorders. Four *FKBP5* SNPs (rs9470080, rs1360780, rs9296158, rs3800373) are significantly associated with at least five diseases. Most of these SNPs have been reported in bipolar disorder, anxiety, depression and PTSD. Introns are represented by rectangles. (Online version in colour.)

irritability, sleep problems and decreased energy [38,39]. Each of these symptoms has been linked to a physiological response to stress through cortisol regulation [40,41]. *FKBP5* SNPs interact with childhood abuse to increase risk for major depression or depressive symptoms [42–44]. This increased risk may be mediated by changes in limbic circuit structure

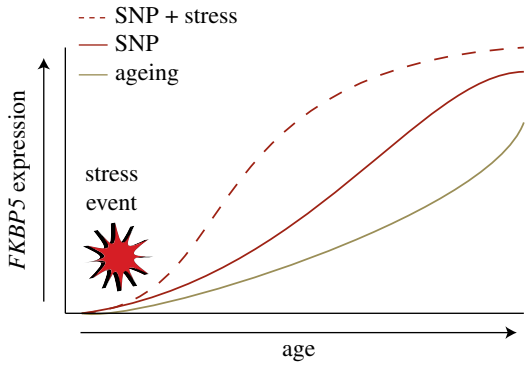

Figure 3. Graphic representation of how SNPS and stress regulate *FKBP5* expression through ageing. Along with ageing, common variants of the *FKBP5* gene are known to increase expression of *FKBP5*. These SNPs and their interaction with environmental factors (ex. stress event) are associated with augmented *FKBP5* expression leading to a higher risk of developing psychiatric disorders. (Online version in colour.)

and function observed with *FKBP5* genotypes. In support of this, altered brain activity was measured by functional magnetic resonance imaging (fMRI) during an attentional focus task in patients with major depression who carry the T risk allele of the *FKBP5* SNP rs1360780 [42]. Additionally, risk SNP carriers with major depression presented with reduced *FKBP5* DNA methylation as well as reduced grey matter volume in the prefrontal cortex [45].

There is also evidence that suggests that these genetic, neurophysiological and neuroanatomical changes can impact the efficacy of current antidepressant therapeutics. For example, the rs1360780 risk allele was correlated with increased FKBP51 protein in lymphocytes, more depressive episodes and faster responses to antidepressants [21,46]. Other researchers found the rs4713916 risk allele (A compared to G) positively correlates with better antidepressant treatment [46]. In another study, levels of *FKBP5* were found to be lower in patients who responded favourably to antidepressant treatment [47]. Since FKBP51 operates in several adaptive feedback loops, it is difficult to draw conclusions about the meaning of altered *FKBP5* mRNA levels in these studies. Studies in mammalian cells, which were correlated to antidepressant response in human ex vivo cell culture models, suggest that this response is regulated through the levels of FKBP51 altering autophagy activation [48,49]. Taken together, these studies demonstrate that *FKBP5* expression can regulate response to antidepressants; however, additional clinical studies are needed to further understand the role of FKBP51 in the clinical manifestation of anxiety and depressive disorders.

(b) Post-traumatic stress disorder

PTSD is characterized by flashbacks of traumatic events, increased arousal or startle state, evasion of places and people, and a decline in cognitive and emotional functions [50]. Patients with PTSD have been shown to exhibit low basal levels of cortisol and enhanced cortisol suppression following dexamethasone (DEX) [34,51,52]. Interestingly, patients with PTSD displayed increased GR protein levels in peripheral lymphocytes without changes in other GR signalling regulators like Hsp90 [53,54]. However, another study reported unchanged cortisol and HPA function in patients with PTSD [55]. This inconsistency may be attributed to factors such as type of trauma, number of individuals in the study, comorbidity with other illness or genetic predisposition.

It is important to mention that even though most people will experience a traumatic situation in their lives, only some will develop PTSD [55]. Current exposure therapy and pharmacological interventions can alleviate some PTSD symptoms [56], but, similar to depression, these therapies have not been effective for all PTSD patients [34]. Some differences in 'resiliency' have been attributed to the interaction between *FKBP5* variants or expression differences and environmental factors [57,58]. An increased number of studies highlight the influence of *FKBP5* SNPs and their interaction with stressful environments as a risk factor for the development of PTSD. Additionally, Mehta and colleagues observed an increase in GR sensitivity only in PTSD carriers of *FKBP5* SNP, rs9296158 [59]. In general, four SNPs in *FKBP5* have been associated with child abuse severity and increased risk to develop PTSD in adulthood [26,60]. Moreover, Watkins *et al*. reported that child abuse coupled with distinct *FKBP5* SNPs significantly correlated with a higher PTSD symptom severity in a sample of European-American U.S. military veterans [61]. Another study duplicated this association in African-Americans but not in European-Americans [62]. Taken together, this suggests that the effect of *FKBP5* on PTSD risk may be influenced by other factors such as context-specific trauma.

(c) Anxiety

Similar to depression, anxiety disorders can present with a variety of symptoms including nervousness, irritability, sleep problems and decreased energy [38]. Despite these commonalities, the role of *FKBP5* in the development and heritability of anxiety disorders has gone largely unexplored in the patient population. Recently, however, *FKBP5* polymorphisms were associated with increased risk of anxiety in patients with cancer [35]. Since other studies have failed to link *FKBP5* variants with anxiety [63–65], this suggests that *FKBP5* may specifically affect stress-induced anxiety.

To elucidate the potential roles for *FKBP5* in anxiety disorders, we must examine the literature pertaining to the extensive studies conducted in animal models. Recent studies in rodent models have provided supporting evidence and further insight into the role of *FKBP5* in psychiatric disease (table 1). Many studies have demonstrated that anxiety is controlled by the amygdala [77–79]. Although a global knockout of *FKBP5* in mice did not alter anxiety-like behaviour under basal [36] and stress conditions [72,80], selectively reducing FKBP51 in the amygdala with viral vectors reduces stress-induced anxiety-like behaviours in mice [75]. Similarly, pharmacological disruption of FKBP51 signalling locally in the amygdala also produces an anxiolytic effect [69]. In support of this, viral-mediated overexpression of FKBP51 in the basolateral or central amygdala enhanced anxiety-like behaviour [69]. In contrast, anxiety was not altered by overexpressing FKBP51 in the dorsal hippocampus of mice [69] or by knocking down *FKBP5* in the prelimbic cortex of rats [76]. The region-specific influence of FKBP51 in the amygdala is critical for anxiety regulation. In fact, stress-related mechanisms have also been shown to modulate FKBP51 in the amygdala. One study found that chronic stress increases amygdalar FKBP51 in mice through a mechanism involving neuropsin-mediated cleavage of the tyrosine receptor kinase, EphB2 [75]. A more recent study found that microRNA-15a inhibits

Table 1. Summary of rodent studies manipulating FKBP51 expression. Affected brain structures and behavioural observations are described according to the stress model or molecular manipulation performed. FKBP51 = FK506 binding protein 51; CORT = corticosterone; DEX = dexamethasone; CA1 = Cornu Ammonis 1; DG = dentate gyrus; PVN = paraventricular nucleus; CeA = central amygdala; CSDS = chronic social defeat stress; CMS = chronic mild stress; HPA = hypothalamic–pituitary–adrenal axis; KO, knock-out; SAFit2 = selective antagonist of FKBP51 by induced fit; shRNA, short hairpin RNA; IL = infralimbic cortex; Increase (↑) or decrease (↓) FKBP51 levels or activity. (Online version in colour.)

manipulation/stress model	FKBP51 levels/ activity	brain region affected	rodent	behavioural outcome	references
CORT/DEX	↑	hippocampus (CA1 and DG), PVN, and CeA	mice	—	[66]
restrained stress and food deprivation	↑	PVN and CeA	mice	—	[66]
food deprivation	↑	hippocampus	mice	—	[66]
CSDS	↑	—	mice	resilient phenotype in response to CSDS	[67]
CMS	↑	increased mRNA expression in ventral hippocampus and prefrontal cortex. — *effect reverted by duloxetine*	rat	—	[68]
FKBP5-virus	↑	increased expression in amygdala	mice	increased anxiety	[69]
FKBP51 KO +aging	↓	all	mice	— resilience from anxiety and depressive-like behaviour	[70]
			mice	— enhanced cognitive flexibility in a reversal paradigm	[71]
FKBP51 KO +15-min restraint stressor	↓	all	mice	— increased active stress coping behaviour (measured in the forced swim test) — reduced HPA activity	[72]
FKBP51 KO *female KO mice*	↓	all	mice	— reduced HPA activity and no response to acute stress	[73]
SAFit2 (FKBP51 antagonist)	↓	amygdala and intraperitoneal injections	mice	reduced anxiety-related behaviour	[69]
SAFit2 (FKBP51 antagonist)	↓	intraperitoneal injection	mice	active stress-coping behaviour (measured in force swim test)	[74]
FKBP5-shRNA	↓	amygdala (infusion)	mice	enhanced resilience to restraint stress exposure (reducing anxiety)	[75]
FKBP5-shRNA	↓	infralimbic and prelimbic (infusion)	rat	enhanced resiliency to fear learning only in IL infused rats	[76]

amygdalar FKBP51 expression, which reduced anxiety levels in mice [81]. They also found that selectively reducing amygdalar microRNA-15a increased FKBP51 and anxiety-like behaviour in a chronic stress paradigm. Besides anxiety, FKBP51 can also modulate stress resiliency in rodents. *FKBP5*$^{-/-}$ mice have been shown to be more resilient to the effects of various stress paradigms compared to wild-type littermates [72,73,80]. Moreover, *FKBP5* knockout mice have lower HPA activity and reduced changes in sleep, demonstrating a pro-resilience sleep phenotype that is a common symptom in anxiety disorders [82]. While relating these results to humans can be difficult, the data demonstrate that FKBP51 has a clear role in regulating stress response and risk of phenotypes in animal models, reminiscent of the role of FKBP51 in human affective disorders.

(d) Other *FKBP5* risk SNPs and altered protein expression

Common *FKBP5* SNPs have also been shown to increase risk for schizophrenia [28], bipolar disorder [83], suicide attempt

[84] and psychosis [85]. Many of these SNPs alter *FKBP*5 expression and are risk factors for more than one of these disorders (figure 2). Increased *FKBP5* expression was found in the prefrontal cortex of patients diagnosed with schizophrenia [28] and bipolar disorder [86]. Additionally, *FKBP5* expression was found to be increased in the medial temporal and frontal gyrus in patients with Alzheimer's disease [32] and autism spectrum disorders [87]. Inversely, *FKBP5* expression was shown to be reduced in the amygdala of post-mortem brains from suicide victims [88]. More studies need to be done to understand the mechanism underlying these *FKBP5* expression changes and how this change in FKBP51 levels effects disease onset and/or progression.

Closely linked to *FKBP5* expression, *FKBP5* DNA methylation has been shown to be altered following prenatal and postnatal stress. In fact, a recent study showed that prenatal maternal stress induced methylation changes in genes regulating the HPA axis [89]. Although they assessed a small number of participants (24 newborn–mother dyads), *FKBP5* cg03546163 methylation was higher in placenta and maternal blood in the traumatized group. In line with this study, Paquette and colleagues investigated whether placental *FKBP5* methylation changes could alter fetal neurodevelopment related to HPA dysregulation. They found that higher methylation in *FKBP5* intron 7 was associated with greater infant motor activity [90]. These results are consistent with the hyperarousal associated in PTSD [91] and suggest *FKBP5* may regulate vigilance. Methylation changes were also observed in a recent study including 174 ethnically diverse children who were exposed to physical or emotional maltreatment. In comparison to controls, children who reported moderate or severe maltreatment also showed lower levels of *FKBP5* methylation at the two regulatory regions in intron 7 [92]. Similar alterations in *FKBP5* DNA methylation have also been associated with preterm birth. *FKBP5* DNA methylation was lower in preterm infants compared to term equivalent-age infants [93]. This decreased methylation was restored to normal levels by 1 year of age. Additional studies are necessary to evaluate if these alterations increase any risk long-term. Just recently, the interaction of *FKBP5* risk SNPs with early life stress in preterm infants was investigated. This study revealed that risk SNPs, combined with the stress in the neonatal intensive care unit, increased risk for neurodevelopmental impairments [94]. Additional studies are needed to both confirm these associations and to evaluate the longitudinal effects of this interaction.

4. FKBP51: a potential biomarker and therapeutic target for mental health disorders

The use of FKBP51 levels as a potential biomarker to predict clinical outcomes and risk for neuropsychiatric disorders is currently being investigated. Since expression of *FKBP5* in neural tissues is practically impossible to determine in living patients, peripheral correlates are being examined. In mice, *FKBP5* methylation in whole blood and the brain was positively correlated following chronic stress [30,31], but whether this correlation translates to humans with peripheral expression or epigenetic changes has not been determined. However, in human studies, FKBP51 levels were found to be significantly higher in lymphocytes in depressed individuals with common *FKBP5* SNPs. These changes correlated with faster antidepressant responses, but more frequent depressive episodes [21]. Another study showed that *FKBP5* expression was significantly decreased in whole blood from patients with PTSD [34]. So, while alterations in *FKBP5* have been identified in peripheral tissue of humans with mood disorders, to understand the relevance of *FKBP5* as a biomarker, more studies need to be performed to understand the relationship between FKBP51 levels in the periphery and the brain and how this relates to risk, progression and treatment outcomes of neuropsychiatric disease.

Since high expression of FKBP51 has been linked to increased susceptibility to develop mood disorders, decreasing FKBP51 levels or activity may be beneficial in preventing or treating these neuropsychiatric disorders. This has been supported in several independent preclinical studies. *FKBP5*$^{-/-}$ mice are not only viable, they are resilient to depressive-like behaviours when compared to wild-type littermates, without affecting cognition or locomotor functions [70,72,80]. Thus, it has been proposed that inhibition of FKBP51 activity or expression could be advantageous in stress-related and depressive disorders. However, since FKBP51 is highly homologous to other FKBP proteins, like FKBP52, developing treatments with selectivity for FKBP51 has been difficult [74]. Targeting FKBP52 could be detrimental, since ablating FKBP52 in mice resulted in male infertility, increased stress sensitivity and affected neuroendocrine response [95]. Recently, a selective FKBP51 antagonist was developed by induced fit. This antagonist, SAFit2, has higher selectivity for FKBP51 than FKBP52 and was shown to enhance neuronal cell and stress-coping behaviour [69,74]. While these developments are promising, additional studies are needed to better characterize SAFit2 and to identify alternative therapeutic interventions that can specifically regulate FKBP51 activity or levels.

5. Limitation of studies and concluding remarks

Despite the increasing number of studies examining the role of glucocorticoids and FKBP51 in various CNS disorders, we should be aware of the limitations that each study presents. Some limitations are: (i) lack of longitudinal assessments; (ii) inclusion of patients with multiple medications; (iii) limited number of patients causing low-powered statistical analyses; (iv) limited information about environmental factors through lifespan; (v) variations in type of assessments (e.g. self-reported versus clinician administrated); (vi) absence of formal meta-analysis; (vii) not including sex as a biological variable. In the case of PTSD, some studies are limited by variations in the years after trauma, type of trauma (war veterans versus childhood abuse) and type of controls (trauma-exposed versus general population).

One of the major limitations in current studies is the high comorbidity presented among patients. For example, at least half of the patients suffering from PTSD have also been diagnosed with depression [96]. This is because both stress-related diseases have overlapping symptoms and risk factors (childhood adversity and abuse) [44,97]. Different approaches like functional neuroimaging, HPA function assays and identification of genetic markers may allow us to distinguish differences. In line with this, GR signalling and *FKBP5* genotypes also differ between these disorders.

Although more studies are needed to understand the mechanism by which *FKBP5* alters the risk of numerous disorders, *FKBP5* may be beneficial as a biomarker for increased

risk to stress and trauma exposure. By combining genetic, epigenetic and transcriptional measures, we may gain a more thorough understanding of the role of *FKBP5* in affective disorders. This knowledge may be beneficial for diagnosing and treating patients suffering from these disorders.

Data accessibility. This article has no additional data.

Competing interests. The authors have no competing interests to declare.

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