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COMMENTARY

Time-dependent effect of FKBP12 loss in the development of dilated cardiomyopathy

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Introduction

The work being commented on: the ryanodine receptor type II (RyR2) is a homotetrameric Ca^{2+} channel that is essential for excitation–contraction (EC) coupling in cardiomyocytes. Embedded in the sarcoplasmic reticulum (SR) membrane, RyR2 releases SR Ca^{2+} in response to binding cytosolic Ca^{2+} following influx via the L-type Ca^{2+} channel. This mechanism is known as Ca^{2+}-induced Ca^{2+} release (CICR), which provides the Ca^{2+} required for cardiac contraction (Bers, 2002). Numerous studies have demonstrated that changes in RyR2-mediated Ca^{2+} release influence cardiac function. The large size of RyR2 (~2.2 MDa) provides the ability for many proteins to interact with the channel to regulate Ca^{2+} release, including FK506-binding proteins (FKBPs) (Brillantes et al., 1994).

Within mammalian cardiomyocytes, two isoforms of FKBPs are expressed: FKBP12 and FKBP12.6 (also called calstabin-1 and -2, respectively). These ~12 kDa binding proteins interact directly with the RyR2 tetramer subunits, meaning each RyR2 channel can have up to four FKBP12/12.6 molecules bound (Timerman et al., 1996). It was originally believed that only FKBP12.6 was capable of binding to cardiac RyR2; however, it is now accepted that both isoforms demonstrate this property with competitive binding between isoforms being suggested (Gonano and Jones, 2017). Whilst there is ~85% homogeneity between the two isoforms (Deivanayagam et al., 2000), their binding affinity and expression differ in cardiomyocytes. FKBP12.6 has a higher binding affinity for RyR2 compared with FKBP12; however, only ~20% of RyR2 is reportedly bound by FKBP12.6 (Guo et al., 2010). This disparity is thought to be due to the higher expression of FKBP12 in cardiomyocytes compared with FKBP12.6 (Timerman et al., 1996).

In cardiac disease, RyR2 becomes dysfunctional and exhibits pathological Ca^{2+} release, which occurs in the absence of Ca^{2+} influx. This is known as spontaneous Ca^{2+} release or Ca^{2+} leak, and is associated with arrhythmogenesis and impaired cardiac contractility (Jones et al., 2008). Several studies report that in addition to pathological Ca^{2+} release via RyR2, failing and arrhythmic hearts also demonstrate reduced RyR2-FKBP12.6 binding (Marx et al., 2000; Yano et al., 2000; Wehrens et al., 2003). Mutation of the FKBP binding site on RyR2 has also been shown to promote Ca^{2+} leak and induce cellular arrhythmogenesis, highlighting the importance of these proteins in modulating RyR2 activity (Fernández-Morales et al., 2022). Despite the proven association of FKBP12 with RyR2, research on the impact of this isoform in the heart is less available compared with FKBP12.6 studies. In this issue of *JGP*, Hanna et al. (2025) investigated the role of cardiac FKBP12 by comparing transgenic mice with differentially regulated expression of the protein. Utilizing tissue-specific knockout in mice, they were able to systematically characterize and compare the long-term effect of cardiac FKBP12 deficiency from different stages of embryonic development.

Models of cardiac FKBP12 deficiency

Although the impact of FKBP12 loss in the heart has been explored for over 25 years, there remains debate as to the underlying mechanisms of associated pathological consequences. Global FKBP12-knockout results in lethality during late embryonic development or shortly after birth in mice (Shou et al., 1998). This is associated with significant structural abnormalities in the heart characteristic of dilated cardiomyopathy (DCM), with dilation and thinning of the ventricles, as well as altered trabeculation and septal defects. In adult mice, chemically induced global FKBP12 knockdown (using proteolysis-targeting chimeras; PROTACs) leads to the development of cardiac hypertrophy and functional impairment (Sun et al., 2019). However, it has been questioned whether it is FKBP12 loss from the cardiomyocytes or other cell types that is responsible for these effects (Chen et al., 2013; Maruyama et al., 2011; Tang et al., 2004).

Maruyama et al. (2011) generated mice with cardiomyocyte-specific conditional knockout of FKBP12 (driven by the α-myosin heavy chain [αMHC] promoter), which demonstrated no change in gross cardiac structure or function. However, alterations in

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cardiac conduction were reported (Maruyama et al., 2011). In this *JGP* issue, Hanna et al. (2025) utilized an independently developed αMHC-conditional FKBP12 knockout mouse, which demonstrated the structural and functional hallmarks of DCM pathogenesis. This discrepancy in phenotype development may in part be attributed to differences in the sex and age of the adult mice investigated between the two studies. Hanna et al. (2025) report differences in the severity of phenotype development between sexes, which warrants further investigation. It has also been suggested that the background strain used for developing FKBP-transgenic mice influences the observed phenotype (Gonano and Jones, 2017). To further elucidate the role of FKBP12 deficiency in cardiac pathogenesis, Hanna et al. (2025) characterized this latter cardiac FKBP12-deficient mouse model (MHC-FKD) alongside mice with conditional muscle creatine kinase (MCK)-driven FKBP12 knockdown (MCK-FKD). These two promoters enabled the generation of mice with knockout of FKBP12 expression in cardiomyocytes from embryonic day E9 or E13.5, respectively. This resulted in the progressive loss of FKBP12 in the adult heart, with up to ∼90% reduction in protein expression seen at 6 mo of age in male mice of both genotypes (Hanna et al, 2025). Despite a similar extent of protein loss in the adult heart, the two mouse models demonstrated divergence in the resulting phenotype from 3 mo of age (Fig. 1), revealing new insights into the role of developmental FKBP12 deficiency in cardiac pathogenesis.

The time-dependence of FKBP12 expression during cardiac development

FKBP12 expression is high throughout the heart during mammalian embryonic development, particularly in the endocardium, myocardium, and septum (Shou et al., 1998). FKBP12 mRNA is also abundant in chick embryos (particularly in the heart) but progressively declines with development (Obata et al., 2001). Unlike FKBP12-null mice, cardiac-specific FKBP12 deficient mice survived past embryonic development, through to adulthood. Mice with reduced cardiac FKBP12 expression from embryonic day E9 showed significant left ventricular dilation at birth, which persisted into adulthood (Hanna et al, 2025). This was accompanied by impaired cardiac function with reduced ejection fraction and fractional shortening in adult mice. However, as discussed above, this was not observed by others using a similar mouse model, despite the presence of conduction disturbances and the occurrence of sudden cardiac death (Maruyama et al., 2011). Interestingly, apart from subtle thickening of the anterior left ventricle wall at 3 mo, the hearts of MCK-FKD mice appeared structurally normal up to 6 mo of age (Hanna et al, 2025). This was coupled with an absence of functional impairment, despite significant FKBP12 deficiency from embryonic day E13.5 (Hanna et al, 2025). This suggests that normal development of the mouse heart is dependent on FKBP12 expression up to at least embryonic day E9, but not from day E13.5 onwards.

A critical role for FKBP12 during chick cardiac development has also been identified, with Obata et al. (2001) previously demonstrating that artificial reduction of FKBP12 mRNA using the immunosuppressant FK506 in the developing chick has a time-dependent effect. Early disruption of FKBP12 expression in 5-day-old embryos led to complete lethality, while FK506 administration at 7–9 days resulted in embryos that developed enlarged, dilated hearts with cardiac failure, indicative of DCM pathogenesis. However, 11-day-old chick embryos demonstrated normal development following artificial FKBP12 reduction (Obata et al., 2001). While it should be noted that the technique utilized to reduce FKBP12 expression in this study would also regulate FKB12.6, it has been reported that FKBP12.6 isoform expression begins later than FKBP12 during embryonic development (Yazawa et al., 2003). Combined with the findings from Hanna et al. (2025), this reveals a time-critical window for FKBP12 expression during early embryonic development, with functional consequences apparent in the adult heart.

Mechanisms of RyR2 regulation in FKBP12-deficient mice

There has been a long-standing debate surrounding how FKBP12 modulates RyR2 activity. While FKBP12-null mice show an increase in the subconductance state of RyR2 (Shou et al., 1998), the literature is divided on whether FKBP12 inhibits, activates, or has no effect on the cardiac channel. Research from Marks and colleagues suggested that FKBPs stabilize RyR2 (or RyR1) in its closed state, thereby reducing the occurrence of Ca^{2+} leak (Brillantes et al., 1994; Miotto et al., 2024). Subsequent studies oppose this theory, as others have not been able to reproduce these findings, with some suggesting FKBPs regulate the termination, but not activation, of Ca^{2+} release (Zhang et al., 2016). More recent single-channel studies indicate that FKBP12 has a biphasic effect on RyR2, increasing channel activity at low concentrations and inhibiting activity at high concentrations, suggesting negative cooperativity (Richardson et al., 2023; Galfré et al., 2012).

Whole-heart remodeling in MHC-FKD mice was associated with unaltered transients but an increased occurrence of proarrhythmic RyR2 activity in isolated cardiomyocytes, in the form of both Ca^{2+} sparks and waves (Hanna et al, 2025). Additional analyses further confirmed that this is unlikely to be due to SR store-overload, but rather via direct modulation of RyR2 channel open probability. However, despite a comparable level of FKBP12 deficiency in the adult heart, MCK-FKD mice do not display the same propensity for Ca^{2+} leak as MHC-FKD mice (Hanna et al, 2025). This indicates that reduced FKBP12 expression in the adult heart alone cannot explain this observation. One of the most widely investigated mechanisms linking FKBPs to channel regulation is RyR2 phosphorylation. Several groups suggest this modification promotes the dissociation of FKBP from RyR2, which results in channel destabilization; however, this mechanism has been disputed by others (for review see Gonano and Jones [2017]). Regardless, Hanna et al. (2025) report no changes in total RyR2 expression, nor in the degree of channel phosphorylation by protein kinase A (PKA) at site S2807, or by striated muscle-preferentially expressed kinase (SPEG; sites S2367/8) in their mouse models. Combined with FKBP12 expression data, this suggests that the extent of residual FKBP12-RyR2 binding is similar between FKD genotypes, although this was not directly assessed. One consideration is whether compensatory upregulation of FKBP12.6 expression occurs in

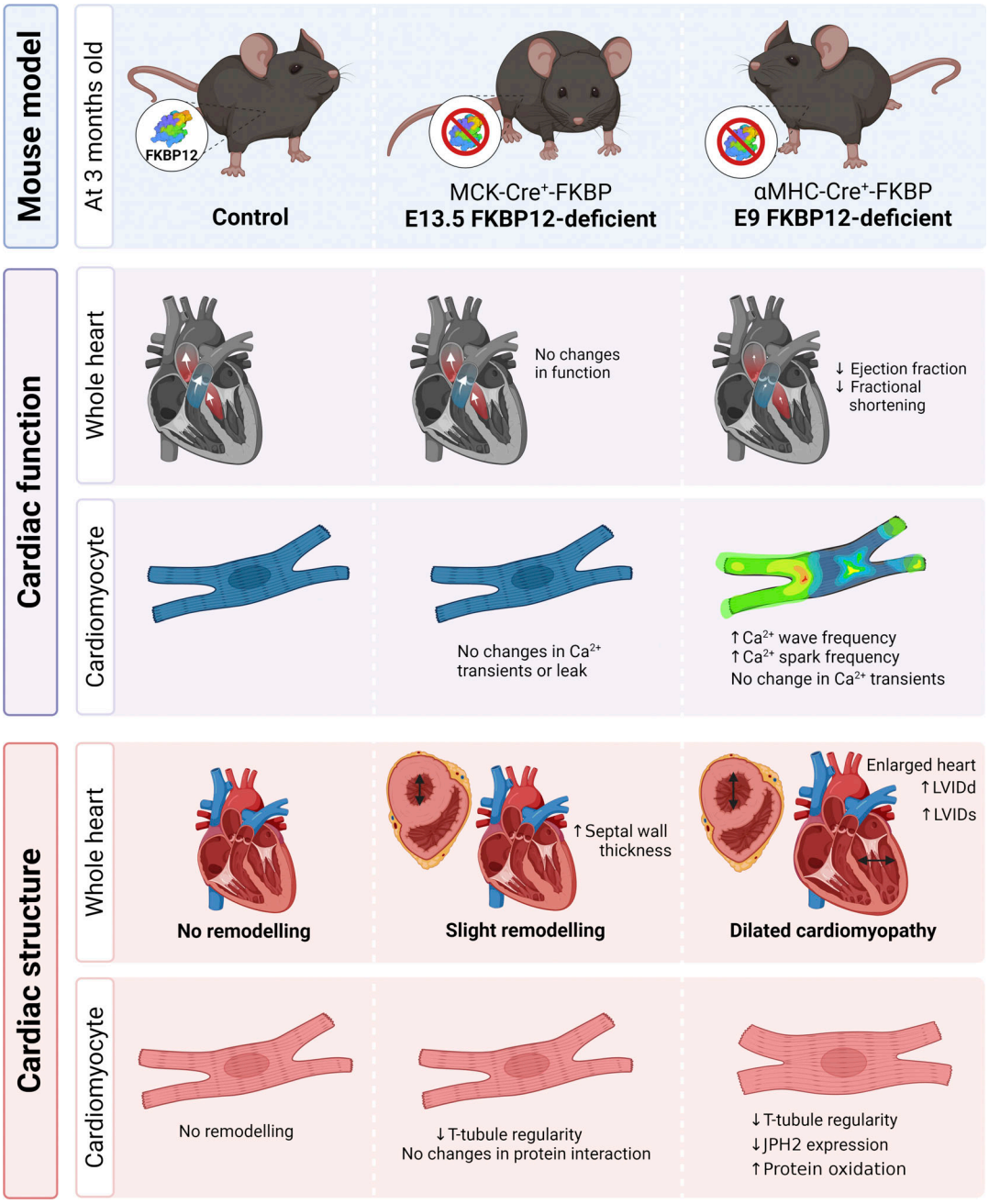

Figure 1. **Comparison of the impact of early or late developmental cardiac FKBP12 deficiency in the adult mouse heart.** Comparison of control, MCK-FKBP, and αMHC-FKBP-deficient mice and the alterations in cardiac structure and function observed at a whole heart and cardiomyocyte level at 3 mo of age. Findings from Hanna et al. (2025) illustrate that FKBP12 expression is crucial at embryonic day E9 as cardiac structure and function are altered in the αMHC-FKBP-deficient mice. These notable cardiac changes are absent in MCK-FKBP-deficient mice lacking FKBP12 expression from embryonic day E13.5. Created with BioRender.

response to cardiac FKBP12 deficiency. However, findings from Hanna et al. (2025) suggest this is not the case.

In contrast, overall protein oxidation is increased in MHC-FKD mice (Hanna et al, 2025). While oxidation of RyR2 has been reported to enhance Ca^{2+} leak (Waddell et al., 2016; Terentyev et al., 2008), the degree of redox modification on the channel itself in MHC-FKD mice is unclear. Previous work has also demonstrated the arrangement of RyR2 tetramers into clusters to modulate channel activity, with FKBPs and phosphorylation both influencing the structural properties of clusters. Increased FKBP12 (or 12.6) levels promote the formation of tighter clusters, which reduces Ca^{2+} leak due to steric hindrance of neighboring channels (Asghari et al., 2020). This suggests the converse would occur in settings of FKBP loss. Given the similar protein expression and phosphorylation reported between FKBP-deficient mouse strains, it is unlikely that this mechanism underlies the enhanced Ca^{2+} leak in MHC-FKD mice (Hanna et al, 2025). However, the role of oxidative modification on RyR2

regulation has yet to be explored in the context of cluster organization and may provide further insights (Waddell et al., 2023).

Hanna et al. (2025) also report a reduction in full-length junctophilin-2 (JPH2) and an increase in the cleaved JPH2 peptide fragment in MHC-FKD, but not MCK-FKD mice. JPH2 is important for the formation of the dyadic space and transverse (t-) tubules—structures that are critical for EC coupling (Takeshima et al., 2000). Consequently, t-tubule disruption is associated with increased Ca^{2+} leak and impaired cardiac function. Reduced t-tubule regularity is observed in MHC-FKD mice in agreement with this mechanism; however, similar disruption was also reported in MCK-FKD mice, despite the absence of functional impairment (Hanna et al, 2025). Interestingly, JPH2 is also implicated in regulating RyR2 channel activity via direct association and cluster formation (Munro et al., 2016; Beavers et al., 2013), suggesting an alternative mechanism for the involvement of JPH2 in DCM pathogenesis in MHC-FKD mice. However, whether JPH2 cleavage or RyR2 dysfunction occurs first is unclear. Of note, JPH2- or RyR2-null mice demonstrate embryonic lethality at days ~E9–11, overlapping with the window of developmental FKBP12 deficiency explored by Hanna et al. (2025) (Takeshima et al., 2000; Takeshima et al., 1998). This provides evidence that there is potential interplay between these proteins during this critical period of cardiac development.

Conclusion

Cardiac FKBP12 expression is essential during the early stages of embryonic development. Developmental cardiac deficiency of FKBP12 leads to pathological alterations in cardiac structure, Ca^{2+} handling, and contractile function, which persist into adulthood. This occurs despite the absence of traditional mechanistic changes known to regulate RyR2 activity, suggesting that further investigation into this developmental window is needed to understand DCM pathogenesis.

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