FK506-binding proteins as emerging bridges linking proteostasis to multi-system pathogenesis and therapeutic strategies (Review)

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Abstract. Protein homeostasis, or proteostasis, refers to the integrated quality control systems that regulate protein synthesis, folding, post-translational modification, trafficking and degradation to maintain proteome stability and function. Disruption of these processes, including abnormal synthesis, misfolding or impaired degradation, results in proteostasis collapse and underlies the pathogenesis of cancer, neurodegeneration, cardiovascular disease and metabolic syndromes. Recent studies have highlighted FK506-binding proteins (FKBPs), a family of immunophilins defined by a conserved peptidyl-prolyl cis-trans isomerase domain, as pivotal modulators of proteostasis. By modulating protein folding, stabilizing complexes, regulating endoplasmic reticulum stress and directing selective degradation, FKBPs establish direct links between proteostasis regulation and disease progression. This review presents the first comprehensive synthesis of FKBP-mediated control of proteostasis across diverse clinical contexts. It analyzed how their structural features confer regulatory potential and elucidate their roles in proteome remodeling in cancer, pathogenic protein aggregation in neurodegenerative disorders, ion channel stabilization in cardiovascular dysfunction and kinase phosphorylation in metabolic regulation. By integrating these diverse actions within a unified proteostasis framework, FKBPs are proposed as versatile regulators and promising therapeutic targets, providing new perspectives on the proteostasis-disease axis and opportunities for precision intervention across multiple organ systems.

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Abbreviations: AD, Alzheimer's disease; AF, atrial fibrillation; AKT, protein kinase B; AMPK, AMP-activated protein kinase; AR, androgen receptor; ASO, antisense oligonucleotide; BiP, binding immunoglobulin protein; CAF, cancer-associated fibroblast; CaMKII, calcium/calmodulin-dependent protein kinase II; CRC, colorectal cancer; ER, endoplasmic reticulum; FKBP, FK506-binding protein; HF, heart failure; Hsp90, heat shock protein 90; mTORC1, mechanistic target of rapamycin complex 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NSCLC, non-small cell lung cancer; PD, Parkinson's disease; PPIase, peptidyl-prolyl cis-trans isomerase; PROTAC, proteolysis targeting chimera; PTM, post-translational modification; ROS, reactive oxygen species; RyR2, ryanodine receptor 2; Ub, ubiquitin; UPR, unfolded protein response

Key words: proteostasis, FK506-binding proteins, neurodegenerative diseases, cancer, cardiovascular diseases, metabolic dysregulation

Contents

1. Introduction

Proteins are fundamental components of cells and form the essential material basis for sustaining and regulating life processes. Disturbances in protein abundance, folding, function or localization can disrupt physiological homeostasis, underscoring the importance of maintaining protein homeostasis, or proteostasis (1,2). Proteostasis is maintained by a highly coordinated network of quality control mechanisms that regulate protein synthesis, folding, modification, trafficking and degradation, thereby ensuring the stability and functionality of the proteome (3). When this delicate balance

is perturbed by genetic mutations, environmental stress or aging, misfolded and aggregated proteins accumulate, driving proteotoxic stress, organelle dysfunction and, ultimately, disease (4). Proteostasis collapse has been recognized as a unifying driver of diverse human disorders, including neurodegenerative diseases, malignancies, cardiovascular dysfunction and metabolic syndromes.

Against this backdrop, FK506-binding proteins (FKBPs) have emerged as particularly intriguing regulators of proteostasis. FKBPs are members of the immunophilin family, which also comprises cyclophilins that share conserved peptidyl-prolyl cis-trans isomerase activity but differ in structural domains and functional specialization. Defined by a conserved peptidyl-prolyl cis-trans isomerase (PPIase) domain and diversified by additional modules conferring organelle targeting and chaperone interactions, FKBPs extend far beyond their classical role as immunosuppressant-binding proteins (5-7). Increasing evidence shows that they actively shape proteostasis networks by accelerating conformational maturation, scaffolding protein complexes, modulating stress responses and directing selective degradation, positioning them as key molecular links between proteostasis regulation and disease pathogenesis (8-12).

Despite substantial progress in characterizing individual FKBPs, no review has systematically integrated their diverse roles in proteostasis regulation across multiple disease contexts, yet, to the best of our knowledge. This article provides the first unified framework, linking FKBP structure to proteostatic function and disease relevance. In cancer, FKBPs adjust translation, folding and degradation pathways to sustain the high protein load of malignant cells, driving proteome remodeling and tumor progression (13). In neurodegenerative diseases, FKBPs influence the conformational fate of pathogenic proteins by regulating folding and aggregation processes, thereby determining neuronal survival and function (14). In cardiovascular disease, FKBPs stabilize the conformation of ion channel complexes to preserve calcium signaling homeostasis, ensuring precise cardiac contraction and electrical activity (15). In metabolic regulation, they act as scaffolds to fine-tune kinase phosphorylation, integrating energy sensing with metabolic signaling to maintain systemic balance (16). These functions not only underscore the multifaceted role of FKBPs as central regulators of proteostasis but also establish them as critical bridges linking proteostatic regulation to disease mechanisms. The present study proposes targeting FKBPs as a novel target to correct proteostasis imbalance and halt disease progression, thereby opening new avenues for precision therapies across multiple organ systems.

2. Overview of proteostasis

Proteostasis is the cellular process that maintains a dynamic balance of protein synthesis, folding, modification, trafficking, and degradation, ensuring proteins remain in the proper quantity and functional conformation (8). Its core mechanisms are tightly coordinated. Proteins are synthesized on ribosomes as nascent polypeptides that are often unstable or partially folded, requiring molecular chaperones and foldases for correct folding or assembly into multimeric complexes (Fig. 1A). Before becoming functionally active, many proteins undergo post-translational modifications such as phosphorylation, acetylation, or ubiquitination, which regulate their stability, activity, and interactions (Fig. 1B). Proteins must also be directed with precision to organelles such as the endoplasmic reticulum (ER), mitochondria, or nucleus to execute specific functions. When proteins misfold, become damaged, or accumulate abnormally, two major degradation systems maintain quality control: the ubiquitin-proteasome system (UPS), which removes short-lived and defective proteins, and the autophagy-lysosome pathway (ALP), which clears protein aggregates and damaged organelles. Together, these mechanisms uphold the dynamic equilibrium of the proteome (1,17).

The UPS primarily eliminates short-lived or misfolded monomeric proteins. Substrates are first tagged with ubiquitin chains through a cascade involving E1 activating enzymes, E2 conjugating enzymes and E3 ligases. These ubiquitinated proteins are then directed to the 26S proteasome, where they are unfolded and degraded into short peptides, allowing rapid protein turnover and removal of potentially toxic species (18). In parallel, the ALP is responsible for the clearance of larger substrates, including protein aggregates, damaged organelles and long-lived proteins. During this process, isolation membranes form autophagosomes that engulf the target substrates, which subsequently fuse with lysosomes. Hydrolytic enzymes within the lysosome degrade the contents into amino acids and lipids for cellular reuse (19). Together, UPS and ALP establish an integrated quality control cycle that prevents harmful aggregate accumulation while maintaining metabolic balance (Fig. 1C).

Under conditions of high translational load or environmental stress, large amounts of misfolded or unfolded proteins accumulate in the ER lumen, disturbing folding balance and triggering the unfolded protein response (UPR) (20). The initiation of UPR depends on the molecular chaperone glucose-regulated protein 78/binding immunoglobulin protein (BiP), which serves as a central sensor. Under normal conditions, BiP binds to the three principal ER stress receptors, inositol-requiring enzyme 1α (IRE1α), PKR-like ER kinase (PERK) and activating transcription factor 6 (ATF6), keeping them inactive. When unfolded proteins accumulate, BiP preferentially associates with these substrates and dissociates from the receptors, thereby activating downstream signaling pathways. Activated IRE1α mediates the unconventional splicing of spliced X-box binding protein 1 (XBP1) mRNA, producing the transcription factor XBP1s, which upregulates chaperones, foldases and ER-associated degradation (ERAD) genes to enhance folding and clearance capacity. PERK phosphorylates eIF2α to reduce global translation, while selectively promoting ATF4 translation, which activates antioxidant, autophagy and metabolic pathways. ATF6 is transported to the Golgi apparatus, where proteolytic cleavage releases its cytosolic fragment, which translocates to the nucleus to induce transcription of chaperones and ERAD-related genes (20). Together, these mechanisms restore ER folding and degradation balance under moderate stress, allowing cells to adapt. However, when stress is excessive or persistent, UPR signaling shifts toward apoptosis, e.g. through PERK-ATF4-C/EBP homologous protein (CHOP) induction, thereby converting proteostatic imbalance into pathological

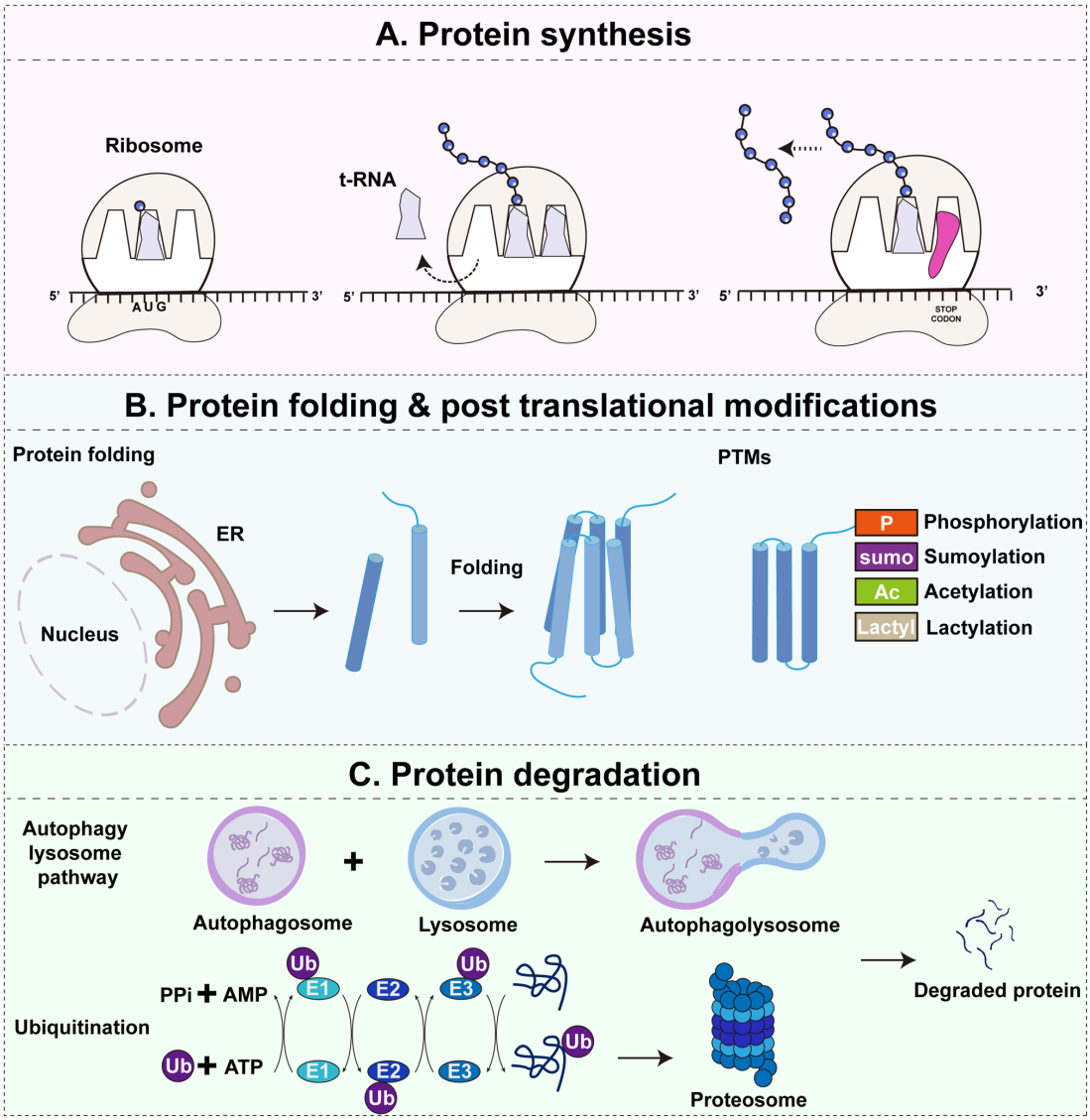

Figure 1. Overview of proteostasis and its core pathways. Proteostasis is maintained through a dynamic balance of protein synthesis, folding and post-translational modifications, and degradation. (A) Protein synthesis. Ribosomes translate mRNA into nascent polypeptide chains, which often require assistance from molecular chaperones and foldases to achieve stable structures. (B) Protein folding and post-translational modifications. Newly synthesized proteins fold in the ER and undergo PTMs, such as phosphorylation, sumoylation, acetylation and lactylation, which regulate protein stability, activity and interactions. (C) Protein degradation. Misfolded, damaged or surplus proteins are eliminated through two major pathways: The UPS, where substrates are sequentially ubiquitinated by E1, E2 and E3 enzymes and degraded by the 26S proteasome into peptides; and the ALP, where cytoplasmic substrates, including protein aggregates and damaged organelles, are sequestered into autophagosomes, fused with lysosomes and degraded into reusable biomolecules. Together, these pathways establish a quality control cycle that preserves proteome integrity and cellular homeostasis under both physiological and stress conditions. P, phosphorylation; sumo, sumoylation; Ac, acetylation; Lactyl, lactylation; UPS, ubiquitin-proteasome system; ALP, autophagy-lysosome pathway; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; ER, endoplasmic reticulum; AMP, adenosine monophosphate; PPi, inorganic pyrophosphate; PTMs, post-translational modifications; Ub, ubiquitin.

injury (20). Thus, the UPR functions as a critical protective mechanism of proteostasis, but also as a decisive switch between adaptation and cell death, with BiP acting as the essential gatekeeper of this process.

Altogether, these processes form a highly integrated proteostasis network that safeguards protein quality and cellular function. Breakdown of this network leads to the accumulation of toxic species, driving pathology in neurodegenerative, oncogenic, cardiovascular and metabolic disorders. Against this backdrop, FKBPs have emerged as critical regulators that interface with multiple proteostatic pathways, highlighting their importance in both physiological adaptation and disease progression.

3. Structural basis of FKBP functions in protein homeostasis

The FKBP family shares a conserved core domain, the PPIase domain (21). This domain catalyzes the cis-trans isomerization of proline residues in polypeptide chains, accelerating folding kinetics and ensuring that nascent proteins rapidly reach their correct conformation (22). This activity is critical for maintaining protein homeostasis, as proline isomerization often represents a rate-limiting step in folding. Under stress or high translational load, PPIase activity facilitates timely restoration of folding equilibrium (23). The smallest members, such as FKBP12 and FKBP12.6, consist almost entirely of the PPIase domain and interact directly with substrates or

complexes, modulating their stability and function through conformational control (24). Larger members often contain multiple PPIase domains, for instance, FKBP52 has two and FKBP65 has four, potentially broadening substrate specificity or enabling cooperative folding of multidomain proteins (25).

Beyond the PPIase core, numerous FKBPs possess additional functional modules that expand their regulatory capacity. The most prominent is the tetratricopeptide repeat (TPR) domain, a 34-amino acid tandem repeat that mediates protein-protein interactions and is found in proteins such as FKBP51 and FKBP52 (26). The TPR domain enables specific binding to the molecular chaperone heat shock protein (Hsp)90, integrating FKBPs into chaperone complexes. Hsp90 is a highly conserved and ubiquitously expressed eukaryotic chaperone that, unlike many other chaperones, primarily acts on partially or fully folded proteins (27). Through ATP-dependent conformational changes, Hsp90 maintains the functional state of client proteins and stabilizes diverse signaling proteins, receptors and transcription factors (28). This association allows FKBPs not only to catalyze substrate folding independently but also to contribute to protein maturation, conformational maintenance and complex stability within the chaperone network (29). FKBP51 and FKBP52 act as molecular scaffolds within this system. FKBP52 promotes hormone receptor maturation and facilitates their active transport to the nucleus, whereas FKBP51 modulates complex conformation or recruit phosphatases to fine-tune signaling output (30,31). These activities directly influence protein complex stability, subcellular localization and signal transduction, thereby exerting precise control over protein homeostasis.

Certain FKBPs contain other specialized domains that confer distinct subcellular localization and regulatory specificity. FKBP13, FKBP19, FKBP22, FKBP23, FKBP60 and FKBP65 possess N-terminal ER signal peptides and localize to the ER lumen, where they regulate the folding and assembly of secretory and membrane proteins (32-35). FKBP25 contains a DNA-binding domain, enabling it to participate in transcriptional regulation and chromatin remodeling (36). FKBP38 features a transmembrane anchor that targets it to mitochondria, where it recruits anti-apoptotic Bcl-2 family proteins to regulate apoptosis and mitophagy (7,37). These additional domains extend the influence of FKBPs to multiple organelles and signaling networks, allowing them to maintain protein homeostasis across diverse cellular contexts (Fig. 2).

In summary, the structural diversity of FKBPs underpins their multilayered roles in protein homeostasis. The PPIase domain directly modulates folding kinetics and conformational stability. The TPR domain connects FKBPs to the molecular chaperone network, mediating complex assembly and maintenance. Specialized domains confer subcellular specificity and functional diversification. Through coordinated action of these modular elements, FKBPs regulate folding, complex stability, localization and degradation, providing a structural and functional basis for maintaining protein homeostasis in physiological and stress conditions, as well as in disease states. In this review, FKBP nomenclature refers to the protein products unless otherwise specified. For clarity, gene symbols such as *FKBP7*, *FKBP9* and *FKBP10* are used to denote their corresponding protein products (FKBP7, FKBP9, FKBP10). This convention is adopted to maintain consistency with other family members (e.g., FKBP12, FKBP51, FKBP52), which are widely recognized by their protein names.

4. FKBPs coordinate proteostasis networks to drive tumor progression

Protein homeostasis is essential for tumor cells to survive the proteotoxic stress generated by rapid proliferation and harsh microenvironments. To cope with the increased burden of protein synthesis and quality control, cancer cells rely on finely tuned proteostasis networks that regulate folding, stability, signaling and degradation (38). Members of the FKBP family have emerged as central regulators in this process, leveraging their structural modules to influence distinct layers of proteostasis. Certain FKBPs within the ER safeguard protein folding and translational balance, others integrate post-translational modifications and selective degradation to adapt the tumor microenvironment, while still others stabilize nuclear receptors to amplify hormone-driven proliferation. Together, these multifaceted functions highlight FKBPs as key molecular nodes linking proteostasis to cancer progression.

ER-resident FKBPs maintain ER proteostasis to promote tumor invasion and metastasis. The ER is the principal site for protein synthesis, folding and quality control, and its homeostasis is indispensable for sustaining the rapid growth and survival of cancer cells. Disruption of ER proteostasis caused by high translational demand and oncogenic stress activates adaptive mechanisms such as the UPR, which enables tumor cells to tolerate proteotoxic stress and resist apoptosis. Several FKBPs localize to the ER lumen. Among them, FKBP7, FKBP9 and FKBP10 (hereafter referring to the protein) have been most extensively studied in the context of tumor biology.

FKBP9 and FKBP7 help tumor cells adapt to increased protein synthesis and folding pressure by regulating the ER proteostasis network. FKBP9 forms a complex with the molecular chaperone BiP to support correct protein folding and assembly, maintaining folding equilibrium within the ER. In glioblastoma, FKBP9 inhibits the IRE1α-XBP1 signaling pathway and suppresses CHOP-mediated apoptosis, preventing overactivation of the UPR and enhancing resistance to ER stress (39). FKBP9 expression correlates positively with BiP levels, and their co-expression is associated with poor prognosis, underscoring its key role in ER homeostasis (40).

FKBP7 contributes to proteostasis and extends its influence to the tumor microenvironment. In pancreatic ductal adenocarcinoma, FKBP7 is highly expressed in cancer-associated fibroblasts (CAFs). By competing with BiP, FKBP7 alters the secretion of collagen subtypes, reducing type I and increasing type IV collagen. This promotes a dense extracellular matrix that restricts immune infiltration and supports tumor invasion (41). These functions demonstrate that FKBP7 modulates both ER stress adaptation and extracellular matrix remodeling (Fig. 3).

Unlike FKBP9 and FKBP7, FKBP10 plays a distinct role in protein homeostasis that is less dependent on classical ER stress signaling. FKBP10 primarily contributes to proteostasis by regulating substrate folding and subcellular localization. Through its PPIase domain, FKBP10 binds directly to specific client proteins to influence their conformational maturation

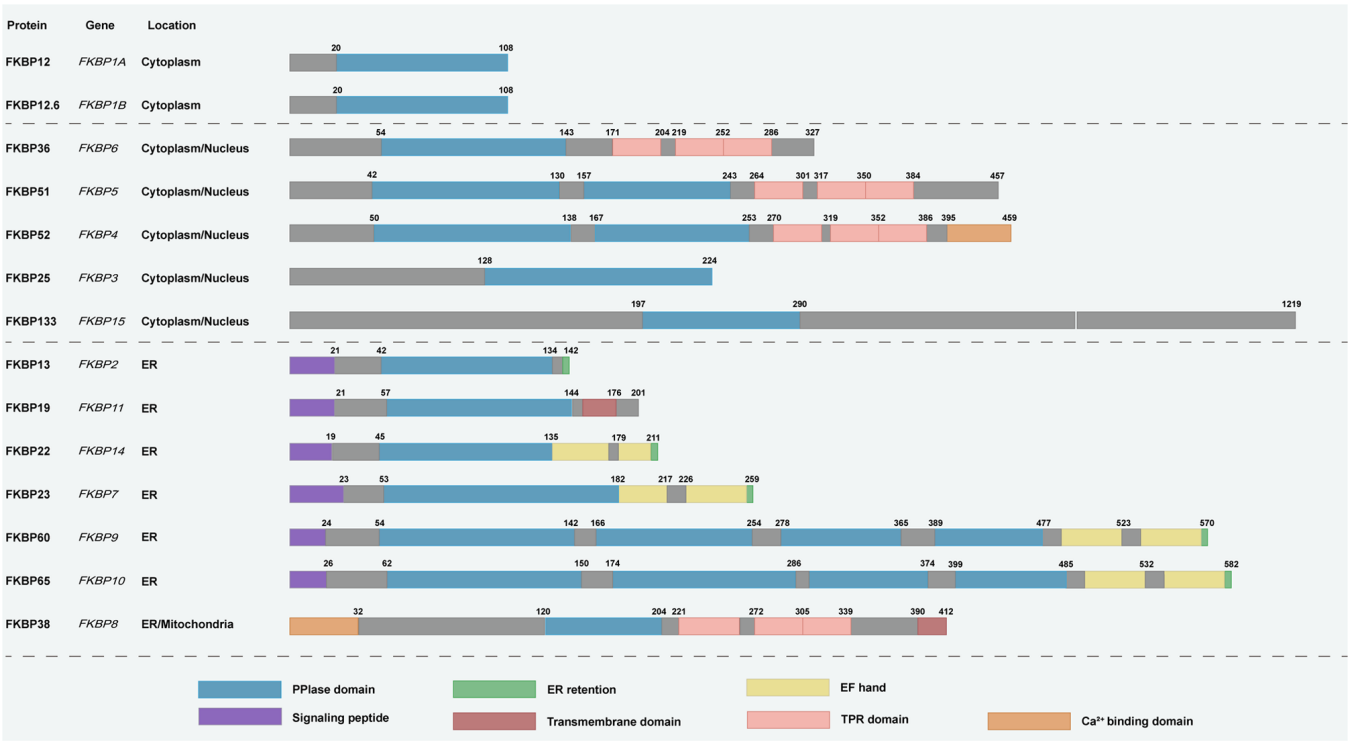

Figure 2. Structural diversity and subcellular localization of FKBP family members. Schematic representation of FKBPs, organized by their predominant localization in the cytoplasm/nucleus or ER/mitochondria. The figure illustrates the modular architecture of FKBPs and highlights how distinct domains support their functional diversity in protein homeostasis. All family members share the conserved PPIase domain, which catalyzes proline isomerization to accelerate protein folding and conformational stabilization. Several larger members, such as FKBP51 and FKBP52, also contain TPR domains that mediate docking to heat shock protein 90, enabling scaffold functions in protein folding, complex stabilization and nuclear receptor trafficking. Members including FKBP13, FKBP19, FKBP22, FKBP23, FKBP60 and FKBP65 harbor N-terminal ER signal peptides and ER retention motifs, which target them to the ER lumen for the folding and assembly of secretory and membrane proteins. FKBP38 contains a C-terminal transmembrane anchor that localizes it to mitochondria and facilitates anti-apoptotic Bcl-2 recruitment, linking FKBPs to apoptosis and mitophagy regulation. Additional modules such as EF-hand motifs and Ca^{2+}-binding domains provide responsiveness to calcium signaling, further expanding functional versatility. Together, this structural heterogeneity enables FKBPs to regulate protein folding, modification, trafficking and degradation across diverse subcellular compartments. PPIase, peptidyl-prolyl cis-trans isomerase; TPR, tetratricopeptide repeat; ER, endoplasmic reticulum; EF-hand, helix-loop-helix calcium-binding motif; FKBPs, FK506-binding proteins.

and intracellular trafficking. In bladder cancer, FKBP10 binds prelamin A, leading to its retention in the ER and preventing its translocation into the nucleus, thereby disrupting Lamin A formation and nuclear structure (42). This results in nuclear atypia and enhances the migratory and invasive capacity of cancer cells. In glioma, FKBP10 interacts with Hsp47 via its third PPIase domain to promote the folding and stabilization of type I procollagen, which directly facilitates extracellular matrix organization and the establishment of a tumor-supportive microenvironment (10).

Beyond its role in folding and localization, FKBP10 also supports translational homeostasis in highly proliferative cancer cells. Its conserved PPIase domain catalyzes the isomerization of proline residues in nascent polypeptides, accelerating translation elongation, particularly for proline-rich ribosomal and structural proteins. Loss of FKBP10 impairs this isomerization process, leading to ribosomal stalling at proline motifs and reduced synthesis of proline-rich proteins, underscoring the dependence of such proteins on FKBP10-mediated PPIase activity. In non-small cell lung cancer (NSCLC), FKBP10 localizes to the ribosomal catalytic center, reinforcing its function in supporting translation (43). Loss of FKBP10 or impairment of its enzymatic activity reduces translation efficiency, impairs cell cycle progression and induces apoptosis. FKBP10 is upregulated in multiple malignancies, including NSCLC, colorectal cancer, renal cell carcinoma, bladder cancer and glioma, and is associated with poor prognosis (44-46). Its knockdown not only inhibits proliferation and migration but also sensitizes tumor cells to chemotherapy and targeted therapies, highlighting its potential as a therapeutic target (Fig. 3).

In conclusion, FKBP7, FKBP9 and FKBP10 are ER-resident FKBPs that regulate proteostasis through distinct mechanisms. FKBP9 and FKBP7 primarily participate in unfolded protein responses and protein folding control, while FKBP10 governs translational efficiency and substrate localization. These proteins enable cancer cells to manage translational stress and maintain proteome integrity under oncogenic pressure, linking ER proteostasis to malignant progression. Targeting the functional domains of these FKBPs may offer promising therapeutic strategies for cancers characterized by dysregulated protein homeostasis and elevated ER stress.

FKBP51 integrates post-translational modifications (PTMs) and selective degradation to promote microenvironment remodeling. PTMs are key regulatory mechanisms that control protein function, stability and subcellular localization. They play a critical role in maintaining cellular homeostasis and in coordinating responses to external stimuli. In the tumor microenvironment, PTMs are extensively involved in signal

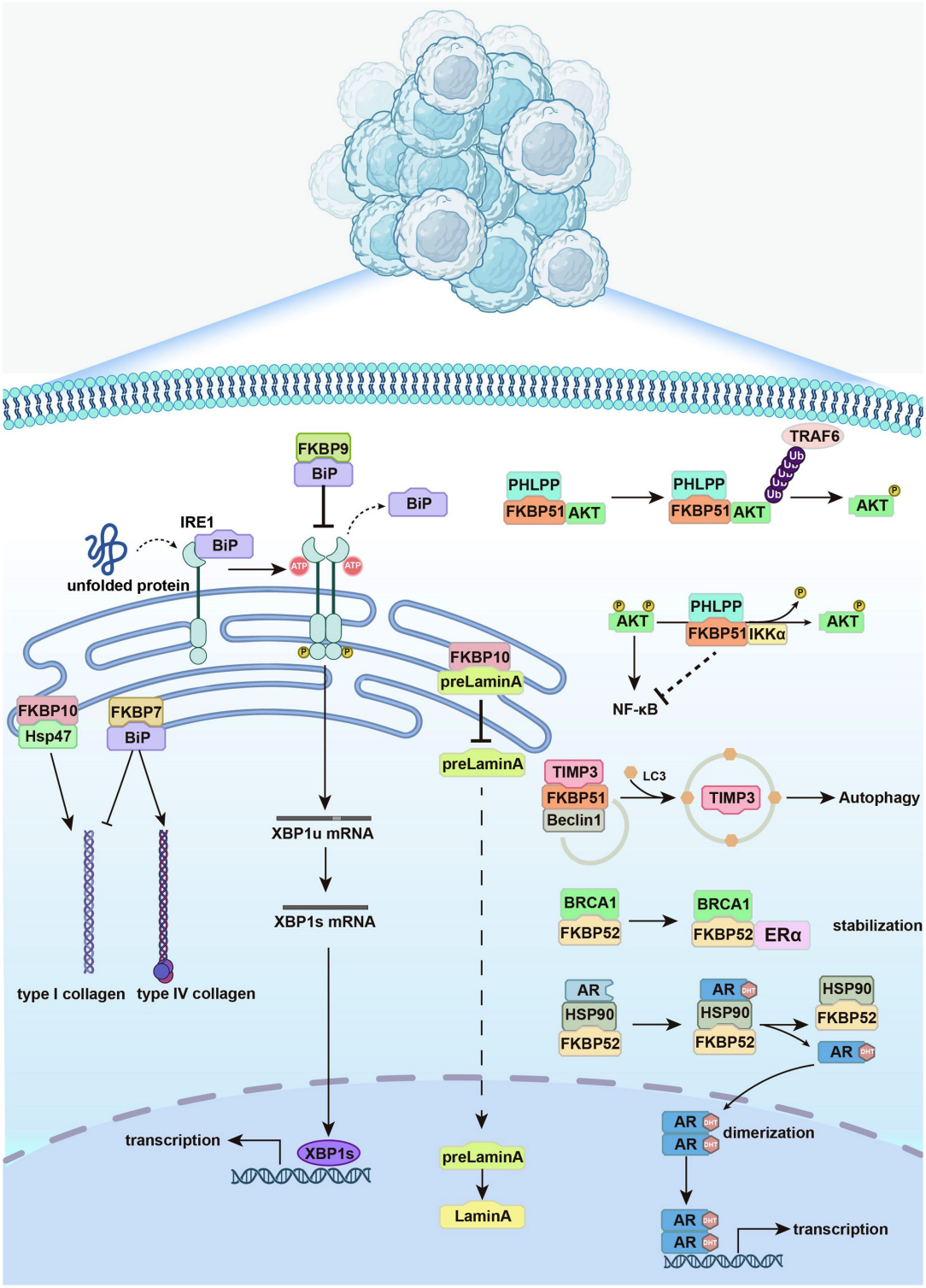

Figure 3. ER-resident and cytoplasmic FKBPs regulate proteostasis to support tumor progression. Schematic illustration of how representative FKBPs contribute to protein homeostasis in cancer. In the ER, FKBP9 binds to BiP to maintain folding equilibrium and suppress excessive IRE1α-XBP1 activation, protecting cells from ER stress-induced apoptosis. FKBP7 interacts with BiP in cancer-associated fibroblasts to modulate collagen subtype secretion, favoring extracellular matrix remodeling and tumor invasion. FKBP10 regulates substrate maturation and localization, including retention of prelamin A in the ER and stabilization of type I procollagen through cooperation with Hsp47, and also supports translational efficiency at the ribosome. Outside the ER, FKBP51 functions as a scaffold that shapes post-translational modifications and autophagic turnover: It recruits PHLPP to regulate AKT dephosphorylation, promotes Akt ubiquitination via TRAF6 and directs TIMP3 degradation through the Beclin1 complex, thereby modulating survival signaling and microenvironment remodeling. FKBP52 acts as an Hsp90 co-chaperone that stabilizes steroid hormone receptors such as AR and ERα, facilitates their nuclear transport via dynein and enhances transcriptional activation of oncogenic programs. Collectively, these mechanisms highlight how distinct FKBPs integrate ER stress responses, protein folding, post-translational regulation and receptor signaling to maintain proteostasis and promote malignant progression. FKBP, FK506-binding protein; ER, endoplasmic reticulum; BiP, binding immunoglobulin protein (GRP78); IRE1α, inositol-requiring enzyme 1α; XBP1s, X-box binding protein 1 spliced isoform; UPR, unfolded protein response; CAF, cancer-associated fibroblast; PPIase, peptidyl-prolyl cis-trans isomerase; AKT, protein kinase B; PHLPP, PH domain and leucine-rich repeat protein phosphatase; TRAF6, TNF receptor-associated factor 6; TIMP3, tissue inhibitor of metalloproteinases 3; AR, androgen receptor; ERα, estrogen receptor α; Hsp, heat shock protein; IKKα, IκB kinase α; DHT, dihydrotestosterone; Ub, ubiquitin; BRCA1, breast cancer 1, early onset.

transduction, cell cycle regulation, metabolic reprogramming and immune evasion (47). Dysregulation of PTMs is closely linked to tumor initiation, progression and treatment resistance.

FKBP51 (also known as FKBP5) has emerged as a critical regulator that integrates PTM-dependent signaling with protein stability and cellular adaptation. FKBP51 contributes to tumor progression by modulating phosphorylation, ubiquitination and acetylation of key signaling proteins, thereby shaping the functional output of oncogenic pathways.

One of the core functions of FKBP51 is to modulate PTMs of key signaling proteins, maintaining the integrity of signaling complexes and regulating downstream signaling outputs. A well-characterized example is its bidirectional regulation of the Akt pathway. In melanoma, FKBP51 interacts with Hsp90 to enhance K63-linked ubiquitination of Akt, which increases Akt stability and activity, thereby activating downstream effectors such as P70S6K and Cyclin D1 to promote cell proliferation (48). By contrast, in prostate and pancreatic cancers, FKBP51 enhances its interaction with PH domain and leucine-rich repeat protein phosphatase (PHLPP), facilitating dephosphorylation of Akt at Ser473 and attenuating Akt activity, thereby suppressing survival signaling (49). The direction of FKBP51-mediated Akt regulation depends on factors such as PHLPP expression, Hsp90 status and FKBP51's own PTM state, reflecting its functional plasticity as a scaffold protein within signaling complexes (Fig. 3).

Furthermore, in castration-resistant prostate cancer, FKBP51 forms a complex with PHLPP and inhibitor of NF-κB kinase subunit α to inhibit both Akt and NF-κB pathways (50). In melanoma, FKBP51 enhances acetylation of the transcription factor YY1, which suppresses the expression of the pro-apoptotic death receptor 5 and reduces sensitivity to apoptosis triggered by TNF-related apoptosis-inducing ligand (51). These findings collectively indicate that FKBP51 modulates key signaling pathways by coordinating phosphorylation, ubiquitination and acetylation, thereby enabling tumor cells to adapt and survive in hostile microenvironments.

In addition, FKBP51 regulates protein stability and degradation by mediating selective autophagic turnover of specific substrates. In clear cell renal cell carcinoma, FKBP51 binds to the metalloproteinase inhibitor tissue inhibitor of metalloproteinases 3 (TIMP3) and recruits it to the Beclin1 autophagy complex, promoting its lysosome-dependent degradation. Since TIMP3 inhibits extracellular matrix degradation, its downregulation facilitates tumor cell invasion (52). This suggests that FKBP51 contributes to tumor microenvironment remodeling by modulating the stability and degradation of specific proteins (Fig. 3).

In summary, FKBP51 maintains protein homeostasis by coordinating PTMs and selective degradation. Through its roles in signal regulation, apoptosis resistance and microenvironment adaptation, FKBP51 supports sustained proliferation, migration and therapy resistance in tumor cells, highlighting its potential as a key regulator of proteostasis and a promising therapeutic target.

FKBP52 stabilizes and translocates nuclear receptors to enhance hormone-driven tumor growth. FKBP52 (also known as FKBP4) is a key co-chaperone within the Hsp90 complex. In various cancers, its oncogenic role is closely linked to the regulation of nuclear receptor stability, activity and subcellular localization. A central mechanism involves its ability to assemble and stabilize hormone receptor-chaperone complexes, enhance receptor conformational integrity and facilitate their nuclear translocation. Through its TPR domain, FKBP52 binds to Hsp90 and forms a stable chaperone complex (53). Its PPIase domain further modulates the conformation of steroid receptors-such as androgen receptor (AR), estrogen receptor α (ERα) and glucocorticoid receptor (GR)-via prolyl isomerization, thereby enhancing ligand binding and transcriptional activity (54,55). In breast and prostate cancers, FKBP52 increases the abundance and activity of ERα and AR, and its elevated expression is strongly associated with tumor progression and poor prognosis (56,57).

Notably, FKBP52 plays a critical role in regulating the subcellular trafficking of nuclear receptors. Upon ligand binding, FKBP52 facilitates the recruitment of the dynein motor complex to the receptor-Hsp90 complex. This interaction promotes active transport of the receptor complex along microtubules toward the nucleus, enabling efficient nuclear import through the nuclear pore complex. This nuclear translocation is essential for receptor-mediated transcriptional activation. For instance, FKBP52 enhances GR nuclear accumulation and transcriptional output by supporting its interaction with the dynein complex (58). Similarly, FKBP52 promotes the nuclear import of RelA (p65) in the NF-κB pathway by stabilizing its association with Hsp70, thereby amplifying NF-κB transcriptional activity and contributing to tumor proliferation and inflammatory signaling (59) (Fig. 3).

In summary, FKBP52 acts as a molecular scaffold that regulates both the stability and nuclear localization of key transcriptional regulators. By coordinating the chaperoning, transport and activation of nuclear receptors and signaling proteins, FKBP52 helps maintain protein homeostasis and promotes cancer cell growth and adaptation. These findings highlight FKBP52 as a critical node in oncogenic signaling and a promising therapeutic target.

5. FKBPs orchestrate the dual regulation of pathogenic proteins in neurodegenerative diseases

Protein homeostasis is a central determinant of neuronal survival, as the brain is particularly vulnerable to the toxic effects of misfolded or aggregated proteins. In neurodegenerative diseases, the collapse of proteostatic control leads to the pathological accumulation of proteins such as α-synuclein (α-Syn) and tau, which form aggregates that disrupt synaptic integrity, impair intracellular trafficking and ultimately drive neuronal death (60,61). Maintaining the balance between protein folding, degradation and aggregation is therefore critical for preventing neurotoxicity. FKBPs have emerged as important regulators of pathogenic protein dynamics. By modulating conformational states, post-translational processing and degradation pathways, FKBPs directly shape the fate of disease-related proteins, positioning them as key players in the onset and progression of Parkinson's disease (PD) and Alzheimer's disease (AD).

FKBP12 drives α-Syn misfolding and aggregation to exacerbate PD pathogenesis. PD is a prevalent neurodegenerative disorder

primarily characterized by the selective degeneration of dopaminergic neurons in the substantia nigra, leading to impaired motor function (62,63). Although the precise mechanisms underlying the disease remain incompletely elucidated, accumulating evidence indicates that the aberrant aggregation of α-Syn constitutes a critical pathological hallmark of PD (64). α-Syn is a widely expressed cytoplasmic protein that normally participates in the regulation of synaptic function. However, in PD, α-Syn undergoes pathological aggregation into fibrillar structures within neurons, forming Lewy bodies, which in turn induce neurotoxicity and contribute to neurodegeneration (65).

Investigations have revealed that the PPIase activity of FKBPs and their role in modulating protein folding are intricately linked to the aggregation of α-Syn (66). FKBP12 contributes to the pathogenesis of PD through multiple mechanisms that disrupt proteostasis. It directly interferes with the folding and aggregation of α-Syn by binding to its proline-rich C-terminal region and catalyzing cis/trans isomerization of terminal prolines, inducing pathogenic conformational changes in the monomer. This markedly accelerates and alters aggregation kinetics, promoting the formation of highly branched dendritic structures (66). In addition, FKBP12 forms a complex with calcineurin under conditions of sustained cytosolic Ca^{2+} elevation induced by α-Syn toxicity. This complex drives pathological dephosphorylation of key presynaptic proteins involved in vesicle trafficking, endocytosis and cytoskeletal organization, including growth associated protein 43 and brain acid soluble protein 1. The resulting synaptic dysfunction destabilizes dopamine transporters at the plasma membrane, reduces dopamine release and leads to neuronal death (67). Given FKBP12's pivotal role in the disease process, targeting this protein represents a promising strategy for disease-modifying therapeutic interventions. A recent study demonstrated that rapamycin, through the inhibition of FKBP12 independent of the mTORC1 pathway, confers neuroprotective effects, underscoring FKBP12 as a novel therapeutic target for PD (68). Furthermore, non-immunosuppressive FKBP12 inhibitors, such as ElteN378, have shown efficacy in preventing α-Syn aggregation, presenting a potential new class of therapeutics for early-stage PD treatment (69) (Fig. 4A). However, challenges remain in achieving adequate brain penetration and isoform selectivity for these compounds, which may limit their translational applicability and require further optimization.

In summary, FKBP12, through its PPIase activity, disrupts neuronal proteostasis via multiple pathways, including the regulation of α-Syn conformation, alteration of its aggregation dynamics and calcineurin-dependent dephosphorylation of synaptic proteins. These processes collectively drive the onset and progression of PD. The multifaceted role of FKBP12 in disease pathogenesis not only reveals a new dimension of proteostasis imbalance in PD but also provides a solid theoretical foundation and potential avenues for the development of disease-modifying therapies targeting FKBP12.

FKBP51 and FKBP52 modulate tau aggregation-degradation balance to shape AD pathology. AD is a progressive neurodegenerative disorder characterized by cognitive decline, with hallmark pathological features including β-amyloid plaque deposition and neurofibrillary tangles composed of hyperphosphorylated tau protein (70-72). Tau, a microtubule-associated protein, undergoes conformational alterations and aggregation that are considered central to the neuronal dysfunction and cell death observed in AD (71,73-75). In recent years, FKBP51 and FKBP52 have garnered increasing attention for their regulatory roles in tau pathology.

FKBP51 promotes tau oligomer formation through cooperation with Hsp90. Hsp90 functions as a scaffold, precisely positioning the proline-rich region of tau into the PPIase catalytic pocket of FKBP51, thereby catalyzing proline cis/trans isomerization. This process alters tau conformation and phosphorylation status, accelerating oligomer accumulation. The resulting changes enhance tau pathogenicity, disrupt neuronal proteostasis and drive the progression of neurodegeneration (76). By contrast, FKBP51 can also form a complex with the Hsp90 co-chaperone p23, whose negatively charged C-terminal tail binds to the positively charged, aggregation-prone repeat domain of tau, inhibiting its fibrillization kinetics. When p23 and FKBP51 are both present, a p23-FKBP51-tau ternary complex may form, partially counteracting the aggregation-promoting effect of FKBP51 and exerting a protective regulatory influence on tau aggregation (77). These findings indicate that FKBP51 can either exacerbate or suppress tau aggregation depending on its interaction partners, with the functional outcome determined by the composition and dynamic balance of the chaperone network (Fig. 4B).

In parallel, FKBP52 plays a pivotal role in regulating tau protein homeostasis, influencing both its degradation and the formation of pathological aggregates (78). Under tau proteotoxic stress, FKBP52 localizes to perinuclear lysosomal clusters and supports the function of the ALP, promoting lysosomal degradation of tau and preventing its abnormal secretion, thereby limiting extracellular tau propagation (12). By contrast, abnormally elevated FKBP52 levels markedly enhance tau hyperphosphorylation and aggregation, with a more pronounced pathological effect in the aged brain. This pro-aggregation activity is not only associated with its regulation of tau conformation and aggregation kinetics through the Hsp90 chaperone network, but may also involve activation of glial cells and the release of inflammatory mediators, creating a feedforward loop between tau aggregation and neuroinflammation that accelerates neuronal injury (79). These findings indicate that FKBP52 exerts dual, context-dependent effects on tau pathology, with its regulatory direction shifting under different physiological and pathological conditions, providing important insights into the progression of tauopathies and potential therapeutic strategies (Fig. 4C).

Collectively, FKBP51 and FKBP52 play multifaceted and context-dependent roles in tau proteostasis. They act through distinct yet overlapping mechanisms, including PPIase activity, Hsp90 co-chaperone interactions and regulation of the autophagy-lysosome pathway. Depending on the cellular context, they can either promote or restrain tau aggregation. This dual regulation shifts the balance between neuronal resilience and degeneration, highlighting their importance as modulators of AD progression and as potential therapeutic targets. An important unresolved question is what specific

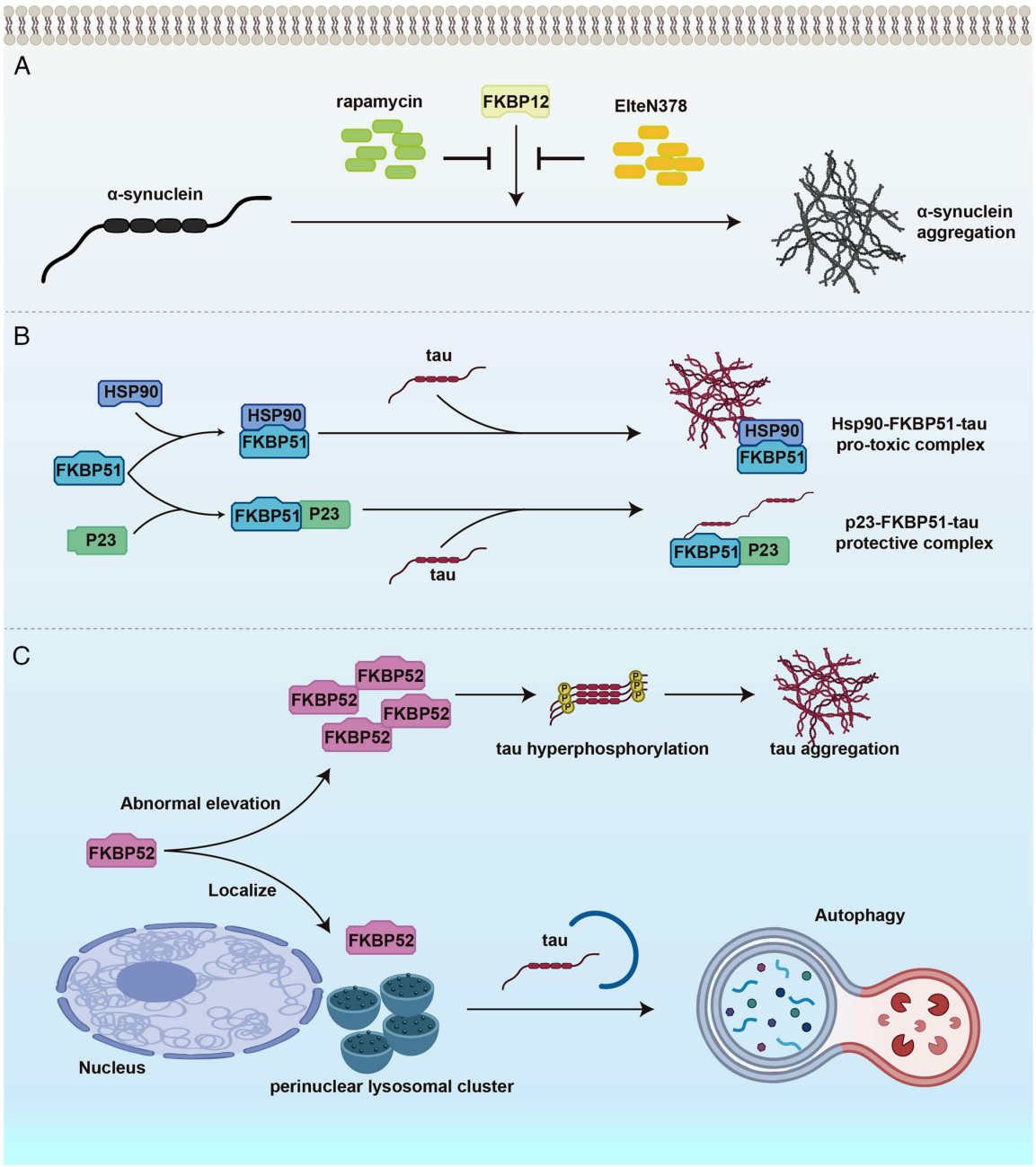

Figure 4. FKBPs regulate neuronal protein homeostasis through distinct mechanisms in neurodegenerative diseases. (A) FKBP12 accelerates α-synuclein misfolding and aggregation via prolyl isomerization, promoting Parkinson's disease pathology. Pharmacological inhibition of FKBP12 by rapamycin or the non-immunosuppressive compound ElteN378 suppresses α-SYN aggregation, conferring neuroprotective effects. (B) FKBP51 modulates tau proteostasis through the Hsp90 chaperone complex, balancing tau aggregation and stabilization in Alzheimer's disease. The Hsp90-FKBP51-tau complex promotes pathogenic tau oligomerization, while the p23-FKBP51-tau complex stabilizes tau in a non-aggregated state, exerting a protective effect. (C) Under physiological conditions, FKBP52 facilitates tau degradation through the autophagy-lysosome pathway. However, its abnormal elevation enhances tau hyperphosphorylation and aggregation, contributing to neurofibrillary tangle formation and neurodegeneration. α-SYN, α-synuclein; PD, Parkinson's disease; AD, Alzheimer's disease; FKBP, FK506-binding protein; Hsp, heat shock protein.

cellular or pathological cues dictate whether FKBP51 and FKBP52 act to promote or suppress tau aggregation, a topic that warrants further investigation.

6. FKBPs stabilize ion channel conformation to protect against cardiac dysfunction

Protein homeostasis is central to cardiovascular physiology, where the stability of ion channel complexes and contractile proteins is indispensable for maintaining cardiac excitability and pump function. Disruption of proteostasis under pathological stress contributes to electrical instability, impaired contractility and progressive remodeling, forming the basis of numerous cardiovascular diseases (80,81). Within this framework, FKBPs have emerged as critical modulators of protein conformation and complex stability. Among them, FKBP12.6 plays a particularly important role in governing ion channel regulation, positioning it as a key determinant of cardiac function and a potential therapeutic target in heart failure and arrhythmias.

FKBP12.6 stabilizes ryanodine receptor 2 (RyR2) conformation to prevent diastolic calcium leak in heart failure (HF) and arrhythmia. In cardiomyocytes, RyR2 is the primary calcium release channel on the sarcoplasmic reticulum (SR), and its protein homeostasis is essential for regulating cardiac contractility and rhythm (82,83). During excitation-contraction coupling, RyR2 channels open in response to membrane depolarization, releasing stored Ca^{2+} from the SR into the cytosol to initiate contraction. In diastole, RyR2 channels are expected to remain closed to prevent abnormal Ca^{2+} efflux and allow for Ca^{2+} reuptake and myocardial relaxation (84,85). However, in HF and arrhythmias such as atrial fibrillation (AF), dysregulation of the RyR2 macromolecular complex leads to pathological diastolic Ca^{2+} leak, disrupting cytosolic Ca^{2+} homeostasis (86,87). This Ca^{2+} dysregulation promotes delayed afterdepolarizations and triggered activity, forming a shared pathological basis for HF and AF (88).

Within the RyR2 complex, FKBP12.6, also known as calstabin2, acts as a key stabilizer of channel structure and function. Cryo-electron microscopy studies reveal that RyR2 assembles as a homotetramer, with one FKBP12.6 molecule binding to each protomer at specific interfacial regions. These sites are located between the helical domain and SPRY domains, where FKBP12.6 stabilizes the closed conformation of the channel (89). Its binding extends the mean closed time of RyR2, suppresses spontaneous openings and promotes coupled gating between adjacent channels, thereby preventing Ca^{2+} leakage in the resting state (90).

Under pathological conditions, particularly during sustained sympathetic activation or oxidative stress, RyR2 homeostasis becomes disrupted. Post-translational modifications such as protein kinase A-mediated hyperphosphorylation at Ser2808, cysteine oxidation and S-nitrosylation result in the dissociation of FKBP12.6 from the channel complex (15). This destabilizes the closed conformation of RyR2, increases the open probability and promotes diastolic Ca^{2+} leak, which in turn contributes to Ca^{2+} overload, electrophysiological instability and progressive cardiac dysfunction (91,92).

Multiple animal models support the central role of FKBP12.6 in RyR2 regulation. In murine models of HF, RyR2 channels exhibit increased Ser2808 phosphorylation and oxidative modifications, accompanied by reduced FKBP12.6 binding. These alterations correlate with enhanced Ca^{2+} leak and reduced contractility (93). Mice lacking FKBP12.6 develop spontaneous arrhythmias, whereas FKBP12.6 overexpression or treatment with rycals such as S107 restores FKBP12.6 binding to RyR2, stabilizes channel closure, reduces aberrant Ca^{2+} release and improves cardiac function. Importantly, rycals do not directly block RyR2 openings but enhance FKBP12.6 affinity for the channel, thereby stabilizing the RyR2 macromolecular complex at a structural level (94). Similar mechanisms are observed in AF, where atrial myocytes from patients with AF and animal models show increased RyR2 phosphorylation and oxidation, decreased FKBP12.6 binding and elevated diastolic Ca^{2+} spark frequency. FKBP12.6-deficient mice, despite having structurally normal hearts, exhibit enhanced susceptibility to pacing-induced AF. Treatment with S107 suppresses this phenotype only in the presence of FKBP12.6, indicating its essential role in the therapeutic effect (94) (Fig. 5).

In summary, maintenance of RyR2 protein homeostasis is critical for normal cardiac function. FKBP12.6 plays a pivotal role in stabilizing the RyR2 complex and preventing pathological Ca^{2+} leak. Therapeutic strategies targeting the FKBP12.6-RyR2 interaction, particularly with rycal compounds, offer a promising approach for precision treatment of HF and arrhythmias.

7. FKBPs control metabolic kinase activity to maintain metabolism balance

Metabolic homeostasis depends on the precise regulation of key kinases that govern glucose utilization, lipid turnover and energy sensing. The stability and activity of these kinases are tightly controlled by proteostasis networks, which ensure their correct folding, modification and timely degradation (95,96). As pivotal regulators within this system, FKBPs influence metabolic adaptation through multiple proteostatic mechanisms. Among them, FKBP51 stands out for its role as a molecular scaffold that shapes post-translational modifications, particularly phosphorylation, thereby fine-tuning the activity of central metabolic kinases and linking stress responses to metabolic balance.

FKBP51 serves as a scaffold to modulate kinase phosphorylation in metabolic regulation. In the central nervous system, FKBP51 influences metabolic balance by modulating the activity of key kinases in the autophagy pathway. Autophagy initiation requires activation of AMP-activated protein kinase (AMPK) and is inhibited by mechanistic target of rapamycin complex 1 (mTORC1) (97). AMPK activation depends on phosphorylation of its upstream kinase liver kinase B1 (LKB1) at Thr172, whereas mTORC1 activity is suppressed by the tuberous sclerosis complex (TSC)1/2 complex (98). Members of the WD repeat domain phosphoinositide-interacting (WIPI) protein family, WIPI4 and WIPI3, act as scaffolds for LKB1-AMPK and TSC2, respectively, coupling energy sensing to autophagy regulation (99,100). FKBP51 interacts with WIPI4 to recruit LKB1 to the AMPK complex, enhancing Thr172 phosphorylation and promoting UNC-51-like kinase 1 (ULK1) phosphorylation at Ser555 to initiate autophagy. In parallel, FKBP51 binds the WIPI3-TSC2 complex to cooperatively inhibit mTORC1 activity, further relieving autophagy suppression (16).

The physiological relevance of these scaffold-based mechanisms is supported by *in vivo* findings demonstrating their dose-dependent effects on energy homeostasis and autophagy regulation. *In vivo*, this regulation shows a clear dose dependency. Mediobasal hypothalamus-specific deletion of FKBP51 reduces AMPK-ULK1 activation, enhances mTORC1 signaling, decreases autophagy and leads to obesity, impaired glucose tolerance and increased food intake. Moderate FKBP51 overexpression enhances AMPK activity and autophagy in skeletal muscle and adipose tissue, inhibits mTORC1 signaling, improves insulin sensitivity and limits weight gain under high-fat diet conditions (101). By contrast, excessive FKBP51 expression activates AKT-mTORC1 signaling, suppresses autophagy and disrupts proteostasis. This bidirectional effect of deficiency and overexpression highlights FKBP51 as a dose-sensitive regulator of autophagy

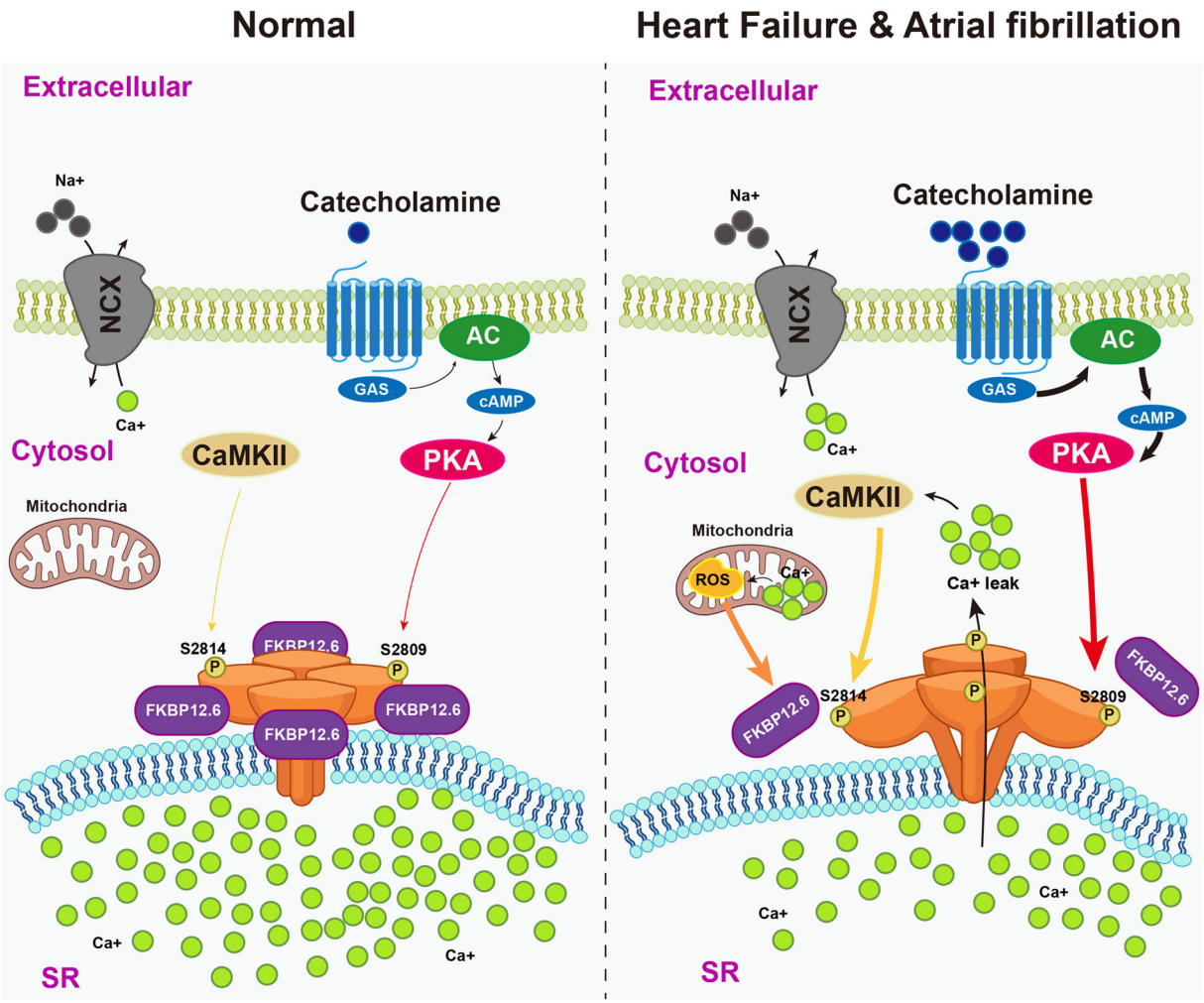

Figure 5. FKBP12.6 stabilizes RyR2 conformation to prevent pathological Ca^{2+} leak in heart failure and atrial fibrillation. Under physiological conditions (left), catecholamine stimulation activates PKA and CaMKII, but RyR2 channels on the SR remain stabilized in the closed state by FKBP12.6, preventing diastolic Ca^{2+} leak and preserving Ca^{2+} cycling. In pathological settings such as heart failure and atrial fibrillation (right), sustained sympathetic drive and oxidative stress induce PKA hyperphosphorylation at Ser2809, CaMKII phosphorylation at Ser2814 and oxidative modifications of RyR2. These alterations disrupt FKBP12.6 binding, destabilize the channel complex and promote aberrant Ca^{2+} leak. The resulting cytosolic Ca^{2+} overload contributes to delayed afterdepolarizations, arrhythmogenic activity and progressive cardiac dysfunction. FKBP12.6, FK506-binding protein 12.6; RyR2, ryanodine receptor 2; SR, sarcoplasmic reticulum; PKA, protein kinase A; CaMKII, calcium/calmodulin-dependent protein kinase II; ROS, reactive oxygen species; P, phosphorylation; GAS, GMP-AMP synthase; NCX, sodium-calcium exchanger; AC, adenylyl cyclase.

and metabolic balance (102) (Fig. 6A). In glucose metabolism, FKBP51 modulates the AKT-forkhead box protein O1 (FOXO1) signaling axis in pancreatic β cells to regulate cell function and survival. AKT is a serine/threonine kinase activated by phosphorylation at Thr308 and Ser473 downstream of insulin receptor-PI3K-pyruvate dehydrogenase kinase 1/mTORC2 signaling (103). Activated AKT phosphorylates the transcription factor FOXO1 at Ser256, promoting its nuclear export and repressing the transcription of target genes (104,105). FOXO1 is essential for β-cell differentiation, maturity and stress adaptation (106,107). As a scaffold protein, FKBP51 recruits the phosphatase PHLPP to AKT, facilitating dephosphorylation at Ser473 and reducing AKT activity. This decreases FOXO1 Ser256 phosphorylation, promotes its nuclear retention and preserves transcriptional activity. Under inflammatory stress, this mechanism helps maintain β-cell function, enhance survival and sustain glucose-stimulated insulin secretion, forming a protective FKBP51-PHLPP-AKT-FOXO1 regulatory pathway (16,108) (Fig. 6B).

In lipid metabolism, FKBP51 influences two key nuclear receptors in adipocytes, peroxisome proliferator-activated receptor γ (PPARγ) and glucocorticoid receptor (GR), to balance lipogenesis and lipolysis. The p38 mitogen-activated protein kinase phosphorylates PPARγ at Ser112, decreasing its transcriptional activity and suppressing lipogenesis, while phosphorylation of GR enhances its transcriptional activity, promoting lipolysis (109). FKBP51 suppresses AKT activity, which indirectly reduces p38 activation, thereby lowering GR phosphorylation and lipolytic gene transcription while relieving inhibitory phosphorylation of PPARγ to enhance lipogenic activity (16). FKBP51, as part of the Hsp90 chaperone complex, also retains GR and PPARγ in the cytoplasm, preventing their nuclear translocation and phosphorylation (31). Upon ligand binding, FKBP52 replaces FKBP51 in the GR complex, enabling GR nuclear import, whereas PPARγ is released from FKBP51 by protein phosphatase 5 to dephosphorylate Ser112 and restore activity (16). Notably, during early adipocyte differentiation, FKBP51 translocates from mitochondria to

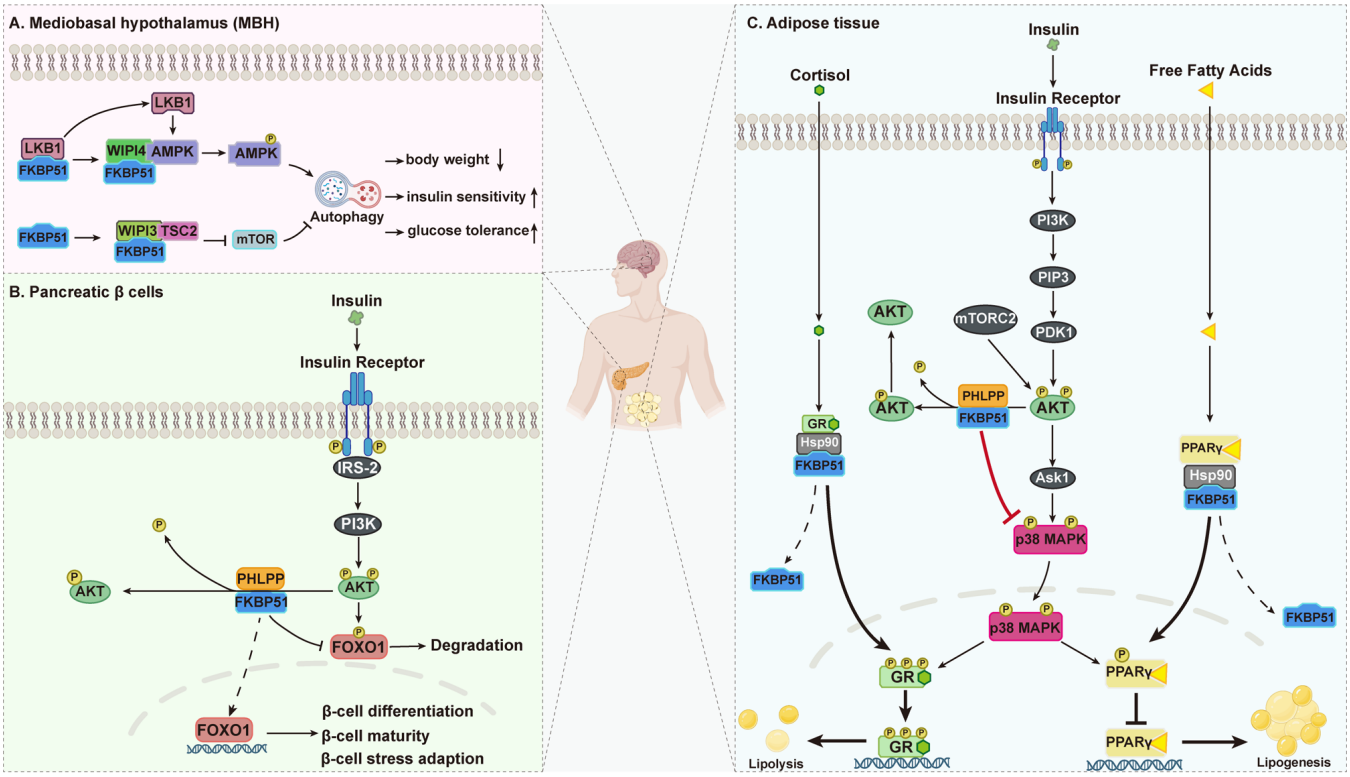

Figure 6. FKBP51 regulates metabolic homeostasis by scaffolding kinase phosphorylation across multiple tissues. Schematic representation of FKBP51-mediated regulation of metabolic signaling. (A) In the MBH, FKBP51 interacts with WIPI4 to recruit LKB1 to the AMPK complex, enhancing AMPK phosphorylation and ULK1 activation to promote autophagy, while binding WIPI3-TSC2 to inhibit mTORC1 signaling. (B) In pancreatic β cells, FKBP51 scaffolds the phosphatase PHLPP to AKT, facilitating dephosphorylation of AKT at Ser473 and decreasing FOXO1 phosphorylation, which preserves FOXO1 transcriptional activity and supports β-cell differentiation, maturity and stress adaptation. (C) In adipose tissue, FKBP51 suppresses AKT activity, indirectly modulating p38 MAPK-mediated phosphorylation of PPARγ and GR, thereby balancing lipogenesis and lipolysis. Together, these mechanisms highlight FKBP51 as a dose-sensitive scaffold that fine-tunes kinase phosphorylation to coordinate glucose utilization, lipid storage and energy sensing, ultimately maintaining systemic metabolic homeostasis. AMPK, AMP-activated protein kinase; mTORC1, mechanistic target of rapamycin complex 1; ULK1, UNC-51-like kinase 1; LKB1, liver kinase B1; WIPI, WD repeat domain phosphoinositide-interacting protein; PHLPP, PH domain leucine-rich repeat protein phosphatase; AKT, protein kinase B; FOXO1, forkhead box protein O1; GR, glucocorticoid receptor; PPARγ, peroxisome proliferator-activated receptor γ; MAPK, mitogen-activated protein kinase; MBH, mediobasal hypothalamus; HSP90, heat shock protein 90.

the nucleus, where it binds GRα and inhibits its transcriptional activity, linking stress signaling to lipid metabolic gene expression in a time-dependent manner (110) (Fig. 6C).

Collectively, these findings establish FKBP51 as a central scaffold that orchestrates kinase phosphorylation to fine-tune metabolic signaling. By bridging phosphatases and kinases such as AKT, p38, AMPK and mTORC1, FKBP51 exerts precise control over glucose utilization, lipid storage and autophagy. This scaffold-dependent regulation allows cells to dynamically adapt to nutritional and stress cues, thereby safeguarding systemic metabolic balance. Importantly, the dose-sensitive nature of FKBP51 underscores its dual capacity to either maintain homeostasis or drive metabolic dysfunction, highlighting its significance as a pivotal regulator of proteostasis within energy metabolism.

8. Therapeutic targeting of FKBPs to restore proteostasis

Targeting FKBPs offers a novel and unifying therapeutic strategy to correct proteostasis imbalance across diverse diseases. Given their structural modularity and central positioning in protein quality control, FKBPs provide actionable nodes for pharmacological intervention. As summarized in Table I, representative FKBP members participate in distinct pathological contexts-from neurodegeneration and cancer to cardiovascular and metabolic disorders-through diverse proteostasis-related mechanisms and corresponding therapeutic strategies. In neurodegenerative diseases, FKBP12 accelerates α-Syn misfolding and aggregation in PD, making it a candidate for non-immunosuppressive inhibitors such as ElteN378, which block its interaction with α-Syn and thereby mitigate proteotoxic stress (69). FKBP51 and FKBP52, on the other hand, regulate tau conformational fate in AD. Ligands or interface inhibitors that selectively modulate FKBP51-Hsp90 or FKBP52-tau complexes may restore tau homeostasis and attenuate neurotoxicity (12,77).

In oncology, ER-resident proteins FKBP9, FKBP7 and FKBP10 enable tumor cells to adapt to translational overload and ER stress. FKBP9 sustains glioblastoma growth by restraining IRE1α-XBP1 signaling, while FKBP7 in pancreatic cancer-associated fibroblasts remodels collagen deposition to enhance invasion (40,41). FKBP10, overexpressed in multiple solid tumors, supports ribosomal translation and stabilizes structural proteins (10,42). These functions highlight FKBPs as tractable targets for either enzymatic inhibition, interference with client binding (e.g., BiP, Hsp47), or RNA interference/antisense oligonucleotide-based knockdown to impair tumor proteostasis and sensitize cancers to therapy.

Table I. FKBPs as therapeutic targets to restore proteostasis.

FKBP (protein; *gene*)	Disease context	Proteostasis axis leveraged	Therapeutic strategy	(Refs.)
FKBP12 (*FKBP1A*)	Parkinson's disease (α-synuclein aggregation)	Protein folding and aggregation control	Non-immunosuppressive PPIase inhibitors (e.g., ElteN378), peptidomimetics disrupting FKBP12-α-syn interaction	(66,67,69)
FKBP51 (*FKBP5*)	Alzheimer's disease (tau aggregation)	Chaperone-dependent folding and oligomer stabilization	Selective FKBP51 ligands; inhibitors of FKBP51-Hsp90-tau interface	(77)
	Cancer (melanoma, prostate, pancreatic)	Post-translational modification scaffolding (Akt/PTM balance)	Scaffold modulators; PROTACs/ASOs to downregulate overexpression	(50-52)
	Metabolic disorders (obesity, insulin resistance)	Kinase phosphorylation scaffolding (AKT, AMPK, mTORC1)	Small-molecule FKBP51 modulators; PROTACs; siRNA/ASO therapies	(16,101,102)
FKBP52 (*FKBP4*)	Alzheimer's disease (tau degradation/ aggregation)	Autophagy-lysosome pathway and Hsp90 co-chaperone network	Allosteric inhibitors of PPIase pocket; inhibitors disrupting FKBP52-tau/ Hsp90 interaction	(12,78,79)
	Prostate/breast cancers (hormone-driven growth)	Nuclear receptor folding and trafficking	Inhibitors of FKBP52-dynein interaction; blockade of FKBP52-Hsp90-AR/ER complexes	(56-58)
FKBP12.6 (*FKBP1B*)	Heart failure, atrial fibrillation (RyR2 destabilization)	Ion channel complex stabilization	Rycals (e.g., S107) to strengthen FKBP12.6-RyR2 binding	(94)
FKBP9/FKBP60 (*FKBP9*)	Glioblastoma (ER stress adaptation)	ER proteostasis (BiP-mediated folding and UPR tuning)	RNAi/ASO knockdown; inhibitors of FKBP9-BiP interface	(40)
FKBP7/FKBP23 (*FKBP7*)	Pancreatic ductal adenocarcinoma (CAF-mediated ECM remodeling)	ER proteostasis and extracellular matrix modulation	Inhibitors preventing FKBP7-BiP competition; stromal-targeted strategies	(41)
FKBP10/FKBP65 (*FKBP10*)	NSCLC, CRC, RCC, bladder cancer, glioma	Translational homeostasis and collagen/protein maturation	PPIase inhibitors; blockade of FKBP10-Hsp47 or FKBP10-prelamin A interactions; RNAi/ASO knockdown	(10,42,45,46)

FKBP, FK506-binding protein; α-syn, alpha-synuclein; PTM, post-translational modification; AKT, protein kinase B; AMPK, AMP-activated protein kinase; mTORC1, mechanistic target of rapamycin complex 1; Hsp90, heat shock protein 90; AR, androgen receptor; ER, endoplasmic reticulum; RyR2, ryanodine receptor 2; BiP, binding immunoglobulin protein; UPR, unfolded protein response; CAF, cancer-associated fibroblast; ECM, extracellular matrix; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; RCC, renal cell carcinoma; RNAi, RNA interference; ASO, antisense oligonucleotide; PPIase, peptidyl-prolyl cis-trans isomerase.

In the cardiovascular system, FKBP12.6 stabilizes the RyR2 calcium channel and prevents diastolic calcium leak. Small molecules such as rycals (e.g., S107) that strengthen FKBP12.6-RyR2 binding have shown promise in preclinical HF and arrhythmia models by restoring calcium homeostasis (94). In metabolism, FKBP51 acts as a scaffold to fine-tune kinase phosphorylation, balancing AKT, AMPK and mTORC1 signaling. Selective FKBP51 modulators, degraders or oligonucleotide-based strategies represent emerging tools to correct its dose-dependent bidirectional effects on glucose tolerance, lipid balance and autophagy (16,100,101) (Table I).

Collectively, these examples establish FKBPs as a novel class of proteostasis regulators that bridge molecular folding networks with system-level disease mechanisms. Therapeutic strategies tailored to individual family members and disease contexts not only expand our understanding of the

Table II. Proteostasis-regulating roles of less-studied FKBPs across disease contexts.

FKBP (protein; *gene*)	Disease context	Mechanism of proteostasis regulation	(Refs.)
FKBP38 (*FKBP8*)	Inflammatory bowel disease	Binds MLCK1 to facilitate its recruitment to the perijunctional actomyosin ring, regulating epithelial barrier protein stability	(111)
	Glioblastoma	Modulates Bcl-2 stability and participates in protein folding and autophagy, maintaining tumor cell proteostasis	(112)
FKBPL	Neuronal injury (axon degeneration, RGC death)	Interacts with DLK to inhibit its kinase activity and promotes lysosome-dependent degradation, regulating axonal proteostasis	(113)
FKBP22 (*FKBP14*)	Connective tissue disorders (vascular Ehlers-Danlos syndrome)	ER-resident PPIase catalyzing proline isomerization in collagen, ensuring proper collagen folding and secretion	(33)
FKBP25 (*FKBP3*)	Cancer	Suppresses mTORC1 activity and promotes autophagy; its stability is regulated by ubiquitination, influencing protein degradation and tumor growth	(36)
FKBP51 (*FKBP5*)	Huntington's disease	PPIase activity modulates folding and aggregation of mHTT; inhibition enhances autophagic clearance of mHTT	(9)

FKBP, FK506-binding protein; MLCK1, myosin light chain kinase 1; Bcl-2, B-cell lymphoma 2; RGC, retinal ganglion cell; DLK, dual leucine zipper kinase; ER, endoplasmic reticulum; PPIase, peptidyl-prolyl cis-trans isomerase; mTORC1, mechanistic target of rapamycin complex 1; mHTT, mutant huntingtin.

proteostasis-disease axis but also provide a foundation for precision interventions targeting multi-organ disorders.

9. Proteostasis-regulating roles of less-studied FKBPs across disease contexts

While much attention in the literature has focused on canonical FKBPs such as FKBP51, FKBP52 and FKBP12, emerging evidence highlights the functional significance of other, less-studied FKBP family members in regulating proteostasis across diverse disease contexts. FKBP38 (FKBP8) regulates epithelial barrier integrity in inflammatory bowel disease by recruiting MLCK1 to the perijunctional actomyosin ring, and also modulates Bcl-2 stability and autophagy in glioblastoma to preserve tumor cell proteostasis (111,112). FKBPL has been shown to interact with DLK to inhibit its kinase activity and promote lysosome-dependent degradation, thereby maintaining axonal proteostasis in neuronal injury (113). In connective tissue disorders such as vascular Ehlers-Danlos syndrome, FKBP22 (FKBP14) functions as an ER-resident PPIase that ensures proper collagen folding and secretion (33). FKBP25 (FKBP3) influences proteostasis by suppressing mTORC1 activity and promoting autophagy, while its stability is tightly regulated by ubiquitination (36). Table II summarizes the current understanding of these underexplored FKBPs, their associated pathologies and the key mechanisms by which they influence protein homeostasis.

10. Conclusion

Protein homeostasis is fundamental to the preservation of cellular integrity and its disruption represents a common pathological axis across cancer, neurodegeneration, cardiovascular dysfunction and metabolic disorders. This review highlights FKBPs as versatile modulators of proteostasis, acting through diverse mechanisms including conformational control, chaperone-assisted folding, complex stabilization, stress adaptation and selective degradation. By integrating these processes, FKBPs emerge not merely as accessory factors but as central regulators that shape the fate of disease-related proteins and determine cellular resilience or vulnerability.

The synthesis of the present review demonstrates that distinct FKBP isoforms exert disease-specific functions: ER-resident members such as FKBP7/9/10 orchestrate tumor proteome remodeling, FKBP12 drives pathogenic protein aggregation in PD, FKBP51 and FKBP52 modulate tau balance in AD, FKBP12.6 safeguards cardiac rhythm by stabilizing RyR2 and FKBP51 fine-tunes metabolic kinase signaling to maintain systemic balance. These findings collectively establish FKBPs as critical bridges linking proteostasis to multi-system pathogenesis.

Importantly, their structural modularity and context-dependent functions position FKBPs as novel and druggable nodes within proteostasis networks. Therapeutic strategies targeting FKBP-client interactions, their scaffold functions or their enzymatic activity provide unprecedented opportunities to restore proteostasis in disease states. Moving forward, integrating chemical biology, structural proteomics and translational studies will be essential to exploit FKBPs as precision targets. By reframing FKBPs within the proteostasis paradigm, this review not only expands our conceptual understanding of disease biology but also charts a new course for therapeutic innovation across multiple organ systems.

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Authors' contributions

ZL was involved in the conceptualization of the study and in writing-original draft, writing-review and editing. XL contributed to the writing-review and editing, performed visualization and provided supervision. HZ obtained resources, acquired funding and was involved in writing-review and editing. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Declaration of generative AI in scientific writing

During the preparation of this work, artificial intelligence tools ChatGPT (GPT-5; 2025 version; OpenAI) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript'

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