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FKBP5/FKBP51 on weight watch: central FKBP5 links regulatory WIPI protein networks to autophagy and metabolic control

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ABSTRACT

Stress and changes in energy stores are perceived by hormone- and nutrient-sensing nuclei of the hypothalamus, which orchestrate an adaptive physiological body response to maintain homeostasis. Macroautophagy/autophagy is a fundamental lysosomal degradation system contributing to preservation of proteome balance and metabolic homeostasis. Its dysregulation is linked to diverse human pathologies, including neuropsychiatric and metabolic disorders. Autophagy is coordinated by cellular nutrient sensors, including AMPK and MTORC1 that interact with WIPI proteins. Studies suggest that WDR45/WIPI4 interacts with the stress-sensitive co-chaperone FKBP5/FKBP51, which has emerged as a key autophagy scaffold. However, the impact of FKBP5 on autophagy signaling in response to metabolic challenges, such as a high-fat diet, is elusive. Therefore, we manipulated FKBP5 in the mediobasal hypothalamus (MBH) and studied autophagy signaling and protein interactions in their physiological context. We identified FKBP5 as a scaffold of the STK11/LKB1-AMPK complex with WDR45/WIPI4 and TSC2 with WDR45B/WIPI3 in response to metabolic challenges, positioning FKBP5 in major nutrient-sensing and autophagy-regulating networks. Intriguingly, we could demonstrate that *FKBP5* deletion in the MBH strongly induces obesity, whereas its overexpression protects against high-fat diet-induced obesity. Our findings suggest a crucial regulatory and adaptive function of FKBP5-regulated autophagy within the MBH in response to metabolic challenges.

Abbreviations: AKT: thymoma viral proto-oncogene; AMPK: AMP-activated protein kinase; BECN1: beclin 1, autophagy related; eWAT: epididymal white adipose tissue; FKBP5/FKBP51: FK506 binding protein 5; KO, knockout; MBH, mediobasal hypothalamus; MTORC1, mechanistic target of rapamycin kinase complex 1; p: phosphorylated; PHLPP: PH domain and leucine rich repeat protein phosphatase; RPS6KB/p70S6K: ribosomal protein S6 kinase; SKP2: S-phase kinase-associated protein 2; SM: soleus muscle; SQSTM1/p62, sequestosome 1; STK11/LKB1: serine/threonine kinase 11; TSC: TSC complex; ULK1: unc-51 like kinase 1; WIPI: WD repeat domain, phosphoinositide interacting; WT: wild type

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Being overweight and exposure to stress are prevalent phenomena in our societies and contribute to socioeconomic health problems. Nutrient- and hormone-sensing nuclei in the hypothalamus orchestrate complex central and peripheral body responses to maintain energetic homeostasis. Alterations in metabolism can negatively affect hypothalamic proteostasis and regulatory functions, such as circadian rhythmicity and endocrine stress response. The latter is strongly modulated by the stress-sensitive protein FKBP5/FKBP51, which – in addition to its function in the stress response – has emerged as a key scaffold in various types of autophagy, connecting stress and metabolism. Autophagy is initiated and inhibited by the metabolic sensors AMPK and MTORC1, respectively, that both interact with WIPI/WDR45 proteins. Interestingly, previous studies have shown that WDR45/WIPI4 interacts with FKBP5. To elaborate on the role of FKBP5 in autophagy, we studied FKBP5 autophagy-relevant signaling and protein interactions in the context of metabolically challenging conditions and in a hypothalamus (MBH) tissue-specific manner [1].

Following nutrient deprivation *in vitro*, murine neuroblastoma cells lacking FKBP5 fail to induce autophagy to the same extent as WT cells. This is reflected by reduced STK11/LKB1-AMPK pathway activity and enhanced negative regulation of BECN1 through the AKT-SKP2 complex, which no longer is inhibited by the FKBP5-mediated recruitment of PHLPP. In fact, autophagy signaling is attenuated under baseline conditions already, as is evident by increased levels of branched-chain amino acids and p-RPS6KB/p70S6K (T389), a downstream target of activated MTORC1. In contrast, ectopic FKBP5 increases autophagy signaling through p-AMPK (T172), and largely reverts the metabolic phenotype of FKBP5-deficient cells. From a metabolic perspective, these data highlight the importance of FKBP5 in the autophagic stress response after starvation and suggest a tight control on STK11/LKB1 and AMPK.

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To position FKBP5 into nutrient-sensing and autophagy-regulating protein networks, we built on previous work and identified novel interaction partners of FKBP5, and characterized their inter-regulation. In addition to the already known interaction of FKBP5 with WDR45/WIPI4, we revealed a novel association with WDR45B/WIPI3. Both WIPI proteins are scaffolds for STK11/LKB1-AMPK-TSC signaling circuitries that play essential roles in cellular energy response pathways, autophagy and MTORC1 signaling. We confirmed that FKBP5 interacts with the AMPK master upstream kinase STK11/LKB1 and AMPK subunits PRKAA1/α1 and PRKAG2/γ2 and also uncovered an association with the non-catalytic PRKAB1/β1 subunit. Interestingly, deletion of *Wdr45/Wipi4* not only weakens binding of FKBP5 to AMPK but also reduces p-AMPK (T172). Similarly, interaction of WDR45/WIPI4 with AMPK depends on FKBP5. We also investigated the functional relevance of WDR45B/WIPI3-FKBP5 binding and identified TSC2 as a WDR45B/WIPI3-dependent interaction partner of FKBP5, whereas the association of WDR45B/WIPI3 with the TSC1-TSC2 complex is independent of FKBP5.

Thus, we define two novel FKBP5-containing protein heterocomplexes that are both critical to nutrient sensing and autophagy throughout the whole body. Most importantly, these complexes are not only subject to their regulating signals, but also to fine-tuning by FKBP5, whose expression is controlled by the activity of glucocorticoids secreted by the stress-hormone axis.

Translating our findings to an *in vivo* model, we went on to investigate the relationship between FKBP5 expression and autophagy in the context of a metabolic stressor (high-fat diet; HFD) and characterized autophagy markers in peripheral, metabolically-active tissues, SM, eWAT and in the MBH, a key brain region involved in nutrient-dependent metabolic regulation. Animals fed an HFD display increased MBH FKBP5 and decreased SQSTM1/p62 levels, indicative of an active central autophagic flux after HFD. However, in peripheral tissues SM and eWAT, HFD leads to a reduction or even blockage of autophagy, leading to SQSTM1/p62 accumulation. Also,

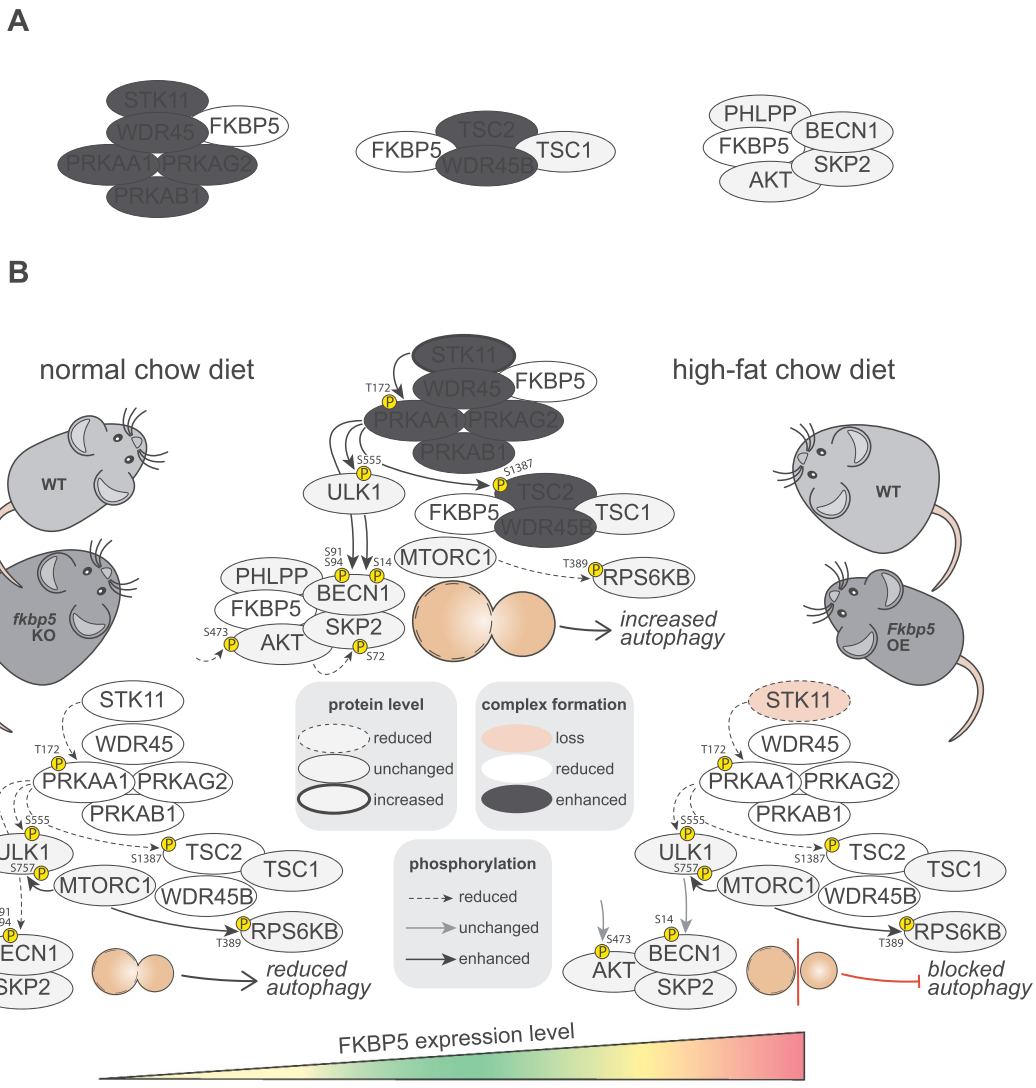

Figure 1. FKBP5 in the MBH regulates autophagy in an inversed U-shaped manner. (a) FKBP5 regulatory heterocomplexes. (b) FKBP5 protein levels determine protein interactions relevant for autophagy activity in the MBH. Deletion of *Fkbp5* in the MBH strongly induces obesity, whereas its overexpression protects against HFD-induced obesity.

FKBP5 levels do not significantly change in peripheral tissues, SM and eWAT.

To further assess the effects of FKBP5 on whole-body autophagy signaling and metabolism *in vivo*, we then specifically manipulated central FKBP5 expression levels in the MBH. Interestingly, *fkbp5* MBH-KO mice rapidly accumulate bodyweight within six weeks post *fkbp5* deletion, despite regular diet. In addition, *fkbp5* MBH-KO mice display decreased glucose tolerance and increased food intake – phenotypes resemblant of many metabolic disorders. Confirming our *in vitro* results, deletion of *Fkbp5* in the MBH reduces heterocomplex formation around AMPK and TSC2 via WDR45/WIPI4 and WDR45B/WIPI3, respectively. This causes less active AMPK, and AMPK and ULK1 downstream targets, ultimately favoring AKT-MTORC1 signaling at the expense of autophagy.

Remarkably, ectopic FKBP5 in the MBH of animals that are fed an HFD, leads to a significant reduction in bodyweight gain, which is paralleled by a reduced food intake, improved glucose tolerance and insulin sensitivity when compared to the corresponding control group. To our surprise, excessive upregulation of FKBP5 in the MBH dampens autophagy and even suggests a blocked central autophagic flux.

Contrary to *fkbp5* MBH-KO mice, *Fkbp5* MBH-OE mice display enhanced heterocomplex formation in peripheral tissues, resulting in increased AMPK activity, and AMPK and ULK1 downstream targets, indicating enhanced autophagy initiation in the periphery, while MTORC1 signaling is reduced. Because the MBH regulates sympathetic outflow to peripheral tissues, we assessed whether *Fkbp5* MBH-OE influences sympathetic tone of the brain to the periphery. Indeed, catecholamine turnover rates in muscle and eWAT are reduced, indicative of a dampened sympathetic outflow. Thus, the balance between active MBH MTORC1 and active autophagy signaling in the periphery is one driving factor that contributes to the lean phenotype of *Fkbp5* MBH-OE mice. Conversely, peripheral autophagy is diminished in *fkbp5* MBH-KO and contributes to the obese phenotype.

Overall, these findings led us to hypothesize that FKBP5 expression levels directly correlate with the degree of autophagy signaling. By gradually titrating FKBP5 *in vitro* in murine neuroblastoma cells, we demonstrate an inverted U-shaped relationship between FKBP5 expression and autophagy, with moderate increases of FKBP5 supporting autophagy and excessive levels inhibiting it, while supporting AKT-MTORC1 signaling.

In our study, we identified FKBP5 as a central nexus for recruiting STK11/LKB1-AMPK complexes to WDR45/WIPI4 and TSC2 to WDR45B/WIPI3, balancing autophagy and MTORC1 signaling in response to metabolically challenging conditions. FKBP5 in the MBH regulates both central and peripheral autophagy in a dose-dependent manner, with deletion of *Fkbp5* in the MBH inducing obesity, and overexpression of it leading to protection against HFD-induced obesity (see Figure 1 for a graphical summary). Understanding interconnected cellular metabolic and neuroendocrine responses will ultimately aid in the treatment of systemic illness of stress-related disorders.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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