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Synphilin-1 in Neuroprotection and Metabolic Regulation: Implications in Parkinson Disease and Obesity

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ABSTRACT

Synphilin-1, a cytosolic protein, interacts with a variety of proteins involved in an array of cellular activities. Synphilin-1 links multiple signaling pathways and is implicated in Parkinson's disease (PD) and obesity-related metabolic disorders, although its normal physiological function is not fully understood. Recent studies suggest that synphilin-1 interacts with various proteins to form an interaction network that regulates various signaling events. Here, we review these findings on synphilin-1 and its protein interaction partners to elucidate its potential role in protein aggregation, neuroprotection, and control of energy balance underlying the pathogenesis of PD and obesity. These insights into synphilin-1 may provide new avenues into the understanding of the pathogenesis of PD and obesity and aid in identifying potential therapeutic targets for intervention.

Key words: Synphilin-1; neuroprotection; energy balance; α-synuclein; LRRK2; food intake; obesity; AMPK; Parkinson's disease

INTRODUCTION

The human synphilin-1 gene encodes a 919 amino acid cytoplasmic protein, initially identified as an α-synuclein interacting protein via yeast two-hybrid analysis [1]. The interaction between these two proteins has been reported to promote the formation of Lewy body-like inclusion [2–7]. PD is a common neurodegenerative disorder characterized by the selective loss of dopaminergic neurons and the presence of Lewy bodies. Mutations in α-synuclein gene cause early onset genetic PD [8–10]. α-synuclein is a major protein component in Lewy bodies and Lewy neurites of sporadic PD [11,12]. Synphilin-1 has also been detected as an intrinsic component of Lewy bodies along with α-synuclein in PD cases [13]. However, the normal physiological function of synphilin-1 is not fully understood. Recent studies suggest that synphilin-1 interacts with various proteins to form an interaction network that regulates signaling events involved in neuronal survival, protein aggregation and energy balance. Here, we review these findings on synphilin-1 and its protein interaction partners to delineate its potential role in neuroprotection and control of energy balance. We call for more research on further studying synphilin-1-linked pathways and validating synphilin-1 and its interaction partners as potential targets for the intervention of PD and obesity.

1. SYNPHILIN-1 PROTEIN AND EXPRESSION PATTERN

Human synphilin-1 gene is located on Chromosome 5q23.1-23.3, comprises 10 exons, and encodes a protein with 919 amino acid residues [1]. The synphilin-1 protein has four predicted ankyrin-like repeats, an ATP/GTP binding domain and a coiled-coil domain (**Fig. 1**, top panel) [1]. Synphilin-1 is expressed diffusely in the cytoplasm of many tissues and cell types [1,5,15]. In the brain, it is expressed in various regions including the substantia nigra (a main PD-affected area) and hypothalamic nuclei (involved in control of food intake) [16]. Synphilin-1 has been detected in presynaptic nerve terminals, where it is associated with synaptic vesicles [15]. In young rats, synphilin-1 is located in neuronal cell bodies, but gradually migrates to neuropil during development. In adult rats, synphilin-1 has been detected in neuropil and presynaptic nerve terminals [15]. Synphilin-1 expression is elevated in human PD brain tissues [52]. Genetic studies of synphilin-1 gene in familial and sporadic German PD patients identified the R621C mutation in two sporadic PD patients, suggesting a putative disease associated role in PD [2,14].

There is one splice variant, synphilin-1A (14) (**Fig. 1**, lower panel), which lacks the N-terminal 394 amino acids of synphilin-1, but includes an additional 28 amino acids at the N-terminus and 51 amino acids at the C-terminus [14]. This variant has a different start codon with a different initial reading frame. Synphilin-1A is aggregation-prone and neurotoxic, exhibiting an effect opposite to that of synphilin-1 [14]. Synphilin-1A also interacts with α-synuclein and synphilin-1, promoting their recruitment to protein inclusion bodies [14]. Synphilin-1A is also detected in Lewy bodies in patients with PD and Diffuse Lewy Body Disease [14]. Detailed discussion on synphilin-1A can be found in previous reviews [2,17] and is not the focus here.

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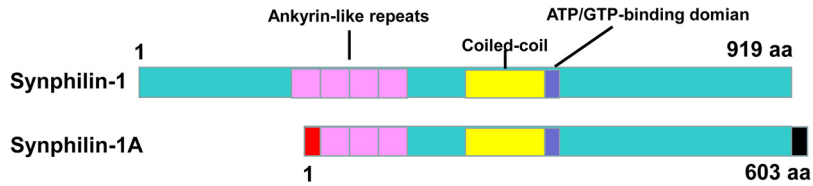

Figure 1. Predicted domains of synphilin-1 and synphilin-1A.
Top: Synphilin-1 (919aa) with putative ankyrin-like repeats (4), coiled-coil and ATP/GTP-binding domains. Bottom: Synphilin-1A lacks the N-terminal 394 amino acids of synphilin-1, but has similar putative domains as synphilin-1 except with shorter ankyrin-like repeats (3).

2. SYNPHILIN-1 INTERACTOME

The coiled-coil domain and four ankyrin-like repeats of synphilin-1 may likely facilitate its interaction with other proteins. Figure 2 lists the reported synphilin-1 interaction partners, which are involved in a variety of cellular pathways and regulate multiple biological processes. In PD, synphilin-1 interactome has been reported to contribute to protein degradation and aggregation and neuronal toxicity. Here, we summarize the potential consequences of syphilin-1 and its linked cellular pathways or functions based on published literature (**Fig. 3**).

2.1. Synphilin-1 promotes protein aggregation

Protein aggregation and deposition resulting in Lewy bodies are major pathological hallmarks of PD. Synphilin-1 is a major constituent of Lewy bodies and can be detected in 80–90% of the Lewy bodies in PD brain samples [13]. Synphilin-1 interacts with multiple proteins involved in protein ubiquitination and aggregation, and these interactions are crucial for Lewy body formation.

Synphilin-1 interacts with PD causing and/or related proteins and alters protein degradation and aggregation. The first reported synphilin-1 interaction protein is α-synuclein. Amino acid residues 30–543 of α-synuclein bind with synphilin-1, promoting α-synuclein-containing aggregates [1–7,51]. Synphilin-1 is predominantly present in the central core of Lewy bodies, whereas α-synuclein is more widespread [13]. In cultured cells, co-expression of α-synuclein and synphilin-1 results in the formation of Lewy-body-like protein inclusions that containing ubiquitin [2–6]. Increase of α-synuclein phosphorylation at serine 129 promotes synphilin-1 ubiquitination and inclusion formation [4]. Synphilin-1 increases the formation of aggresomes containing α-synuclein under oxidative stress and/or proteasome inhibition [4,33,34]. Studies suggest that aggresomes containing α-synuclein and synphilin-1 may have a neuroprotective role by sequestering the toxic proteins [33] and facilitating their removal from cells by autophagy [35]. Some studies indicate that synphilin-1 may promote the formation of aggresome-like inclusions in mouse brains by increasing beclin-1 and LC3 II expression [7].

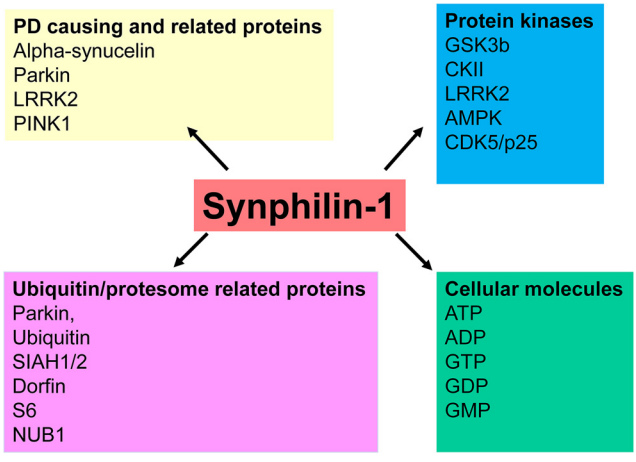

Figure 2. Synphilin-1 interaction network.
Synphilin-1 interacts with four categories of proteins or molecules: 1) PD-related proteins (α-synuclein, Parkin, Pink1 and LRRK2); 2) Ubiquitin/proteasome related proteins (Parkin, ubiquitin, SIAH1/2, Dorfin, S6, NUB1); 3) Protein kinases (GSK3B, CKII, LRRK2, AMPK, and CDK5/p25); and 4) Cellular molecules (ATP, ADP, GTP, GDP and GMP).

Synphilin-1 interacts with leucine-rich repeat kinase 2 (LRRK2) [18]. Mutations in the LRRK2 gene are a common cause of familial PD with autosomal-dominant pattern and pleomorphic pathology, also contributing to sporadic PD. Patients with LRRK2 mutations often display dopaminergic neurodegeneration, Lewy bodies and tau pathology with a good response to L-DOPA treatment, similar to sporadic PD [19]. LRRK2 interacts with the N-terminal 1-349 aa of synphilin-1 [18], which partially overlaps with the binding sites for α-synuclein and Parkin [1,6]. Synphilin-1 primarily interacts with LRRK2's C-terminal regions, including the COR, kinase, and WD domains [18]. This interaction may limit LRRK2 activity and/or functions by suppressing LRRK2 GTPase and kinase domains. Our studies found that co-expression of synphilin-1 with LRRK2 reduces LRRK2 kinase activity and increases LRRK2-induced cytoplasmic aggregation [18].

Synphilin-1 interacts with multiple proteins that are involved in the ubiquitin/proteasome pathways [17]. It binds to E3 ubiquitin-ligases, including Parkin, SIAH (seven in absentia homologs)-1, SIAH-2, and Dorfin, playing a role in ubiquitin-mediated protein degradation and aggregation [20–22]. Synphilin-1 interacts with Parkin at 214-556 aa and is a Parkin substrate, promoting the development of ubiquitinated aggregates containing α-synuclein, parkin and ubiquitin [6]. Mutations in *Parkin* cause early-onset familial PD through a loss of function mechanism. Parkin ubiquitinates synphilin-1 predominantly in a proteasomal-independent manner via K63-linked polyubiquitin chains, leading to protein aggregation formation [36]. SIAH ubiquitinates synphilin-1 predominantly via K48-linked polyubiquitin linkage chains, which causes synphilin-1 degradation (24-26). While Dorfin can ubiquitylate synphilin-1, but the consequences are not clear and remains to be further investigated [37]. In PD, synphilin-1 may promote both K48- and K63- linked ubiquitination of itself to alter interactions with other protein patterners, resulting in the clearance of toxic proteins by degradation and sequestration in Lewy bodies. Overwhelming synphilin-1-linked ubiquitination or hyperphosphorylation of synphilin-1 (leading to reduce ubiquitination) may contribute to PD pathogenesis.

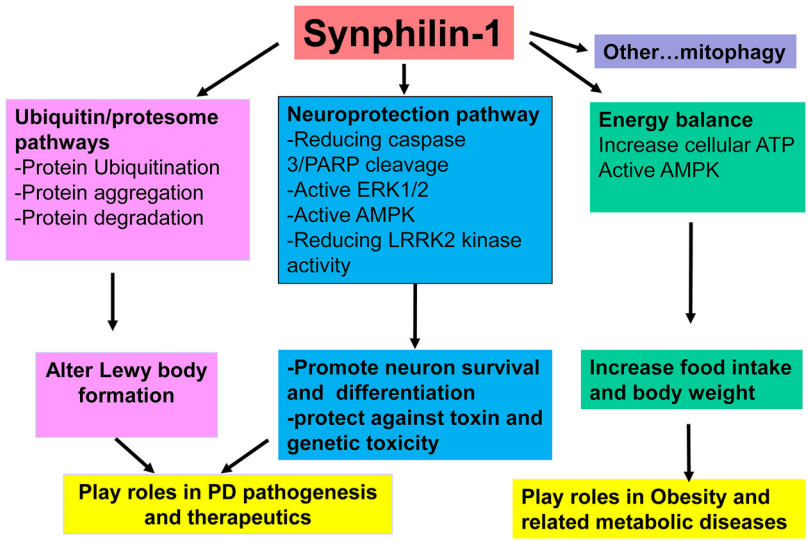

Figure 3. Synphilin-1-related signaling pathways.
Synphilin-1 has been reported to be involved in regulating multiple cellular pathways. 1) Ubiquitin/proteasome pathway, regulating protein ubiquitination, aggregation and degradation; 2) Neuroprotection pathway regulating caspase3/PARP cleavage, and ERK1/2, AMPK and LRRK2 activities; 3) Energy balance pathway, regulating food intake and controlling body weight; 4) other pathways (e.g. mitophagy) [15,54,55]. Synphilin-1 may alter pathways 1) and 2), thereby contributing to PD pathogenesis, and may modulate pathway 3), thereby contributing to the pathogenesis of obesity and related disorders.

Synphilin-1 interacts with proteasome subunits/regulators, specifically S6 [23,24] and NUB1 [25–27]. Synphilin-1's association with the proteasome component S6 reduces proteasome function and increases the formation of synphilin-1-containing inclusions [23,24]. NUB1 is a potent down-regulator of the ubiquitin-like protein, NEDD8. NUB1 binds with synphilin-1 through its NEDD8-binding site [25–27]. NUB1 reduces the formation of synphilin-1-positive inclusions and induces its proteasomal degradation of synphilin-1 [25–27]. NUB1 co-presents with abnormal α-synuclein in the brain of dementia with Lewy body patients [26,27].

Synphilin-1 interacts with PINK1 and promotes its translocation to the mitochondria, thereby leading to increased mitochondrial depolarization and induced mitophagy [21]. Furthermore, synphilin-1 knockdown impairs PINK-1-linked mitophagy. PINK1 disease mutants also fail to recruit synphilin-1 to mitochondria and do not activate mitophagy [21]. These findings suggest that syphilin-1/PINK1 interaction may promote the clearance of damaged mitochondria in PD, leading to neuroprotection.

Synphilin-1 also interacts with multiple protein kinases that regulate cellular signaling cascades. Besides LRRK2, protein kinases GSK3b interacts with and phosphorylates synphilin-1 [22,28]. Activation of GSK3b decreases synphilin-1 ubiquitylation and inclusion formation [22,28]. Casein kinase II (CKII) also binds with and phosphorylates synphilin-1 [29,30]. Synphilin-1 also interacts with and activates AMP-activated protein kinase (AMPK), thereby being involved in the control of energy balance [31,32], which may possibly contribute to the energy needs of protein aggregation. A recent study showed that CDK5 interacts with and phosphorylates synphilin-1 at serine 566 by conjunction with p25 [52]. This phosphorylation reduces synphilin-1′s interaction with SIAH1, resulting in decreased ubiquitination and subsequent accumulation [52]. Moreover, phosphorylation of synphilin-1 by CDK5 also reduces its interaction with PINK1, there by promoting mitophagy. In PD cases, increased brain CDK5/p25 levels may induce synphilin-1 phosphorylation, reducing its interactions with protein partners (PINK1, SIAH) and impairing its ability to support mitophagy and maintain neuronal process homeostasis [52].

The mechanisms by which synphilin-1 promotes protein aggregation in PD pathogenesis are still not fully understood and remain further investigation. Structurally, synphilin-1 includes a signal sequence for protein aggregation [14] and may act as a bridge protein to trap pathogenic proteins, forming inclusions. In PD or other disease conditions, the local brain area may undergo oxidative stress and proteasomal inhibition induced by neurodegeneration and/or neuroinflammation, which, in turn, promotes synphilin-1 interaction with toxic proteins to form aggregates. Supporting this idea, in vitro studies demonstrated that exposure H_2O_2 increases synphilin-1 and α-synuclein inclusions in cell models [4].

2.2. Synphilin-1 acts as a neuroprotective protein

Synphilin-1 has been shown to exhibit trophic and neuroprotective properties against toxin and genetic toxicity in PD cell and mouse models. Expression of synphilin-1 promotes proliferation and differentiation of mouse neuroblastoma cells (NIE-115) via activation of ERK1/2 signaling pathway [39]. Knockdown of synphilin-1 disrupts neurite outgrowth in N1E-115 cells and induces cell death compared with naïve control cells. Transient and stable overexpression of synphilin-1 protects against staurosporine and 6-hydroxydopamine-induced apoptosis in human embryonic kidney 293 cells, SH-SY5Y neuroblastoma cells, and telencephalon-specific murine 1 neurons [40,41] by inhibiting caspase-3-linked poly (ADP-ribose) polymerase cleavage, thereby reducing apoptotic cell death. Conversely, caspase-3 can cleave synphilin-1 [41] and the resulting in C-terminal fragment also possesses an anti-apoptotic role. Synphilin-1 may also decrease p53 transcriptional activity, reducing p53 promoter transactivation and mRNA levels to protect against toxin-induced cell death [41].

Synphilin-1 appears to protect against neuronal toxicity induced by PD-linked toxins such as Rotenone and 1-methyl-4-phenylpyridinium (MPP +). Rotenone, a mitochondrial complex I inhibitor (a commonly used as a natural pesticide) can induce apoptosis by increasing

oxidative damage, activation of the caspase-dependent pathway and deplete cellular ATP levels [42]. Chronic systemic exposure to rotenone in animals induces dopaminergic neurodegeneration and Parkinsonism [42]. Overexpression of synphilin-1 significantly protects against Rotenone-induced apoptotic cell death in cultured cells by reducing caspase-3 activation and PARP cleavage [39], and increasing AMPK phosphorylation (activation) and ATP levels [39]. Synphilin-1 expression also protects against MPP^+ (an inhibitor of mitochondrial complex I)-induced apoptosis in SH-SY5Y cells [43] by reducing caspase-3 cascades and cytochrome c release from mitochondria into the cytosol [43].

Synphilin-1 has been shown to protect against genetic mutation-induced neural toxicity. Co-expression of synphilin-1 and LRRK2 inhibits the protein kinase activity of mutant G2019S-LRRK2 and protects against neurodegeneration in a cultured cell model and in double transgenic Drosophila models. Synphilin-1 increases G2019S-LRRK2 fly survival, improves locomotor deficit, and reduces dopaminergic neuron degeneration. In a double transgenic mouse model, co-expression of synphilin-1 and A53T α-synuclein in mice protects against PD-like phenotypes including improving locomotor impairment and reducing brain astrogliosis and neurodegeneration [7]. Transgenic mice expressing synphilin-1 alone display some subtle changes in brain tissues but have no detectable neurodegeneration or PD-like behavioral and pathological changes [44–46].

2.3. Synphilin-1 regulates energy homeostasis

While studying the role of synphilin-1 in PD pathogenesis, we unexpectedly discovered that synphilin-1 regulates mouse food intake and body weight. Expression of human synphilin-1 in brain neurons of transgenic mice and flies induces an obesity phenotype by increasing daily food intake compared with non-transgenic control animals [16,31,32,47–49]. Pair-feeding synphilin-1 mice with the same amount of as of non-transgenic mice can reverse the body weight gain, fat deposition and prevent hyperinsulinemia, hyperleptinemia, and impaired glucose tolerance [16]. Further studies in synphilin-1 transgenic Drosophila demonstrate that expression of synphilin-1 in neurons induces hyperphagia and obesity phenotypes, but no phenotype change occurs when synphilin-1 is expressed in other peripheral metabolic cells. Moreover, expression of synphilin-1 in dopaminergic or serotonergic neurons appears to increase body weight and fat deposition more significantly than pan-neuronal or ubiquitous expression in flies [31,47]. Given that the critical role of these two types of neurons in controlling appetite, food intake and rewarding activity, synphilin-1 in these neurons may positively regulate food intake and rewarding actions. Further investigation is needed to determine whether synphilin-1 directly regulates appetite-controlling neurons or indirectly altering metabolic signaling to affect food intake.

Although the mechanism of synphilin-1-induced hyperphagia and obesity phenotypes is not fully understood, brain syphilin-1 expression patterns, cellular ATP levels and AMPK signaling may partly contribute to the positive energy balance. Immunohistochemical studies reveal that synphilin-1 is highly expressed in mouse hypothalamic nuclei, such as the paraventricular nucleus (PVN) and arcuate nucleus (ARC) [16], two major brain regions to regulate feeding and body weight. Moreover, fasting non-transgenic normal mice increases synphilin-1 expression levels in the hypothalamus, resulting in a compensatory increase in food intake after fasting. This further suggests that synphilin-1 may play a physiological role in the regulation of energy balance in the hypothalamus. Further study remains to pinpoint the predominant synphilin-1 action site (e.g., NPY, POMC) in regulating food intake.

The synphilin-1 sequence contains multiple ATP binding motifs (KXXXK) at two regions (109–349 aa and 550–660 aa) and binds both ADP and ATP [50], which are the cellular energy currency molecules. The GMP, GDP, and GTP also bind with syphilin-1 with a lower affinity than ATP [32,50], but CTP does not bind. Moreover, expression of synphilin-1 increases cellular ATP levels, which may provide more energy for various cellular activities. Abolishing ATP binding motifs in the region (550-600 aa) of synphilin-1 or knockdown of synphilin-1 by siRNA decreases cellular ATP levels [50].

AMPK is a well-known energy sensor protein which regulates energy balance, and response to the low cellular ATP levels. Recent studies also showed that synphilin-1 interacts with AMPK and enhances AMPK phosphorylation (activation) in cells and in Drosophila [31,32]. Abolishing ATP binding of synphilin-1 reduces AMPK activation but does not alter its interaction with AMPK [50]. Knockdown of synphilin-1 reduces AMPK phosphorylation and regulates its downstream kinase cascades including acetyl CoA carboxylase (ACC) and p70S6K phosphorylation. Treatment with compound C (an AMPK inhibitor) reduces synphilin-1 binding with AMPK [31,32] and decreases AMPK phosphorylation and cellular ATP levels [31,32]. Knockdown of *AMPK* attenuates food intake in non-transgenic flies and further reduces synphilin-1-induced hyperphagia, fat storage, and body weight gain in transgenic flies [31]. Expression of dominant-negative AMPK also reduces food intake in both non-transgenic and synphilin-1 transgenic flies [31]. Further investigation is needed to determine whether synphilin-1 alters other proteins to indirectly alter AMPK activity, such as via upstream kinases of AMPK (e.g. LKB1 or CaMKKβ). Nonetheless, these findings suggest that synphilin-1 appears to directly regulate AMPK activity by interacting with AMPK and providing ATP for its activation.

DISCUSSION AND FUTURE PERSPECTIVES

Continuous research effort is essential to elucidate the functions of synphilin-1 and its implications in human diseases. Current findings suggest that there is most likely an indirect connection between synphilin-1-linked neuroprotection and energy balance control. Given that synphilin-1 contains multiple ATP bindings site and binds with ATP, it may serve as an ATP carrier and/or a donor for cellular processes to maintain the neuronal survival and/or to promote protein ubiquitination and aggregation to sequester the toxic protein into inclusions (protein aggregation). Moreover, overexpression of synphilin-1 increases cellular ATP levels [50] and activates the energy currency sensor, AMPK [31,32], thus providing more energy to maintain normal activity of neurons and/or to protecting against neuronal death in the disease condition. Studies also showed that brain AMPK activation has neuroprotective effect [53]. Together these findings suggest that AMPK may act as the crossing talk point for both synphilin-1's action (neuroprotection and control of energy balance). PD patients often experience the body weight loss. The fact that synphilin-1 increases food intake and body weight may also provide more energy resources for self-defense against PD pathology. In PD patient brains, total syphilin-1 levels are increased compared with control subjects [52], which may represent self-defense mechanism against PD. Overexpression of human synphilin-1 appears to prevent body weight loss in A53T-α-synuclein/synphilin-1 double transgenic mice and delayed PD-like phenotypes, supporting the idea that synphilin-1 fostering a positive energy balance is beneficial for PD. Other direct or indirect pathways may also be involved in the connection

of synphilin-1's roles in neuroprotection and control of energy balance and warrant further investigation.

It's debatable whether protein aggregation is harmful or beneficial to the brain. It is suggested that small protein aggregates may be pro-toxic and induce neurodegeneration. Conversely, large protein aggregates such as Lewy bodies with an aggresome-like structure may serve as a defensive mechanism by sequestering overwhelmed toxic proteins for further autophagy processing and clearance [38]. To support this idea, the sequestration of α-synuclein into aggresomes accelerates its removal from the cell [33]. Synphilin-1 and α-synuclein aggregates appear to be more common in non-apoptotic cells [33]. These findings suggest that synphilin-1 binding with other proteins and regulating inclusion formation may be a protective cellular response to toxic protein accumulation in PD pathogenesis. In fact, overexpression of synphilin-1 appears to increase inclusion formation and rescue PD-like phenotypes in mutant α-synuclein and LRRK2 mouse models of PD [7,18].

Although synphilin-1 appears to benefit PD, there is still no small molecule compound to directly modulate synphilin-1 and its actions to further validate the therapeutic potential for PD intervention. In contrast, for obesity intervention, an opposite alteration of brain synphilin-1 action toward negative energy balance may be required. Currently, there is no synphilin-1 knockout mouse available. Conditional knockout in specific brain cells may further dissect the roles of synphilin-1 in protein aggregation, neuroprotection and control of energy balance. Many questions remains unanswered: How does synphilin-1 regulate protein aggregation and clearance in the protein homeostasis network? How does synphilin-1 regulate energy balance in specific brain cells and regions via which signaling pathway or neuronal circuit? Generation of conditional knockout mice and identification of novel compounds targeting synphilin-1 may provide useful tools to study *in vivo* physiological roles of synphilin-1 and validate whether synphilin-1 and its linked pathways can be therapeutic targets for PD and obesity intervention.

CONCLUSION REMARK

Synphilin-1 interacts with multiple proteins and cellular molecules and is involved in multiple cellular processes. Synphilin-1 plays critical roles in protein aggregation, neuron protection and control of energy balance, which underlie PD and obesity pathogenesis. Further studying the functions of synphilin-1 and its interaction partners may provide new insight into the pathogenesis of PD and obesity and aid in the identification of therapeutic targets and treatment strategies.

AUTHORS' CONTRIBUTIONS

Drafting the manuscript: W.W.S.; X.X.; K.K.; H.F.; H.H.; B.N.; and G.M.

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COMPETING INTERESTS

Authors stated that there is no conflict of interest.

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