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Pharmacological targeting of α-synuclein and TPPP/p25 in Parkinson's disease: challenges and opportunities in a Nutshell

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With the aging of population, neurological disorders, and especially disorders involving defects in protein conformation (also known as proteopathies) pose a serious socio-economic problem. So far there is no effective treatment for most proteopathies, including Parkinson's disease (PD). The mechanism underlying PD pathogenesis is largely unknown, and the hallmark proteins, α-synuclein (SYN) and tubulin polymerization promoting protein (TPPP/p25) are challenging drug targets. These proteins are intrinsically disordered with high conformational plasticity, and have diverse physiological and pathological functions. In the healthy brain, SYN and TPPP/p25 occur in neurons and oligodendrocytes, respectively; however, in PD and multiple system atrophy, they are co-enriched and co-localized in both cell types, thereby marking pathogenesis. Although large inclusions appear at a late disease stage, small, soluble assemblies of SYN promoted by TPPP/p25 are pathogenic. In the light of these issues, we established a new innovative strategy for the validation of a specific drug target based upon the identification of contact surfaces of the pathological SYN-TPPP/p25 complex that may lead to the development of peptidomimetic foldamers suitable for pharmaceutical intervention.

Keywords: drug target; innovative strategy; moonlighting protein; Parkinsonism; TPPP/p25; unstructured protein; α-synuclein

Druggability of intrinsically disordered proteins

Proteins that do not adopt a well-defined native structure in their isolated form are the intrinsically disordered proteins (IDPs) [1–4]. Intrinsic disorder is abundant in eukaryotic genomes, it is estimated that ~ 30% of eukaryotic proteins belong to IDPs or contain disordered regions [2]. A number of these proteins are closely related to human diseases such as neurological disorders, cancer, diabetes, and inflammation [5]. These disease-associated IDPs commonly play principal roles as hub proteins in the disease-associated protein-protein interaction networks that are potential drug targets. There is significant interest in exploiting the relatively unexplored potential of these proteins in drug discovery driven by the need to find new therapeutic targets [6–8]. The IDPs have unique structural properties such as high flexibility and conformational plasticity, which allow them to adopt different conformations when bound to different targets. These disordered proteins may display important biological functions by participating in both 'one to many' and 'many to one' interactions [8].

Abbreviations
CSF, cerebrospinal fluid; HDAC6, histone deacetylase 6; IDP, intrinsically disordered protein; MS, multiple sclerosis; MSA, multiple system atrophy; MT, microtubule; OLG, oligodendrocyte; PD, Parkinson's disease; SYN, α-synuclein; TPPP/p25, tubulin polymerization promoting protein.

Various experimental techniques are applied to characterize the structures and functions of ordered proteins, many of them can also be applied to IDPs. In the case of the X-ray crystallography method, disorder results in missing electron density in the studied crystal structures [2]. However, several techniques have been used to identify IDPs such as NMR, residual dipolar coupling, steady-state fluorescence spectroscopy, circular dichroism, differential scanning calorimetry, surface plasmon resonance, electrospray mass spectrometry, Fourier transform infrared, and Raman spectroscopies ([8] and references therein).

Target-based drug discovery has generally been accepted as the preferred method to discover new chemical entities and develop corresponding therapeutic compounds [9,10]. The rational drug design is usually based on the well-defined 3D structure of globular proteins; however, targeting disordered proteins is a challenging task, since these proteins exist in a highly flexible state and form a dynamic structural ensemble without a well-defined 3D structure. Novel strategies and the combination of computational and experimental methods are necessary to tackle this challenge [6–8,11]. The strategies suggested for targeting IDPs include: (a) the stabilization of the disordered states; (b) inhibition of the interactions with ordered or disordered protein partners; and (c) induction of allosteric inhibition [7]. In this context, biophysical techniques, including NMR and small-angle X-ray scattering coupled with molecular dynamics simulations approaches, are increasingly used to characterize the homo- and hetero-associations of IDPs that may lead to possible strategies to target aggregation-prone IDPs implicated in conformational diseases [12]. In fact, the characterization of structures and functional mechanisms of the assemblies of IDPs is requested for the discovery of therapeutic intervention strategies ([13] and references therein).

Specific drug targeting of the interactions of IDPs is challenging partly due to the ambiguity of contact surfaces [14]. Contact surfaces involving IDPs are often more extensive and flat when compared to those of ordered protein complexes, with most of the binding energy localized in 'hot spots'. The interface between a structured and a disordered partner is generally not flat; but it is still weaker than similar sized interaction between two structured proteins. The IDP interactions display complex binding surfaces having discontinuous and/or multiple binding segments, which are often devoid of groves or pockets [14]. These disordered interface regions are targets for drug discovery, if drug-like compounds can block protein-protein interactions; this issue has to be taken into consideration in the validation of drug target. In fact, ligand binding to IDPs usually may be described 'as ligand clouds around protein clouds' [14].

Compared with the well-developed drug design pipelines that target ordered (folded) proteins, the drug design that target IDPs remains in its infancy. The studied IDP-related systems in drug design are limited and only a few small molecules and short peptides have been achieved to inhibit the function of IDPs ([14,15] and references therein). Most cases of drug targeting of IDPs were carried out by experimental screening, but not by rational design.

The tumor suppressor p53 is an IDP and also a hub protein, which is regulated by its binding to various partners such as MDM2 [16]. Small molecule inhibitors of the interaction exert their effect by binding to MDM2 in the p53-binding pocket [17], therefore this case can be considered as 'drug design involving IDPs', but not 'drug design targeting IDPs'. Examples for direct targeting of IDPs are c-Myc and NUPR1 ([14,15] and references therein). The basic-helix-loop-helix-leucine-zipper domains of the c-Myc oncoprotein and its obligate partner Max are IDPs, their heterodimerization is coupled with folding. Small molecules such as α-helix mimetics have been identified by systematic screening which bind to c-Myc and stabilize it in its monomeric form, thus prevent its interaction with Max [18]. NUPR1 is a multifunctional IDP, over-expressed and involved in pancreatic ductal adenocarcinoma [19]. After screening more than 1000 compounds, the interactions of some selected ones with NUPR1 were characterized both experimentally and by simulation. Although the protein remained disordered upon binding, effective compound could be found by these methods, which arrested tumor development in a mouse model of the disease [19].

A promising approach to successfully target the interaction of IDPs is based on fragment-based drug design, which involves screening proteins against collections of low molecular weight compounds (fragments) to identify possible chemical starting points for drug discovery. Fragment-based drug design can be used to develop potent inhibitors for challenging targets, which have previously been considered 'undruggable' [20,21].

Synucleinopathies

With the aging of society, neurological disorders such as Parkinsonism become more and more widespread causing serious socio-economic problem for the society. The etiology of these diseases is initiated by the

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assemblies of unfolded/misfolded proteins, which form aggregates leading to the formation of inclusion bodies appearing as clinical symptoms [22–24] (Fig. 1). Progressive neuronal cell loss and widespread aggregation of α-synuclein (SYN) forming Lewy bodies and Lewy neurites are the major characteristics of Parkinson's disease (PD) [22]. Similarly, SYN aggregates in glial cytoplasmic inclusions are characteristic for multiple system atrophy (MSA) [25]. SYN accumulation, coupled with aggregation, oxidative and endoplasmic reticulum stress are common findings in the Parkinsonism pathogenic cascade [26,27]. In the case of mitochondrial dysfunction, there is no clear indication as to whether it is a cause of PD or rather correlated with the progression of the disease [27].

Mutations in a series of primary genes are known to cause autosomal dominant, or recessive forms of PD. The mutations in SYN, Parkin, PTEN-induced putative kinase 1, DJ-1, Leucine-rich repeat kinase 2 and Vacuolar protein sorting 35 might be causative in familial forms of PD, whereas diverse genetic defects in other loci, such as Glucocerebrosidase 1, might represent susceptibility associated with sporadic PD without family history [26,28]. DJ-1 has been linked to autosomal recessive familial PD quite recently [29,30]. The physiological function of DJ-1 is unclear, although increasing evidence suggests that it may function as an anti-oxidative protein, or a sensor of oxidative stress, or that it confers protection against endoplasmic reticulum stress and proteasomal inhibition [31]. DJ-1 overexpression clearly antagonizes much of the deleterious effects of SYN including SYN aggregation [32,33]. This issue seems to be supported by our recent collaborative studies with the Gergely Toth's laboratories (Research Center for Natural Sciences) that visualized direct interaction of DJ-1 and SYN through various biophysical measurements (unpublished result).

The motor impairments of PD can be attributed to the loss of dopaminerg neurons in the substantia nigra pars compacta; the phenotype is characterized by rigidity, resting tremor, and bradykinesia [26]. Currently no disease-modifying treatment is available for synucleinopathies, including PD; available treatments can only slow down the progression of symptoms, but not the neurodegenerative process [28,34,35]. The gold standard drug in the clinical practice is L-dopa (or levodopa) and derivatives, which all relieve symptoms through the replacement of the lost dopamine; however, large variability in drug response in terms of efficacy and adverse reactions has been observed [34,35].

The unsatisfactory efficacy of conventional antiparkinson drugs has prompted the search for novel alternatives. New research directions include the potential use of gene therapy, stem cells transplants, and neuroprotective agents [34,36]. Recent advances in therapeutic approaches provide additional options (antibodies, vaccine, antisense-oligonucleotide, and small molecules) that can help to reduce the expression levels of SYN and SYN aggregates in the brain, with some of them currently being tested in clinical trials [34,36,37].

SYN: the old hallmark of Parkinsonism

α-Synuclein is an unstructured protein, prototype of the chameleon proteins [38]; it is predominantly unfolded and capable of adopting structurally

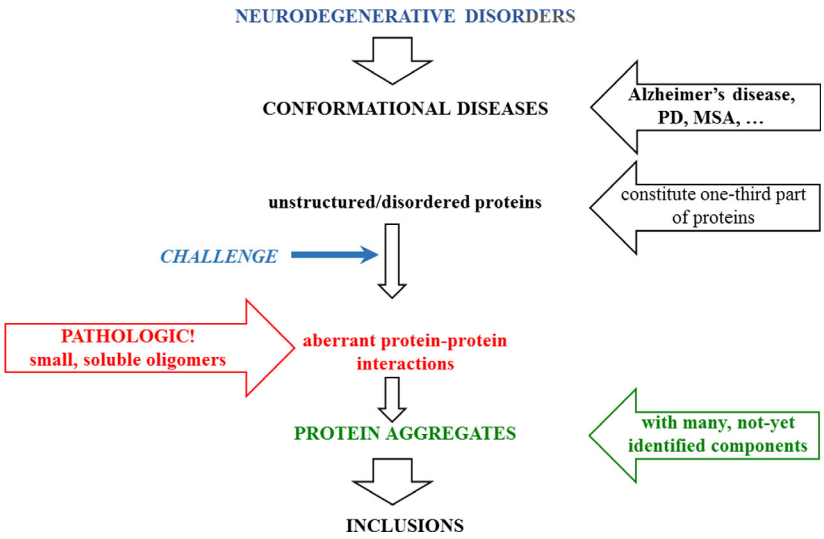

Fig. 1. The etiology of conformational diseases.

unrelated conformations induced by low pH, high temperature, and organic solvent or metal ions. Structurally SYN comprises three regions: the N-terminal region involved in lipid binding; the highly hydrophobic central NAC region; and the acidic unfolded C-terminus, which exhibits chaperone activity and may counteract the aggregative potency of SYN [36,39].

Mutations in the *SYN* gene, which encodes the SYN protein, were the first discovered genetic causes of familial Parkinsonism with Lewy pathology. To date, eight different mutations (A18T, A29S, A30P, E46K, H50Q, G51D, A53E, A53T) are known to cause Parkinsonism [40]. Most mutations accelerate SYN aggregation (A18T, A29S, E46K, H50Q, and A53T); the A30P mutation enhances oligomerization, but impedes the subsequent fibrillation, while mutations G51D and A53E attenuate the aggregation process [41,42]. Familial PD associated with SYN gene is rare, but SYN aggregation is a core feature of sporadic Parkinsonism, including PD, dementia with Lewy bodies, and MSA.

Mutations of SYN are highly clustered between residues 18–53, in the lipid-binding N-terminal region of the protein. A comparative sequence and structural analysis suggested that the 32–58 region of SYN is critical for the stability and the secondary structure of the protein [43]. This is consistent with another study, in which predominantly the 39–45 aa segment, among others, was proposed to be involved in the membrane penetration [44]. The increased oligomerization efficacy of SYN mutants is associated with enhanced propensity to penetrate the membrane [45].

In healthy individuals, SYN has been reported to bind to the surface of synaptic vesicles [36,46]. SYN is highly disordered when isolated in solution, but its micelle-bound form displays a partial helical structure that could be formed into curved α-helices [47,48]. In spite of the data accumulated so far, the physiological function of SYN is still unclear in details. Membrane-bound conformations of SYN are likely to both mediate the physiological function of SYN and have a role in the aggregation and toxicity of the protein. In PD and MSA SYN aggregates appear in a β-structure that can be either soluble or insoluble [46]. It has been suggested that SYN is involved in the modulation of neuronal plasticity, synaptic vesicle pool maintenance, and dopamine metabolism [36,39]. Moreover, SYN has been proposed as a microtubule (MT) regulatory protein (dynamase) [49–51]; as a disordered hub protein it interacts with at least 50 ligands and other proteins [52].

The pathological aggregates are formed through SYN oligomerization that results in the formation of protofibrils and insoluble cytosolic inclusions [53]. In fact, until recently, SYN aggregates were viewed as the major cause of the disease, and they were considered as drug targets; nowadays it seems to be justified that the small, soluble oligomers are the pathogenic species formed at an early stage of the disease [54,55]. SYN oligomers can interact with membrane lipids and disrupt the membranes resulting in pore-like structures [44].

Direct targeting of SYN is still one of the major objectives of the PD research (e.g. targeting oligomers by specific antibody) with the maintenance of the optimal level necessary for its physiological function [56,57].

TPPP/p25: the new hallmark of Parkinsonism

Tubulin polymerization promoting protein (TPPP), being the prototype of the neomorphic moonlighting proteins [58], displays both physiological and pathological functions without changes at gene level. The structural features of TPPP/p25 are well characterized at several organization levels [59,60]. The N- and C-termini of this disordered protein are straddling a middle, flexible CORE region that includes important binding segments [61]. The major physiological partner of TPPP/p25 is the tubulin/MT network; it has been identified as a MT associated protein; the major function of this protein is to regulate the dynamics and stability of the MT network that is ensured by its bundling (MT cross-linking) and tubulin acetylation enhancing activities [62,63]. TPPP/p25 is involved in the modulation of the acetylation level of the MT network by its inhibition of the tubulin deacetylases such as histone deacetylase 6 (HDAC6) and sirtuin-2 [63–67].

The MT network is involved in diverse cellular processes, its stability and dynamics are controlled by post-translational modifications and decoration with cytosolic proteins/enzymes [68–70]. Tubulin acetylation at Lys-40 is involved in both physiological and pathological processes, including the dynein-derived trafficking and the autophagy-aggresome pathway [71,72]. Destabilization of the MT network and defective interplay among cytoskeletal components has been observed in PD and other neurological disorders, as well as in cancer and inflammation [70,73–75]. Drug-like agents that modulate MT stability or inhibit post-translational modifiers affecting the levels of tubulin acetylation constitute the most addressed therapeutic interventions aiming to prevent cytoskeletal damage in neurodegenerative disorders [70,73–76]. MT stabilizers

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such as epithilone D displayed beneficial effects in some PD model [76].

Low tubulin acetylation levels, along with a concomitant impairment in axonal transport, is a common pathological hallmark in several neurodegenerative diseases; the application of drugs targeting MT acetylation is considered to be a useful strategy for therapeutic intervention [77,78]. Indeed, specific HDAC6 inhibitors exerted neuroprotection, rescued transport defects in some PD models [75]. Sirtuin-2 inhibitors also rescued SYN toxicity in different cellular and animal models of PD [79–81]. However, HDAC6, in addition to its tubulin deacetylase activity, also participates in the MT-dependent transport and autophagy, and is involved in aggresome formation, as well as in the fusion of autophagosomes with lysosomes [82–84]. The dysregulation of the autophagy pathway has been observed in the brain of PD patients and in animal models of PD, indicating the emerging role of autophagy in this disease [85]. Indeed, autophagy is increasingly implicated in a number of pathophysiologic approaches [85,86]. Targeting the components of the autophagy pathway has been suggested as a possible strategy for the development of novel therapies for PD [85,87,88]; nevertheless, the degradation of the pathological SYN assemblies by autophagy has not been properly solved so far.

In the healthy brain, TPPP/p25 is expressed primarily in oligodendrocytes (OLGs) and plays a crucial role in the formation of projections during OLG differentiation [89,90]. Differentiated OLGs provide most myelin sheath required for the axon ensheathment [91]. The destruction of the myelination leads to the etiology of multiple sclerosis (MS), a demyelination disease. Indeed, studies on human brain tissue from MS patients revealed the loss of the TPPP/p25-positive OLGs that is indicative for the impaired differentiation and migration capacity of OLGs [92]. In addition, enhanced level of TPPP/p25 was detected in the cerebrospinal fluid (CSF) of MS patients [93]. The drastic reduction of TPPP/p25 in OLGs has been detected in brain tissue of patients suffering from oligodendroglioma [94]. This finding concedes with our earlier observation that cancerous cells do not express TPPP/p25, possibly due to its anti-proliferative activity [60,95]. The TPPP/p25 level in the CSF of PD patients has not been investigated yet. Regarding SYN species, lower level of total SYN and enhanced concentration of oligomeric and phosphorylated SYN have been measured in the CSF of PD patients; further justification is needed [96,97]. Evidence for prion-like cell-to-cell transfer of SYN has arisen from both *in vitro* and *in vivo* studies; neuronal cells (donors) release SYN into the extracellular space, then it is taken up by various acceptor cells [36,98].

Tubulin polymerization promoting protein has been reported to interact with SYN and induce the formation of SYN oligomers and protofilaments [99–102]. TPPP/p25 and SYN co-localize and are co-enriched in both neurons and OLGs in PD and MSA, respectively (Fig. 2) [99,103–108]. In OLG cell models of MSA that involve TPPP/p25 and SYN overexpression, TPPP/p25-induced SYN aggregation was detected [79,109]. In a PC12 cell model, TPPP/p25 promoted the secretion of SYN into the medium by impairing autophagosome-lysosome fusion [110]. In the brain of MSA patients, early redistribution of TPPP/p25 preceded SYN aggregation and the formation of glial cytoplasmic inclusions [111].

Moreover, TPPP/p25 interacts with β-amyloid, a hallmark of Alzheimer's disease and promotes the formation of aggregates tightly coupled with the pathology of Alzheimer's disease [112]. Indeed, partial co-localization of β-amyloid and TPPP/p25 has been visualized by immunohistochemistry in the case of diffuse Lewy body disease with Alzheimer's disease (mixed type pathology; Fig. 2) [112].

All these findings indicate the multifarious significance of both TPPP/p25 and SYN, namely: (a) they are involved in various neurological disorders; (b) their levels in the CSF of patients may function as a biomarker; (c) they are present in the extracellular space, which is of substantial importance in their pathological assembly in both neurons and OLGs.

Targeting SYN and TPPP/p25: a new strategy to address the challenge posed by multifunctional proteins with high conformational plasticity

The interaction of TPPP/p25 with SYN has been extensively characterized in our laboratory by a wide repertoire of methodologies including biochemical, biophysical and bioinformatics methods using wild-type and mutant human recombinant proteins, as well as living cell models for immunofluorescence microscopic studies coupled with or without bimolecular fluorescence complementation technology [100–102].

α-Synuclein and TPPP/p25 as neomorphic moonlighting proteins display both physiological and pathological functions without alterations at gene level [58,113]. Both proteins are IDPs performing chameleon features with high conformational flexibility [38,102]. The drug-targeting of multifunctional (moonlighting) proteins is challenging even in the case of globular ones, since their physiological functions have

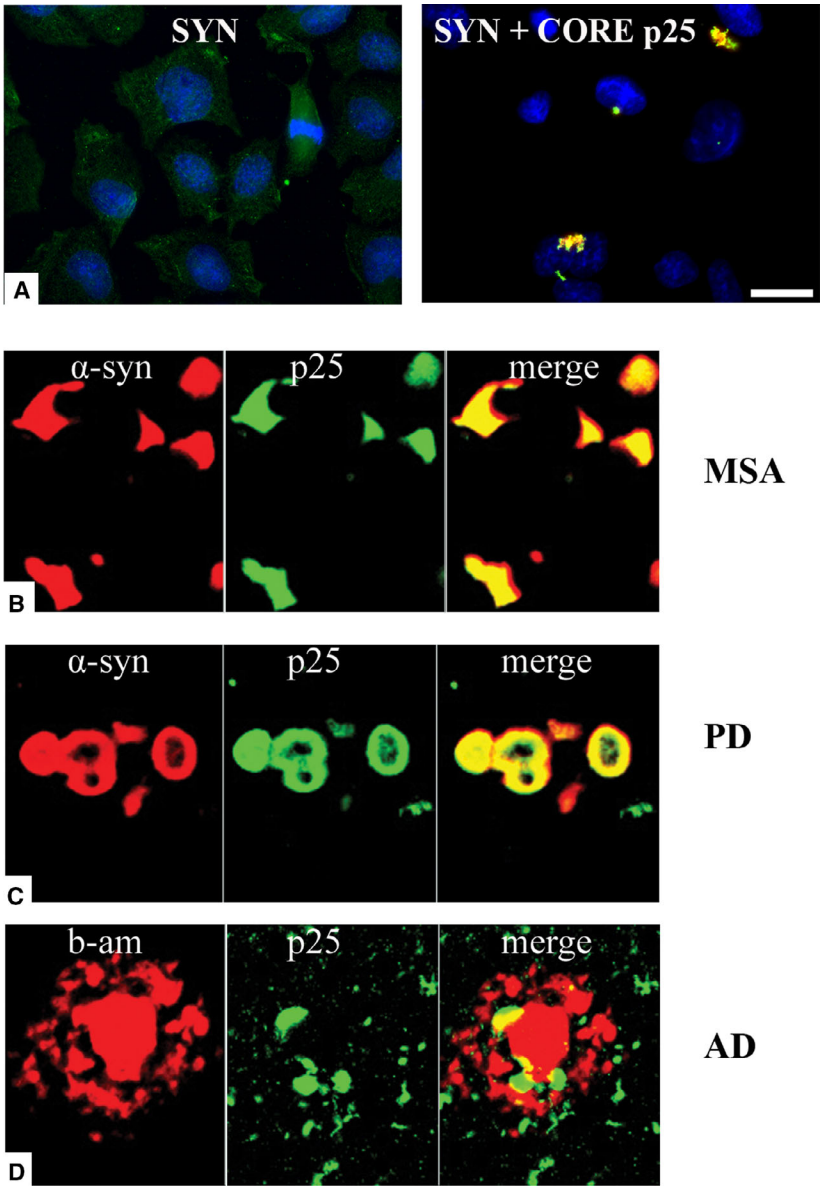

Fig. 2. Co-enrichment and co-localization of TPPP/p25 and SYN in CHO cells taken up from the medium [101] and in human brain tissues of MSA, PD and AD (mixed type pathology) [103]. Figure reproduced from [101,103]. Written permission has been obtained from Elsevier.

to be preserved. The high conformational plasticity of the neomorphic moonlighting unstructured proteins as drug targets causes extra difficulties. We have suggested an innovative strategy for the treatment of PD by development of antiparkinson medication [100–102].

To achieve the selective targeting of the pathological TPPP/p25-SYN complex without affecting the physiological TPPP/p25-tubulin one, the binding segments of TPPP/p25 involved in both types of interactions have been identified at molecular level. The segments of TPPP/p25 that are crucial for the interactions with tubulin and SYN are distinct, namely 178–187 aa and 147–156 aa, respectively (Fig. 3) [100–102]. However, the multinuclear NMR analysis pointed out another, shorter segment (59–62 aa) involved in the hetero-association of SYN and TPPP/p25 [102]. These findings indicate the role of the CORE region of TPPP/p25 in the formation of the pathological SYN-TPPP/p25 complex; in addition, the stable complex is created by the interaction between the two unstructured proteins with sufficient avidity.

Nevertheless, rather surprisingly, additional binding studies with several deletion and/or truncated mutants and synthetized peptides corresponding to the potential binding segments of TPPP/p25, revealed that these TPPP/p25 species displayed similar binding affinity to SYN except one (the two termini free mutant with

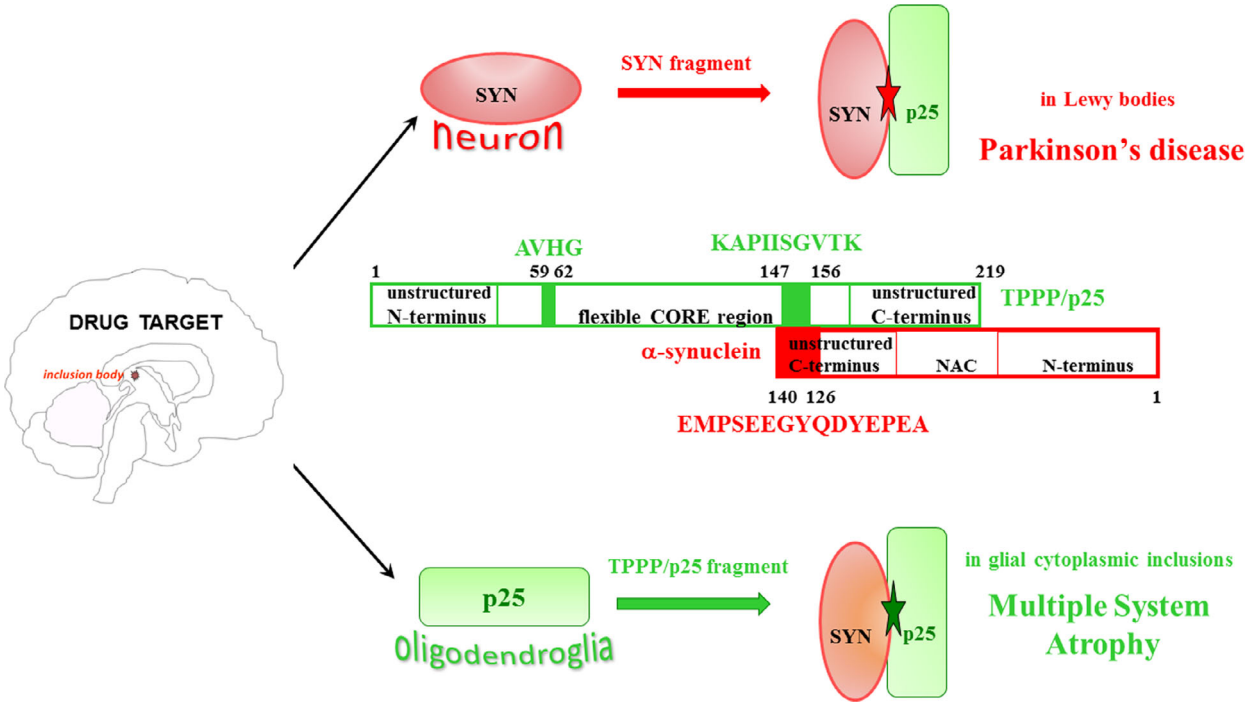

Fig. 3. Interfaces of TPPP/p25 and SYN involved in their pathological complex formation. The interfaces of both proteins are indicated on the scheme symbolizing the sequences of both SYN and TPPP/p25. The color of the stars at the interfaces illustrates the fragments of the given proteins involved in the drug targeting (see on the red and green arrows) [100–102].

deletion of the identified binding segments (59–62 + 147–156 aa) [102]. Thus, it can be concluded that the binding segments could be replaced by other ones ensuring exceptional functional resilience.

In contrast to this, the situation was entirely different with SYN mutants: the deletion of the unstructured C-terminus of SYN diminished its interaction with TPPP/p25, while the isolated recombinant human C-terminus displayed similar binding efficacy as the full-length protein [101]. All these data revealed that although targeting chameleon proteins is a challenging task, nevertheless, the validation of a drug target can be achieved by identifying the interface of complexes of the partner proteins existing at the given pathological conditions.

Design and development of antiparkinson medication

Protein-protein interactions are promising targets for drug discovery [20,21,56]. However, there are a number of protein-protein interactions where their surfaces are hard to be supported for a drug target; the drug development process is difficult and risky, as exemplified by the moonlighting and chameleon proteins. However, despite the difficulties, important progress has been made with fragment-based drug discovery playing a pivotal role in improving their tractability.

Application of small molecules with the capacity to block, or at least modulate, the toxic oligomerization of SYN appears to be a promising approach [35,56,114–116]. This concept was initiated by the definition of an early pathogenic state of SYN accumulation before occurrence of brain damage [36]. For example, the anti-amyloidogenic effect of phthalocyanine tetrasulfonate was found to be correlated with the trapping of prefibrillar SYN species, it stabilizes the helical state of SYN [117].

Recent studies revealed that both the charge and length variations of the C-terminus affected the aggregation propensity of SYN [45]. In fact, charge variation of the C-terminus significantly altered the nucleation rate, a dramatic decrease in lag times was observed for positively charged moieties [45]. Since the highly basic TPPP/p25 interacts with the unstructured negatively charged C-terminus of SYN [101,102], it may explain that TPPP/p25 substoichiometrically induces the assembly of SYN [99–102]. Furthermore, the acidic unfolded C-terminus of SYN modifies the aggregative potency, while the interaction of the

C-terminus with the N-terminus or the central NAC region of SYN can stabilize the protein [118,119].

The unstructured C-terminal segment of SYN appears to be extensively involved in the self-regulation of this chameleon protein, however, it has been recognized that this segment is critical for its chaperone activity in which the 125–140 aa segment is involved [120]. Since we have found that the 126–140 aa segment of SYN binds the CORE segment of TPPP/p25 [101], their interaction may lead to facilitated aggregation with the elimination of chaperone activity of SYN.

The assembly of the unstructured SYN and TPPP/p25 appears to be pathogenic leading to the etiology of synucleinopathies [99,103,104,107]. Indeed, their co-enrichment and co-localization has been detected in both neurons and OLGs in the cases of PD and MSA, respectively, [99,103,104,107] (Fig. 2). The pathological aggregates/inclusions are formed in both cell types, in spite of the fact that the two proteins are expressed in distinct cell types in normal brain (SYN in neurons [121,122]; TPPP/p25 in OLGs [89,90]). The destruction of the toxic heterocomplex of SYN and TPPP/p25 has been suggested as a new innovative strategy, this heterocomplex is formed exclusively at pathological conditions when the hallmark proteins are transported into neuronal/glial cells resulting in their pathological complex [100–102].This unusual situation favors the disease-specific drug targeting concerning the two Parkinsonism diseases, PD and MSA, which is based upon the following idea (Fig. 3): in the case of PD, TPPP/p25 has be to targeted by a fragment of SYN (TPPP/p25 does not have a physiological function in neurons); while in the case of MSA, the targeting of SYN with a TPPP/p25 fragment is needed (SYN does not have a function in OLGs). Thus, targeting the interface of the SYN-TPPP/p25 complex does not interfere with the physiological functions of the hallmark proteins [60,100–102].

Nowadays in the fields of drug research, peptidomimetic foldamers as potential drug-like molecules are in the focus that can bind the contact surface of the protein complexes [123–126]. In the case of unstructured/disordered proteins, peptidomimetics could also be appropriate to adapt their conformation to the target surface. This seems to be the case with proteins of high conformational plasticity such as the hallmarks of PD, as supported by our recent finding that the fragment of SYN (126–140 aa) does counteract the association of SYN with TPPP/p25 [60,100–102]. Therefore, this or related fragments could be promising drug-like agents for antiparkinson medication.

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Author contributions

Both authors have been involved in the manuscript preparation and compilation based upon several common publications focusing on the molecular basis of the neurological disorders.

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