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Original Research

1-L Transcription in Parkinson's Disease

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Abstract

Background: As a chronic degenerative disorder of the central nervous system that affects both motor and non-motor systems, Parkinson's disease (PD) is very complex, and explanations and models are needed to better understand how dopaminergic neurons are affected and microglia are activated. **Methods**: A theoretical protein-RNA recognition code that assumes that the second letter in codons is compatible with specific amino acids involved in protein-RNA recognition was used to search for compatibility of human α-synuclein (α-syn) with mRNAs in the human transcriptome (1-L transcription). **Results**: The 1-L transcription revealed compatible amino acid sequences with the ATTTA ARE (class I), PAS and polyA in α-syn, supporting a protein-RNA regulatory model. In PD, inflammatory microglia reactions, cognitive decline and motor circuit disturbances are observed. The model theoretically explains why α-syn producing neurons are less protected from inflammation and why microglia are activated. Consistent with knowledge of PD, the identified genes showed how the PI3K-AKT pathway is downregulated, how reactive oxygen species (ROS) production and sensitivity are increased, how mitochondria are destabilized, why autophagy is impaired, and why neuronal depigmentation is observed. **Conclusions**: 1-L transcription of α-syn leads to genes/proteins relevant to PD. When α-syn is accepted as a small RNA recognition protein involved in the post-transcriptional regulations, some identified genes indicate that its function is an important regulatory factor associated with intracellular and extracellular transport of RNA vesicles. These vesicles are extremely important in cellular communication. In addition, the spectrum of identified genes strongly indicates that α-syn produced by neuronal cells is required for proper regulation of inflammatory and immune responses.

Keywords: α-synuclein; bioinformatics method; identified genes; Parkinson's disease; protein-RNA recognition

1. Introduction

Parkinson's disease (PD) is classified as the second most common age-related progressive neurodegenerative disease; it is manifested by both motor and non-motor symptoms [1]. Motor symptoms are a classic finding in PD and include resting tremor, bradykinesia, postural instability, and rigidity. Non-motor symptoms of PD have become better identified over time and include cognitive decline, depression, anxiety, anosmia, and dysautonomia [1]. The precise cause of PD is still unknown, but a combination of genetic and environmental factors are thought to play a role [2]. Epidemiological studies have shown that increasing age, male sex (50% higher risk than females), and exposure to pesticides are risk factors, whereas coffee and alcohol drinking appear to be protective [1,2].

In PD, the pathological feature is depigmentation of the substantia nigra and locus coeruleus, with loss of neurons in the pars compacta of the substantia nigra [1]. In PD, the presence of intracellular aggregates/fibrils of α-synuclein (α-syn), known as Lewy bodies (LBs), is observed [3]. LBs usually occur first in the olfactory bulb or the dorsal motor nucleus of the glossopharyngeal and vagus nerves, or both (stage 1), then develops in the medulla oblongata and the pontine tegmentum (stage 2), and then reaches the amygdala and substantia nigra (stage 3). In stage 4, motor symptoms begin to appear and LBs reach the temporal cortex. During stages 5 and 6, LBs appear in the neocortex, and cognitive problems may then appear [3]. LBs are abundant fibrous inclusions of α-syn in brain cells, especially in neurites (Lewy neurites) of dopaminergic neurons (DA-neurons) [4].

Under physiologically normal conditions, "soluble" α-syn is expressed in presynapses and participates in synaptic function, however, some neurons express high levels of α-syn (DA-neurons), and others do not express the protein [5]. The levels of α-syn expression in different neuronal populations appear to be a primary determinant of α-syn prion vaccination [6], and there is evidence that heterogeneity among synucleinopathies is due to distinct pathogenic strains of prion-like α-syn aggregates/fibrils [7]. PD is also known as "aberrant vesicle-trafficking disease" [8]. Exosomes provide an ideal environment for pathogenic strains of α-syn aggregates to promote the propagation of PD pathology [8,9]. Exosomes from PD patients have been shown to be pathological in mice [10]. The cellular machinery involved in exosome biogenesis is associated with metabolism and transport in

membrane organelles including the endoplasmic reticulum, trans-Golgi network, endosomes, lysosomes, and autophagosomes that carry cellular components, especially messenger RNA (mRNA), microRNA (miRNA), interacting RNA with piwi (piRNA), non-coding RNA, and RNA-binding proteins (RBPs) (Fig. 1) [8,9]. RNA is transported throughout the axon; membrane vesicles direct transport, control the sorting of mRNA populations, and even participate in mRNA translation [11]. Soluble (non-aggregated) α-syn interacting with lipid membranes is associated with the vesicle transport [12].

1-L transcription is a very simple method that was introduced recently [13–15] that applies a theoretical protein-RNA recognition code [16,17]. An example can be given here on the RBP DAZL (deleted in azoospermia-like). DAZL binds the 3′UTR of ~2500 protein-coding genes, some of which control RNA metabolism, and binds 3′UTR sites to GUU(C/U) motifs (Fig. 2A, Ref. [18]) . It is interesting that DAZL is one of the RBPs that can use amyloid protein aggregates to regulate translation [19] (Fig. 2B,C) to act as a central regulator of gametogenesis, but is downregulated in physiologically normal DA-neurons [20]. The 1-L transcription method is based on the postulation that RBPs use at least one amino acid sequence that can be 1-L transcribed into the exact nucleotide sequence of the recognized RNA. For example, this was demonstrated on ribosomal release factor 1 (RF1) interacting with the CCA3′-end of tRNA [17]; on human WDR33, which has the N-terminal sequence QQQaMQQ responsible for the reverse read of the PAS signal in the canonical 3′-end processing of pre-mRNA [14], or on ELAVL1/HUR RBP, which is a key regulator of cellular mRNAs that contain adenylate/uridylate-rich elements (ARE) [15]. Using 1-L transcription, the amino acid sequence of DAZL can be written into the nucleotides at the second position in the amino acid codons (Fig. 2A). In the figure, it can be seen that the amino acid sequence of 83GFVSF exactly matches the sequence of GUUCU RNA bound by DAZL.

A single RBP typically recognizes hundreds of transcripts and forms extensive regulatory networks, so it is not surprising that RBPs are evolutionarily more conserved than are transcription factors [21]. In the present study, α-syn is considered to be an important small RBP that recognizes ARE, PAS, and polyA signals involved in post-transcriptional regulations (Fig. 3). Similar to α-syn, many RBPs contain intrinsically disordered amyloidogenic peptide fragments or low-complexity prion regions [22,23] and can form insoluble aggregates/inclusions, e.g., the above-mentioned DAZL. Similarly, viruses can form RBPs as multifunctional aggregation-prone proteins, for example the aggregation-prone envelope protein (E) of SARS-CoV2 can be transcribed in 1-L into a class III ARE sequence and onto compatible sequences of virally dysregulated genes [14], and RBP E alone is capable of causing damage similar to acute respiratory distress syndrome (ARDS) [24]. RBP E modifies α-syn aggregation, it co-oligomerizes with α-syn, and accelerates the formation of parallel β-sheet-containing oligomers [25].

In summary, PD belongs to the α-synucleinopathies and is a disease of aberrant vesicle trafficking, and membrane vesicles control RNA transport and sorting. "1-L transcription" of α-syn and subsequent BLASTn comparison of the transcripts with the human transcriptome revealed potentially dysregulated genes in PD. These identified genes have been comprehensively reviewed here, and the functions and spectrum of the identified genes are consistent with PD knowledge. For example, the genes cover pathways for downregulation of the PI3K-AKT, increased reactive oxygen species (ROS) production and sensitivity, neuronal depigmentation, and PARP1-energy exhaustion-induced apoptosis.

2. Methods

According to the one-letter key, one amino acid per nucleotide (1-L), RBPs use at least one amino acid sequence that is exactly compatible with the recognized RNA nucleotide sequence. A nucleotide is defined by the type of nucleotide at the second position in the amino acid codon (Fig. 2A). This fact can be used to identify RNAs that are potentially controlled/regulated by the tested RBPs (Fig. 4).

2.1 1-L Transcription Procedure

The 1-L transcription method is very simple: the amino acid sequence of RBP is transcribed into an RNA sequence, which is then used for classical BLASTn screening in the human transcriptome. Reading of the 5′-RNA by RBP can be done in both directions, using the amino acid sequence *N*-(AA)n-*C* or the reverse amino acid sequence *C*-(AA)n-*N* (Fig. 2), so the 1-L transcription should be written for two amino acid sequences, one for *N*-(AA)n-*C* and the other for *C*-(AA)n-*N*. Serine (Ser, S) has two types of codons, one type with C (cytidine) at the second position in the amino acid codon and the other with G (guanosine), so for each amino acid sequence two nucleotide sequences are obtained, one with S-C-transcription and the other with S-G-transcription. Thus, four nucleotide sequences are obtained (Fig. 4).

2.2 BLASTn Screening Process

BLASTn screening of the human transcriptome was performed as a standard nucleotide blast at NCBI (https://blast.ncbi.nlm.nih.gov/Blast.cgi) for the four nucleotide sequences separately. "Genomic + transcript databases" and "human genomic plus transcript", "somewhat similar sequences" (blastn), word size 7, maximum number of target sequences 500, and expected threshold 500, were used for the search.

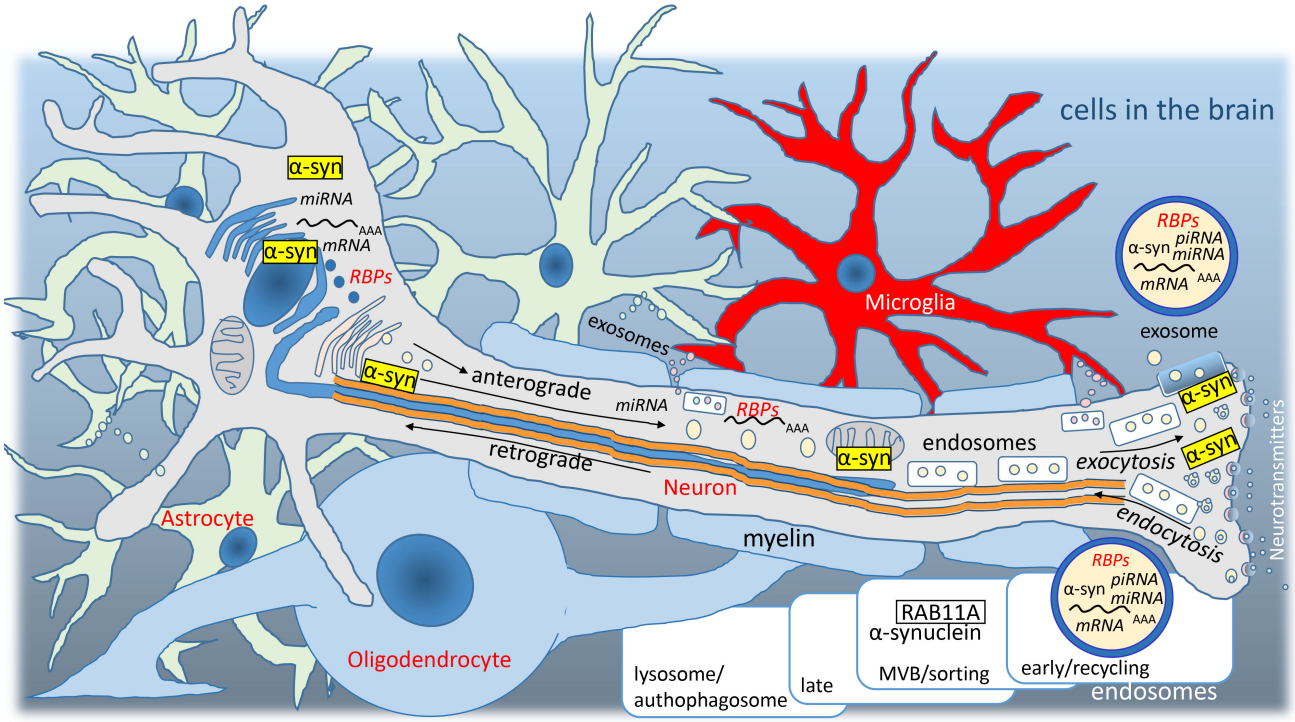

Fig. 1. Graphic representation of cells in the brain. Nerve mRNAs and RNA-binding proteins (RBPs) are transferred from the nucleus via the axon (exosomal pathway, anterograde) and glial RNAs, RBPs and other proteins are transferred from the extracellular space to the nucleus (endosomal pathway, retrograde). Dysregulation of α-synuclein (α-syn) transport and its cytoplasmic aggregates/inclusions (LBs) are a hallmark feature of Parkinson's disease (PD).

3. Results

MicroRNAs are small endogenous RNAs that pair and bind to mRNA sites to induce post-transcriptional repression, such that reducing the level of miRNAs or other small regulatory RNAs promotes translation; alignments with the reverse complement RNA sequences are considered promotive (yellow in the figures). In contrast, alignments with the RNA sequence of the gene are considered repressive (green in the figures) because sequestering and blocking of free mRNA by the test protein represses translation. The identified genes are shown in Figs. 5,6.

3.1 Identified Genes/Proteins with the Function in Plasmatic Membrane, Cytosol, or PM-Cytosol Interface

The genes/proteins are displayed in Fig. 5 and their description is done from the upper left corner down to the right. For the better orientation, the grid divides genes to 8 groups.

3.1.1 The First Group

SRPX2 (sushi repeat containing protein X-linked 2) is a neuronally expressed complement inhibitor that protects synapses from microglial engulfment and elimination [26,27]. SRPX2 regulates complement-dependent microglial synaptic phagocytosis by blocking the classical C1q-mediated complement cascade [26,27].

LCP1 (lymphocyte cytosolic protein 1)/L-plastin/LPL is an actin-bundling protein and a critical regulator of immune cell function, for example, LCP1 can function downstream of FcγR [28]. LCP1/L-plastin significantly increases the assembly of the NLRP3 inflammasome and promotes the inflammatory response [29]. Stimulation of microglia with aggregated α-syn decreased LCP1/L-plastin in microglial cell lysate [30].

TRPM1 (transient receptor potential cation channel subfamily M member 1/transient receptor potential melastatin 1; initially named melastatin/MSLN) is a founding member of the TRPM subfamily of ion channels. TRPM1 is believed to positively regulate melanocyte pigmentation [31]. The main pathological features of PD consist of the progressive loss of pigmented DA-neurons in the substantia nigra pars compacta. Individuals with PD show reduced levels of neuromelanin in both the ventral and dorsal tiers of the substantia nigra [32]. α-Syn has also been detected in cultured melanoma cells and tissues derived from melanoma patients in which there is an inverse correlation between α-syn expression and pigmentation [33].

SYTL4/SLP4 and SYTL2/SLP2 (synaptotagmin-like 4 and 2) are Rab27 effectors responsible for docking secretory vesicles to the plasma membrane prior to exocytosis [34,35]. SLP2 controls the localization of SLP4-mediated vesicle-tethering activity to a single PIP2-enriched initiation site; when SLP2 is disrupted, SLP4 targets vesi-

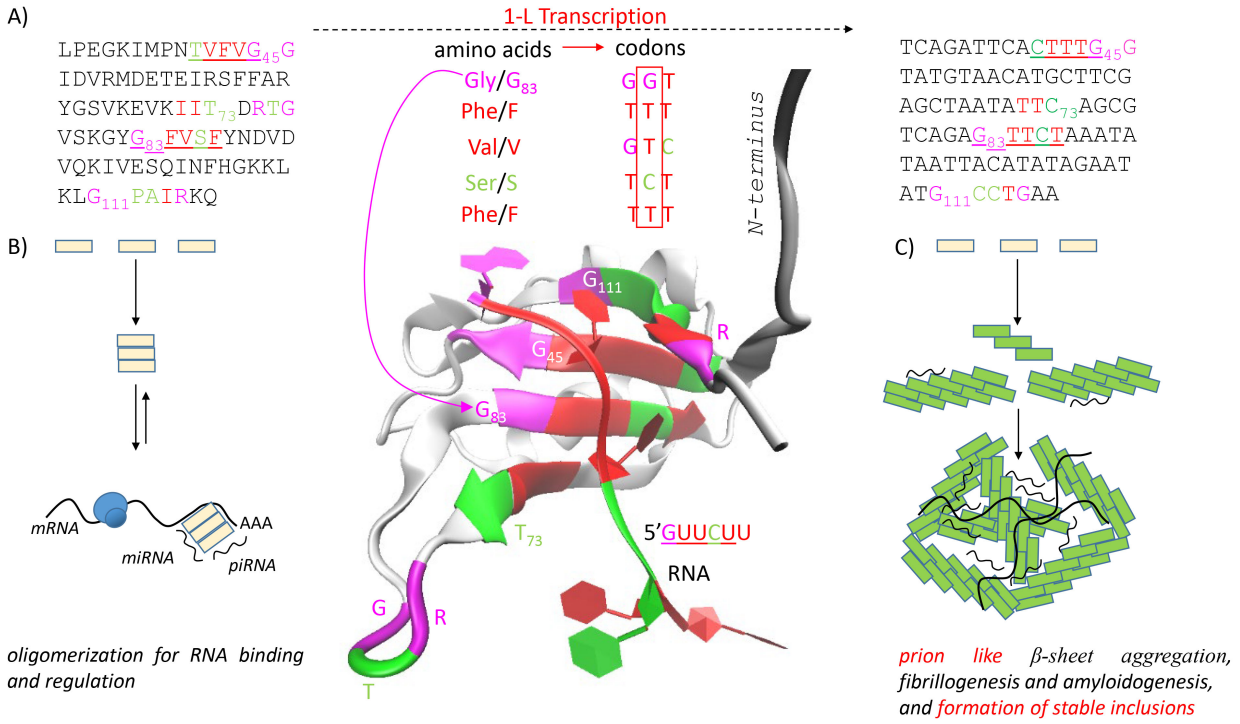

Fig. 2. An RNA binding protein (RBP) named deleted-in-azoospermia-like (DAZL). (A) 1-L transcription of DAZL. RBP DAZL binds a GUU(C/U) motifs [18]. The 1-L protein-RNA recognition code means that RBPs use at least one amino acid sequence that is exactly compatible with the recognized RNA nucleotide sequence, 83GFVSF87 for GUUCU and 45GVFVT41 for GUUUC. 1-L transcription uses the second position in the amino acid codon. The structure 2XS2 shows that both sequences are involved in the RNA binding. (B) A model of RBP oligomerization at low concentrations for RNA binding and regulation. (C) A model of prion like fibrillogenesis and amyloidogenesis at high concentrations, followed by RNA binding and formation of stable inclusions.

cles ectopically to various plasma membrane locations [35]. Rab27a and SYTL4/SLP4 provide multivesicular body (MVB) docking to the plasma membrane [36].

MYO5C (myosin VC) is one of the three myosin V motors; myosin motors use energy derived from ATP hydrolysis to generate movement to control membrane transport, organelle trafficking, and actin dynamics. MYO5C differs from MYO5A or MYO5B, in that it colocalizes with secretory granule markers such as chromogranin A and RAB27b [37]. A unique function of MYO5C in melanosome biogenesis and secretion has been identified, depending on its interactions with RAB32 and RAB38 [38]. LRRK2 (mutations in this kinase represent the most common cause of PD) also interacts with RAB32 and RAB38 to regulate endo-lysosomal trafficking [8,39].

TPTE, TPTE2 (transmembrane phosphoinositide-3-phosphatase with tensin homology) are phosphatases that belong to the PTEN family (five members). PTENs oppose PI3K-AKT activation; as such they activate GSK3β (Fig. 5) and regulate many cellular processes [40]. In PD, activation of the PI3K-AKT signal has a neuroprotective role [41] because α-syn indirectly activates GSK3β and then TAU is phosphorylated by GSK3β and co-aggregated with α-syn (Fig. 5) [42].

TPTEP1 (TPTE pseudogene 1) is a noncoding RNA silenced through DNA methylation in various cancers [43]. In addition, TPTEP1 suppresses high-glucose-induced dysfunction in retinal vascular endothelial cells [44]. TPTEP1 mRNA may function similarly to the PTENP1 pseudogene, which is targeted by PTEN-targeting miRNAs and acts as their decoy [45].

TPTEP2-CSNK1E (TPTEP2-CSNK1E readthrough) fusion may play a role in Wnt signaling similar to CSNK1E, casein kinase 1ε is a canonical Wnt signaling protein. Note that dysregulation of Wnt signaling is known in PD [46]. Activation of Wnt signaling facilitates the derivation of midbrain dopamine neurons from hESCs [47].

RGMB (repulsive guidance molecule b)/DRAGON is a coreceptor and regulator of bone morphogenetic protein (BMP)-signaling [48]. In one epigenomic association study (EWAS), RGMB was identified as a gene related to motor progression of PD [49]. BMP2 has potential for use in the neurotrophic treatment of PD [50]. In contrast to the RGMB-mediated enhancement of signaling observed for BMP2, RGMB inhibits BMP14/GDF5 signaling [51] and BMP14/GDF5 exerts neuroprotection in the α-syn rat model of PD [52].

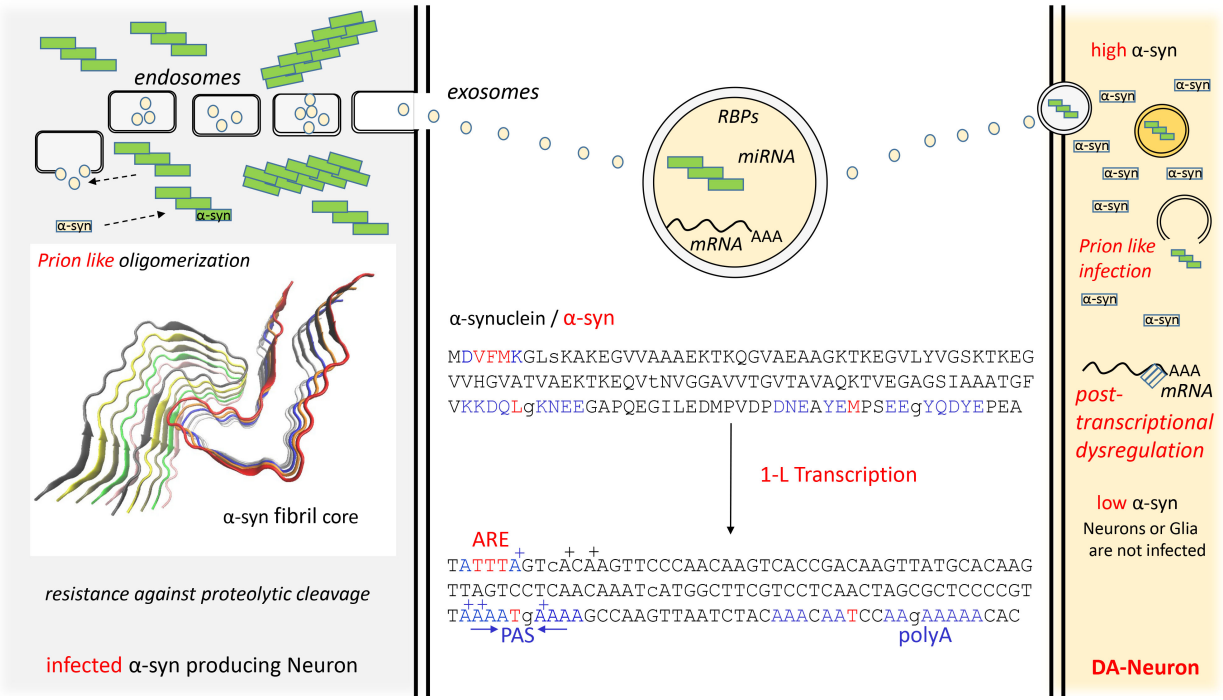

Fig. 3. Spread of PD by exosomes and 1-L transcription of α-syn. Logically, only high α-syn cells will be sensitive to prion-like aggregation and infection. The 1-L transcription revealed compatible amino acid sequences with the ATTTA ARE (class I), PAS and polyA in α-syn, supporting a protein-RNA regulatory model.

3.1.2 The Second Group

AMY1A (amylase alpha 1A), AMY1B, AMY1C, AMY2A and AMY2B are α-amylase genes; α-amylase has an energetic function by degrading glycogen in synapses [53]. In PD patients, total salivary α-syn is significantly reduced [54] and amylase concentrations are increased [55]. In addition, AMY1 has been reported to bind to the N-terminal region of c-MYC and stimulate its transcriptional activity; c-MYC plays a key role in cell proliferation, differentiation, transformation and apoptosis [56].

B3GALT2 (β-1,3-galactosyltransferase 2) is one of the main types of glycosyltransferases. Protein glycosylation plays an important role in proper protein folding, intracellular sorting/processing, export, and extracellular signaling. B3GALT2 may play a beneficial role in the survival of penumbra neurons (ischemia) through the modulation of the Reelin pathway [57], Reelin could be a promising target for the treatment of histopathological changes and improvement of behavioral symptoms associated with PD [58]. It is interesting that intranasal administration of β-1,3-galactosyltransferase 2 confers neuroprotection possibly by inhibiting oxidative stress and the NLRP3 inflammasome [59].

SMG1 (SMG1 nonsense mediated mRNA decay associated PI3K related kinase) is a key kinase involved in the nonsense-mediated mRNA decay (NMD)-pathway, which targets mRNAs containing premature stop codons for rapid degradation and is essential for mammalian embryonic development, brain development, and modulating the stress response [60]. SMG1 was identified as a regulator of PD-associated α-syn; knockdown of SMG1 led to a significant increase in the expression of S129-phosphorylated α-syn [61]. Mitochondrial damage also accelerates Ser129-phosphorylation of α-syn, which may be a signal for α-syn degradation. However, once α-syn aggregates become resistant to degradation, proteasomal targeting mediated by S129-phosphorylation is ineffective, and S129-phosphorylated α-syn remains stored in aggregates [62].

SMAD2 (SMAD family member 2) is one of the major components of the transforming growth factor-β (TGF-β) pathway. TGF-I and II receptors are expressed in dopamine neurons and the role of TGF-β signaling in PD is considered to be protective [63]. However, in neurogenesis, continuous stimulation of SMAD2 signaling leads to inhibition of neural markers [64]. In adult hippocampal neurogenesis, it appears that the transcription factor SMAD2 may play a role in the balance between proliferation and maturation, and in the plasticity of both newborn and mature neurons [65].

OPCML (opioid binding protein/cell adhesion molecule like) is a cell surface glyco-phosphoinositol (GPI)-anchored protein that regulates spine maturation and cognitive behaviors through the ephrin-EphB2-cofilin signaling pathway [66]. It has been identified as one top genes most consistently underexpressed in the aging brain [67] and as one GWAS candidate gene under selection for sporadic PD [68]. OPCML interacts with S129-phosphorylated α-syn [69].

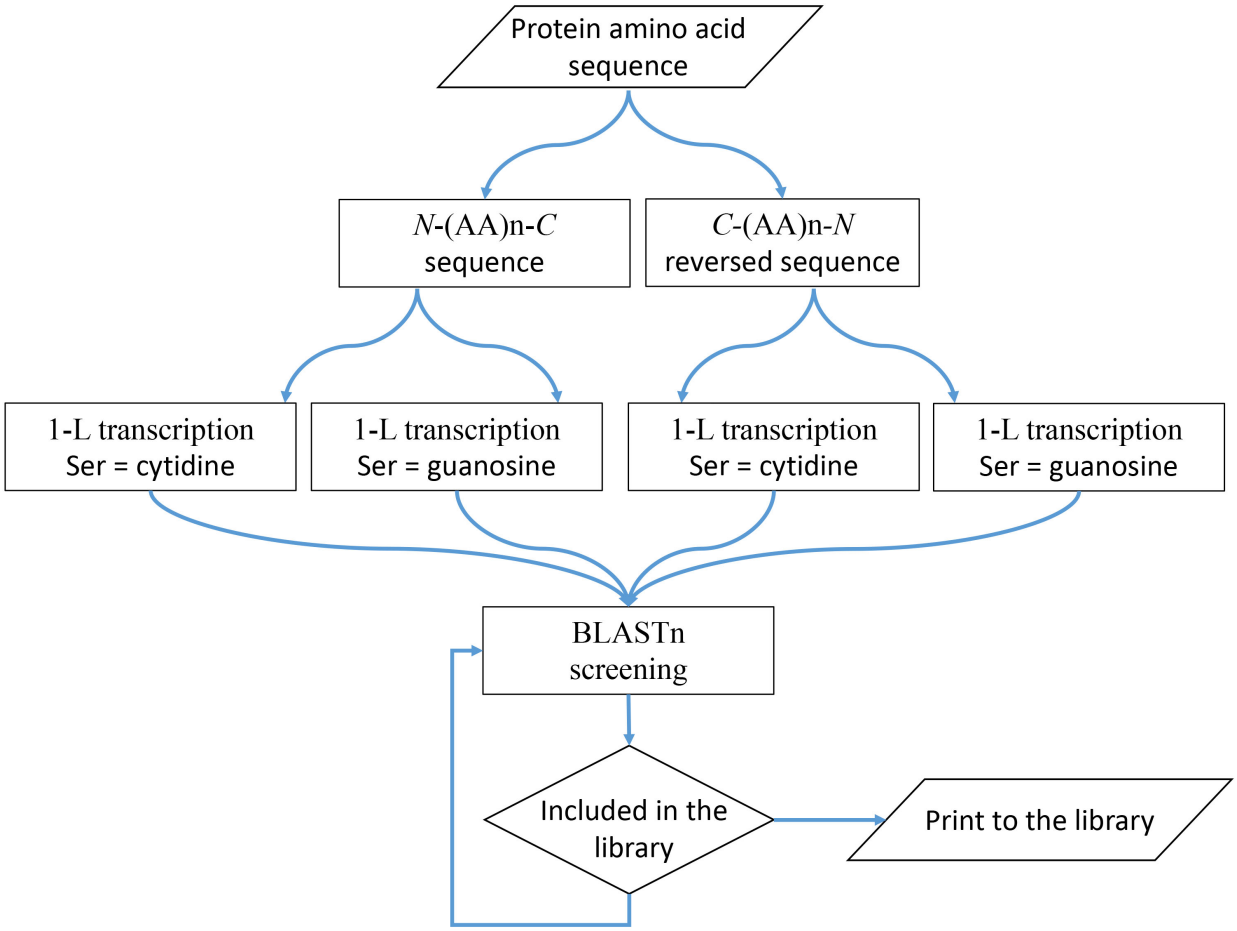

Fig. 4. 1-L transcription method. A schematic diagram that visually represents the steps and concept.

3.1.3 The Third Group

GMPS (guanine monophosphate synthase) converts XMP (xanthosine 5′-phosphate) to GMP in purine salvage and degradation pathways [70,71]. The pool of guanine nucleotides plays an essential role in cell metabolism and proliferation, and the level of guanine nucleotides is important for G-proteins, such as RAB GTPases, which are essential for vesicle trafficking and are dysregulated in PD [72]. Evidence has shown that purine metabolism is dysregulated in PD [70,71].

SPECC1L (sperm antigen with calponin homology and coiled-coil domains 1 like) associates with actin filaments and microtubules through its calponin homology domain and coiled coil domain 2 (CCD2), respectively. It has a role in regulating actomyosin organization during tissue morphogenesis. SPECC1L requires association with microtubules via CCD2 for transport in the cell. The absence of SPECC1L leads to a disorganized accumulation of actin at the cell periphery [73].

PHACTR2 (phosphatase and actin regulator 2) belongs to the family of protein phosphatase 1 (PP1) and actin regulatory proteins [74]. PP1 is a multifunctional phosphatase with diverse roles in the nervous system, likely targeting neuronal substrates associated with the actin cytoskeleton. In the brain, the expression of PHACTR1 and PHACTR2 are remarkably complementary [74]. PHACTR2 has already been nominated as a risk factor for PD [75].

ZNF800 (zinc finger protein 800) is expressed as a long, non-coding RNA (lncRNA) that upregulates PTEN and inhibits the activity of AKT (Fig. 5) [76]. It can be also expressed as an oligodendrocyte-specific circular RNA [77].

RICTOR (RPTOR independent companion of MTOR complex 2/rapamycin-insensitive companion of mTOR) is a scaffold protein that regulates the assembly of the mTORC2 complex, which regulates cell survival and proliferation mainly through PKCα (cytoskeletal remodeling) and SGK1 (serum- and glucocorticoid-inducible kinase homolog 1, cell survival) [78]. mTORC2-SGK1 signaling integrates external signals to regulate mitochondrial autophagic turnover through reactive oxygen species (ROS); loss of RICTOR induces mitochondrial ROS and leads to mitophagy [79].

SLCO4C1/OATP4C1 (solute carrier organic anion transporter family member 4C1/organic anion transporting polypeptide 4C1) is a renal organic anion transporter but can be detected in cultured neurons [80].

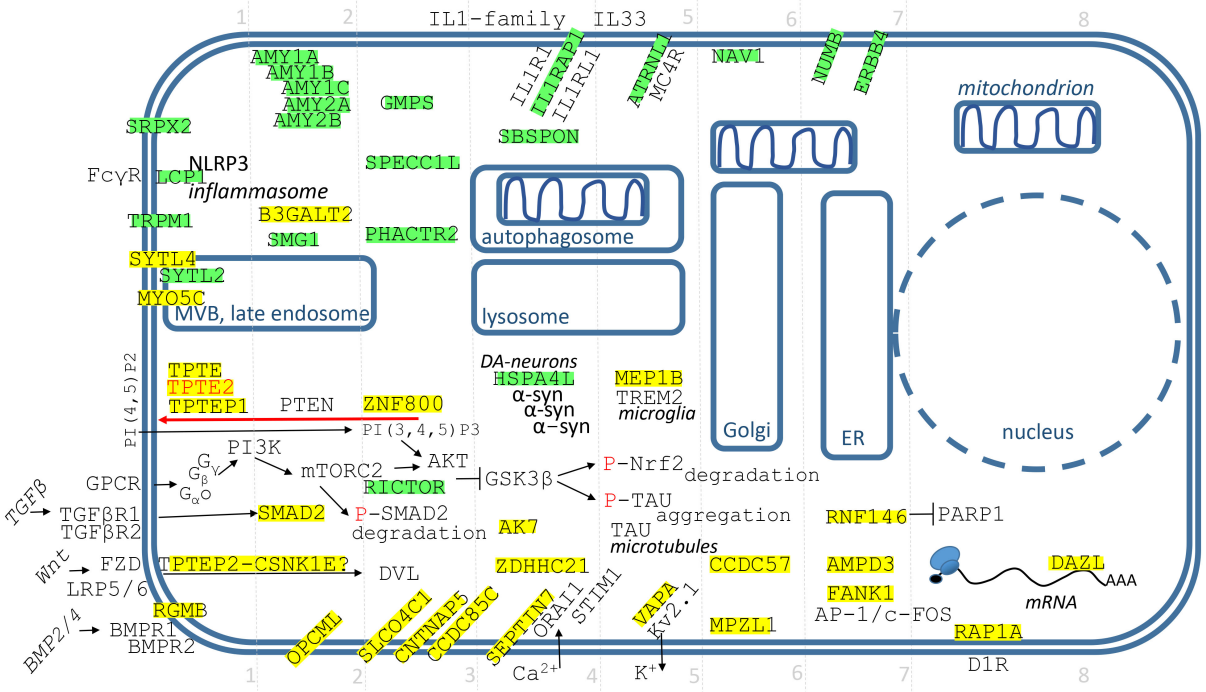

Fig. 5. Identified genes/proteins with function in the plasmatic membrane, cytosol or PM-cytosol interface. The description of genes/proteins is given in the text from the upper left corner down to the right. Green highlights show alignments with the gene transcript RNA sequence (post-transcriptionally repressed), yellow highlights show alignments with the reverse complement RNA sequences (post-transcriptionally promoted).

Asymmetric dimethylarginine, cAMP, CDCA, E1S, GCA, L-homoarginine, T3, and T4 are substrates for SLCO4C1/OATP4C1 [80].

CNTNAP5 (contactin-associated protein family member 5) is a member of the neurexin-like family of cell adhesion molecules and receptors expressed in vertebrate neurons [81]. A genome-wide scan in a cohort of 1130 patients with PD found an association signal at chr2q14.3. The only annotated gene within 1 Mb on either side of the DASH segment is CNTNAP5 [82].

CCDC85C (coiled-coil domain containing 85C) is a protein at the apical junctions of radial glia that is disrupted in mice with hydrocephalus [83]. Hydrocephalus is a disease characterized by the accumulation of cerebrospinal fluid in the brain cavities. PD and α-synucleinopathies coexist with normal-pressure hydrocephalus [84].

3.1.4 The Fourth Group

IL1RAP (interleukin 1 receptor accessory protein)/IL-1RAcP/IL1R3 forms a complex with receptors for IL1-like cytokines and is essential for IL1 signaling, which is involved in several neuroinflammatory diseases, including PD; therapeutic strategies modulating IL1 activity could have neuroprotective effects in PD [85]. IL1β-IL1R1/IL1RAP signaling in the olfactory bulb induces α-syn overexpression and appears to be associated with a higher degree of α-synucleinopathy that spreads to the SN and triggers DA-neuron loss [86].

SBSPON (somatomedin B and thrombospondin type 1 domain containing): its *Drosophila melanogaster* ortholog (CG42339) was identified among the top-associated genes containing single nucleotide polymorphisms that render DA neurons vulnerable to PD [87].

HSPA4L (heat shock protein family A member 4 like) is a member of the Hsp110 chaperone family that alleviates α-synuclein pathology *in vivo* [88]. In the α-syn-HSPA4L double transgenic mouse model, overexpression of Hsp110 (HspA4L/Apg1/Hsph3) was sufficient to prevent templating and spreading of endogenous α-syn after injection of aggregated α-syn seeds into the brain. It is interesting to note that α-syn oligomeric levels were unchanged in α-syn-HSPA4L mice [88].

AK7 (adenylate kinase 7) is unusual in the adenylate kinase family because it is a high molecular weight isoform. AK7 appears to be a marker of cilia; mutations in the *AK7* gene result in animals exhibiting characteristics of primary ciliary dyskinesia and hydrocephalus [89]. Adenylate kinase and downstream AMP-signaling function as an integrated metabolic monitoring system that senses cellular energy states [89]. AK7 was among the three differentially expressed genes in α-syn-APOE mice [90].

ZDHHC21 (zinc finger DHHC-type palmitoyltransferase 21) is responsible for a post-translational lipid modification of proteins called palmitoylation. For example, ZDHHC21 palmitoylates PLCβ1 and mediates endothelial inflammation [91], or palmitoylates amyloid precur-

sor protein (APP) and enhances amyloidogenic processing by targeting APP to lipid rafts and enhancing its BACE1-mediated cleavage [92].

SEPTIN7 (septin 7) is cytoskeletal GTPase, which can bind to other septins and form a core component of most septin complexes. This septin is crucial to the spine morphogenesis and dendrite growth in neurons [93]. SEPTIN7 regulates extracellular Ca^{2+} entry through Orai channels in human neural progenitor cells and neurons [94].

3.1.5 The Fifth and Sixth Groups

ATRNL1 (attractin like 1) directly interacts with MC4R (melanocortin 4 receptor, energy homeostasis, erectile function) and has been proposed to act in MC4R signaling [95]. The link between dopamine and melanocortin systems of the brain has been documented at both structural and functional levels [96], and it appears that ATRNL1 signaling may be involved in the modulation of dopamine systems.

MEP1B (meprin A subunit beta) is a metalloprotease that cleaves TREM2 on microglia and controls phagocytic activity [97]. MEP1B is also involved in APP cleavage and plays an important role in the amyloidogenic pathway and Aβ production *in vivo* [98]. Glial expression of α-syn promotes MEP1B significantly more than does the control [99].

VAPA [VAMP (vesicle-associated membrane protein) associated protein A] interacts with Kv2 channels. The Kv2.1 channel mediates cell death, which is associated with the loss of cytosolic potassium in neurons and, therefore, the targeted disruption of the Kv2.1-VAPA association provides neuroprotection [100].

NAV1 (neuron navigator 1) is an important member of the human neuronal navigator gene family and is involved in axon guidance. Growth-cone macropinocytosis of the neurotrophin receptor and neuritogenesis are regulated by NAV1 [101]. Growth-cone macropinocytosis is important for downstream signaling, neurite targeting, membrane recycling, NAV1 functions at the interface of microtubules, actin, and the plasma membrane organizing the cell periphery [101]. Expression profiling of long non-coding RNAs (lncRNAs) in PD revealed that lncRNA RPS14P3 interferes with miRNA-mediated *NAV1* gene expression [102].

CCDC57 (coiled-coil domain containing 57) interacts with microtubules and microcephalic protein CEP63, and regulates centriole duplication and mitotic progression; centrosome dysfunction is associated with neurodevelopmental disorders [103].

MPZL1 (myelin protein zero like 1) is an immunoglobulin that promotes tumor cell proliferation and migration [104,105]. In bladder cancer, SNCA was highly correlated with MPZL1 protein in activated CD8+ T cells [106].

3.1.6 The Seventh and Eighth Groups

NUMB (NUMB endocytic adaptor protein) is an evolutionarily conserved protein originally identified as an inhibitor of Notch signaling [107]. It determines cell fate for neural progenitor cells, their maintenance and self-renewal. It interacts with the endocytic machinery to control Notch, with cadherin and integrins to control cell adhesion and migration, and with the E3 ubiquitin ligase Itch for ubiquitination and degradation of the Notch ICD [107]. Although NUMB interacts with Itch to promote intracellular trafficking and subsequent degradation of the NOTCH1 receptor ICD [107], NUMB appears to enhances Notch signaling by regulating the ubiquitinating activity of the BAP1–BRCA1 complex [108]. In *Drosophila*, loss-of-function NUMB mutations lead to loss or reduction of DA neurons [109].

ERBB4 (erb-b2 receptor tyrosine kinase 4) is a neuregulin-1 (nerve growth and differentiation factor, NRG1) receptor that regulates extracellular dopamine through p38/MAPK14 signaling [110]. The decreased expression of ERBB4 by RNA interference leads to increased extracellular dopamine [110]. The total number of nigral ERBB4-positive neurons is reduced in PD, but ERBB4 rose in the remaining functional neuromelanin-containing DA-neurons [111]. In microglia, NRG1-ERBB4 signaling exerts anti-inflammatory effects and inhibits the release of inflammatory factors, most likely via ERBB4-dependent inhibition of the NF-κB pathway [112].

RNF146 (ring finger protein 146) is a poly (ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signaling. It directly interacts with poly (ADP-ribose) and promotes the degradation of PARylated proteins [113]. In cell pellets from the nasal lavage of PD patients, the transcript level of RNF146 (mRNA) is decreased, although the transcript level of α-syn is increased [114]. Poly (ADP-ribose) polymerase-1 (PARP1)-dependent programmed cell death leads to progressive degeneration of DA-neurons, but RNF146 is able to inhibit PARP1 not through its E3 ligase function, but rather by binding and sequestering PAR [115].

AMPD3 (adenosine monophosphate deaminase 3) is a cytosolic enzyme that catalyzes the thermodynamically irreversible deamination of AMP to IMP and ammonia (AMP$\rightarrow$ IMP+NH3) [116]. Increased expression of AMPD3 significantly reduces mitochondrial protein synthesis and is sufficient to replicate an atrophy-like metabolic phenotype [116], and AMPD3 is among the most significant PD-risk genes [117].

FANK1 (fibronectin type III and ankyrin repeat domains 1) is a co-regulator of AP-1 in the AP-1-signaling pathway. The transcription factor AP-1 is a dimeric complex composed of members that belong to the Jun, Fos, ATF, and MAF protein families. This TF complex is involved in the regulation of cell proliferation, differentiation, and apoptosis. FANK1-AP-1 can mediate pro-apoptotic and anti-apoptotic signaling [118,119].

RAP1A (member of RAS oncogene family/repressor-activator protein 1a) is a small monomeric GTP-binding protein of the RAS family known to switch between an inactive GDP-bound form and an active GTP-bound form. Acting as a molecular switch linking extracellular signals to intracellular responses, RAP1A is associated with multiple signaling pathways including proliferation, integrin activation, cell adhesion, and migration (https://www.genome.jp/pathway/hsa04015+5906), but it also plays role in inflammation, oxidative stress, and apoptosis involved in the pathogenesis of PD. Actually, RAP1A activation is involved in L-DOPA signaling in medium spiny neurons in D1R (dopamine receptor)-PKA (cAMP-protein kinase A)-RAP1 GEF (Rasgrp2)/RAP1A-MAPK intracellular signaling [120].

DAZL (deleted in azoospermia like) is an RBP (Fig. 2) that mediates a broad translational program regulating the expansion and differentiation of spermatogonial progenitors [121]. DAZL binds the 3′ UTR of ~2500 protein-coding genes, some of which control RNA metabolism, and binds 3′UTR sites to GUU(C/U) motifs (Fig. 2A) [18]. It forms SDS-resistant aggregates in cells undergoing gametogenesis (in testis), but normally not in the brain [19].

3.2 Identification and Function of Genes/Proteins in Membrane Organelles, Mitochondria, and the Nucleus Relevant to Neurological Diseases

The genes/proteins are displayed in Fig. 6 and they are described in order from the endosomes to the nucleus. For the better orientation, the grid divides genes to 5 groups.

3.2.1 The First Group

ATG2B (autophagy related 2B) participates in the early formation of autophagosomes, has membrane binding activity, and lipid transfer activity, which is accelerated by negatively charged lipids and WIPI4 [122,123]. Impaired autophagy significantly contributes to α-syn accumulation and dopaminergic neuron degeneration, two major hallmarks of PD pathology [124].

IKBKE/IKKε (inhibitor of nuclear factor kappa B kinase subunit epsilon, also known as IKK-i) is a serine/threonine protein kinase belonging to the IKK family that promotes the growth, proliferation, and invasion of various cancers by regulating NF-κB, AKT, STAT, Hippo and Wnt/β-catenin signaling pathways [125]. This oncogene was identified as a positive regulator of autophagy [126].

RICTOR (RPTOR independent companion of MTOR complex 2/rapamycin-insensitive companion of mTOR) is a scaffold protein regulating the assembly of mTORC2 complex; mTORC2-SGK1 signaling integrates external signals to regulate mitochondrial autophagic turnover through reactive oxygen species (ROS). Loss of RICTOR induces mitochondrial ROS and leads to mitophagy [79].

FXR1 (FMR1 autosomal homolog 1) is an RNA-binding protein that can be present in an amyloid form in the brains of various mammalian species, including humans [127]. This RBP regulates synaptic homeostasis [128] and is involved in oxidative stress responses; depletion of FXR1 by siRNA increases sensitivity to the mitochondrial ROS [129].

OXR1 (oxidative resistance 1) is present in mitochondria and cytoplasm and is essential for protection against oxidative stress-induced neurodegeneration [130]. Hypothetically, OXR1 functions as an oxidative stress sensor [131].

ATPSCKMT (ATP synthase c subunit lysine N-methyltransferase) is a mitochondrial methyltransferase that trimethylates Lys-43 in the c-subunit of ATP synthase and optimizes mitochondrial ATP synthase function [132]. The C-subunit is an amyloidogenic protein that can spontaneously fold into β-sheets and self-assemble into fibrils; this substrate for ATPSCKMT may be relevant for mitochondrial toxicity when not adequately processed [133].

MGAT4C [mannosyl (α-1,3-)-glycoprotein β-1,4-N-Acetylglucosaminyltransferase, isozyme C] is "neuron-specific" glycosyltransferase involved in N-glycosylation (β-1,4-branch) [134]. This glycosyltransferase is down-regulated in PD substantia nigra neurons [135].

VAPA [VAMP (vesicle-associated membrane protein) associated protein A] and its binding partner CERT (ceramide transporter) control the biogenesis of vesicles containing extracellular RNA at endoplasmic reticulum (ER) membrane contact sites [136].

3.2.2 The Second Group

GJA1 (gap junction protein alpha 1) is a member of the family of connexins, which are gap junction and hemichannel-forming proteins involved in cell death, proliferation, and differentiation. GJA1 higher expression in motoneurons was negatively correlated with genes associated with neuronal activation profiles [137]. GJA1 was strongly associated with β-amyloid and TAU pathologies [138]. It is important that in traumatic brain injury, GJA1-20K, the most abundant isoform, has been reported to promote mitochondrial trafficking from astrocytes to neurons, which may be responsible for the protective function of astrocytes [139].

CA5B (carbonic anhydrase 5B) is a mitochondrial isoform of carbonic anhydrase (CA, conversion of CO_2 to HCO_3^- and H^+) involved in mitochondrial the biogenesis and control of pH homeostasis and lactate production [140]. The neurovascular unit (NVU) is an important multicellular structure of the central nervous system (CNS) involved in the regulation of cerebral blood flow, oxygen and nutrient delivery, immunological clearance, barrier functions, and CNS homeostasis. Recent studies provide evidence that CA inhibition protects NVU cells *in vitro* and *in vivo* in models of stroke and Alzheimer's disease pathology. Silencing of both CA5A and CA5B isoforms was observed to protect against ROS production [141].

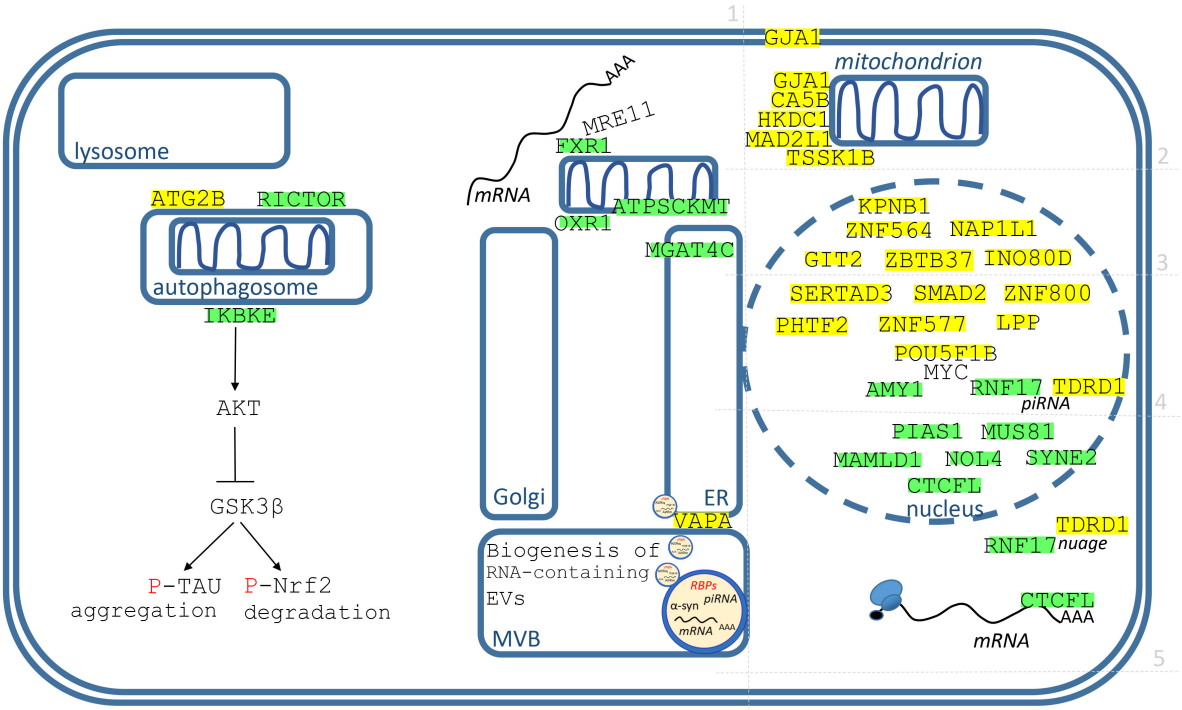

Fig. 6. Identified genes/proteins with function in membrane organelles, mitochondria and nucleus. The description of genes/proteins is made in the text, from endosomes to the nucleus, from left to right. Green highlights show alignments with the gene transcript RNA sequence (post-transcriptionally repressed), yellow highlights show alignments with the reverse complement RNA sequences (post-transcriptionally promoted).

HKDC1 (hexokinase domain containing 1) is a novel fifth hexokinase (the first step in glucose metabolism) that, like HK1 and HK2, has been shown to interact with mitochondria [142]. Flunarizine depletes mitochondria and reduces dopamine concentrations in the striatum [143]. A genome-wide CRISPR KO library and loss-of-function genetic screen revealed that HKDC1 is important in a mitophagy-independent mitochondrial quality control and mitolysosome exocytosis in flunarizine-induced parkinsonism-like symptoms [143].

MAD2L1 (mitotic arrest deficient 2 like 1) is a component of the mitotic spindle assembly checkpoint that prevents the onset of anaphase until all chromosomes are properly aligned in metaphase. This protein also targets the *MYC* gene and is significantly downregulated in tumor dormancy [144], and may be associated with mitochondrial function [145]. Mitochondrial dysfunction is a well-established player in the pathogenesis of PD [146].

TSSK1B (testis-specific serine kinase 1B) belongs to the TSSK group, which is part of the AMPK protein kinase family, but currently there is not much information about TSSK substrates *in vivo* [147]. Targeted deletion of Tssk1 and 2 causes male infertility due to developmental dysregulation and collapse of the mitochondrial sheet in late spermatids [147].

3.2.3 The Third Group

KPNB1/IPO1 (karyopherin subunit beta 1/importin-1) is a component of karyopherin/importin; karyopherin abnormalities have been identified in synucleinopathies including PD and dementia with LBs [148]. KPNB1 is in the list of genetic markers in PD [149]. In PD patients, the proportion of dopaminergic neurons with immunoreactive NF-κB in their nuclei is more than 70-fold that of control subjects [150]. It is interesting that KPNB1 is a key positive regulator for the nuclear import of NF-κB [151].

ZNF564 (zinc finger protein 564) is a transcription factor of unknown function, but it was identified among potential core genes in PD by bioinformatics analysis [152].

NAP1L1 (nucleosome assembly protein 1 like 1) has been identified as a molecular marker of early PD based on gene expression in blood [153]. NAP1L1 has been seems to control the proliferation and differentiation of embryonic neural progenitor cells in the developing brain [154].

GIT2 (GIT ArfGAP 2) acts as a key protein in the aging process and is an ARF-GAP (ADP-ribosylation factor GTPase-activating protein) that controls both DNA repair and glucose metabolism [155,156]. GIT1/2 proteins were originally identified as regulators of GPCR internalization through their influence on ARF-GTP-binding proteins, thereby inactivating all subtypes of ARF proteins. GIT2 potentially plays a multidimensional role in coupling

neuronal and energy-regulatory functions in aging. GIT2-KO mice show anxiety-like behavior and advanced aging. GIT2 appears to protect against oxidative stress, metabolic dysregulation, and inflammation, and appears to promote DNA repair [155].

ZBTB37 (zinc finger and BTB domain containing 37) belongs to a family of 49 transcription factors that are sequence-specific repressors of gene expression that play an essential role in the development of the immune system [157]. ZBTB37 is not yet characterized.

INO80D (INO80 complex subunit D) is an undefined subunit of the INO80-nucleosome complex; an INO80 complex/chromatin remodeler is responsible for nucleosome sliding, histone exchange, and nucleosome spacing [158]. The long noncoding RNA CR933609 acts as a decoy to protect the *INO80D* gene from downregulation by miRNA-5096 [159].

3.2.4 The Fourth Group

SERTAD3 (SERTA domain containing 3) is an interferon-inducible type I antiviral protein that disrupts the formation of the RNA-dependent RNA polymerase complex and inhibits influenza A virus replication [160]. SERTAD3 also promotes the growth, invasion, and migration of prostate cancer cells through the p38-p53-p21 pathway [161].

PHTF2 (putative homeodomain transcription factor 2) may be an immune-related gene; PHTF2 is correlated with immune cell infiltration in cancer [162], but on the other hand, it significantly enriches the fatty acid metabolism pathway in gastric cancer [163].

ZNF577 (zinc finger protein 577) methylation levels in leukocytes from women with breast cancer is modulated by adiposity, menopausal state, and the Mediterranean diet [164].

LPP (LIM domain containing preferred translocation partner in lipoma) is a proto-oncogene that belongs to the zyxin family of LIM domain proteins that mediate actin cytoskeleton remodeling and migration. LPP interacts with α-actinin and mediates TGFβ-induced migration. Interestingly, α-syn also supports TGFβ-signaling by promotion of SMAD2 intracellular transducer (Fig. 5, group 2). In the nucleus, LPP works as a transcriptional coactivator of PEA3 and ER81 [165]. These ETS domain transcriptional factors regulate the differentiation of specific motor neuron pools [166].

POU5F1B (POU class 5 homeobox 1B), also known as OCT4 pseudogene 1 or POU5F1P4, is located near MYC on human chromosome 8q24. POU5F1B, like the transcription factor POU5F1/OCT4, can control the pluripotency and self-renewal capacity of mammalian stem cells [167]. One Oct4 pseudogene transcript in mouse neural stem cells, mOct4pg9, promotes the loss of neural stem cell identity and mediates the inhibitory effects of ethanol on development [167].

AMY1A (amylase alpha 1A), AMY1B, AMY1C are α-amylases found to bind to the N-terminal region of c-MYC and stimulate its transcriptional activity. c-MYC plays a key role in cell proliferation, differentiation, transformation, and apoptosis [56].

RNF17/TDRD4 (ring finger protein 17/Tudor domain containing 4) contains both a RING finger and a Tudor domain and is part of the mammalian germ cell nuage (characteristic cytoplasmic ribonucleoprotein bodies) essential for spermatogenesis [168]. PIWI-interacting RNAs (piRNAs) have a role in the regulation of transposable elements, especially in spermatogenesis [168]. In the piwi pathway, RNF17/TDRD4 represses the ping-pong cycle, an adaptive amplification loop that generates secondary piRNAs and blocks piRNA responses against protein-coding genes [168]. In addition, RNF17 interacts with all four Mad proteins, enhances c-MYC function, and co-regulates some target genes common to glucocorticoids [169]. The 'survival motor neuron' (SMN) protein has been implicated in the formation of membraneless organelles/bodies via its dimethylarginine (DMA)-binding Tudor domain [170]. RNF17/TDRD4 has two Tudor domains that bind DMA and two Tudor domains that do not bind DMA. The inherent multivalency of RNF17/TDRD4 implicates a germinal condensate formation mechanism [170].

TDRD1 (Tudor domain containing 1) belongs to Tudor proteins that contain multiple Tudor domain repeats and form an evolutionarily conserved class of germinal nuage, a characteristic cytoplasmic ribonucleoprotein complex/germinal granule [171]. TDRD1 is required for efficient piwi pathway activity and proper nuage formation [172]. It helps regulate the entry of transcripts into piRNA biogenesis [173]. TDRD1 protein is expressed in most human prostate tumors but not in normal prostate tissue [174].

3.2.5 The Fifth Group

PIAS1 (protein inhibitor of activated STAT 1) can block the DNA-binding activity of STAT1 and is a critical regulator of innate immune responses mediated by IFN-γ or IFN-β. Pias1$^{-/-}$ mice show increased protection against pathogenic infection [175]. PIAS1 is a SUMO E3 ligase that may be involved in pathophysiological ER stress in PD [176].

MUS81 (MUS81 structure-specific endonuclease subunit) binds EME1 and generates a structure-specific endonuclease involved in the rescue of stalled replication forks. MUS81 expression appears to be important in maintaining genomic integrity. MUS81-KO mice show susceptibility to spontaneous chromosomal damage [177].

MAMLD1 (mastermind like domain containing 1) on the X chromosome is one of the causative genes for 46, XY sex differences/disorders; it acts as a transcriptional coactivator and enhances testosterone production in Leydig cells [178]. Using transcriptome data from PD patients, MAMLD1 was identified as gene responsive for Braak stages in PD [179].

NOL4 (nuclear protein 4) is a transcriptional cofactor that regulates LCOR [180]. LCOR is a major transcriptional activator of APM genes (e.g., MHC, major histocompatibility complex class I) that binds to IFN-stimulated response elements (ISREs) in an IFN signaling-independent manner, mediating interferon-independent immunogenicity [181]. LCOR is one of the most differentially expressed genes in PD [182].

SYNE2 (spectrin repeat containing nuclear envelope protein 2)/nesprin-2 is a KASH domain-containing protein critical for nuclear-envelope integrity [183]. Vertebrate skeletal-muscle fibers contain hundreds of nuclei, three to six of which are functionally specialized and stably anchored under the postsynaptic membrane at the neuromuscular junction. SYNE1 and SYNE2 play critical roles in the anchoring of both synaptic and non-synaptic myonuclei, which are important for proper motor neuron innervation and respiration [184].

CTCFL/BORIS (CCCTC-binding factor like/brother of regulator of imprinted sites) is a transcription factor associated with microglia-exclusive enhancer regions [185] and an RBP that is associated with polysomes and active translation in both neural stem cells and young neurons [186]. As a transcription factor, CTCFL regulates membrane receptors that have AKT as a downstream target, the PI3K-AKT pathway [187].

4. Discussion

As mentioned in the introduction, α-syn interacts with lipid membranes and is associated with vesicle trafficking (Fig. 1); PD is an α-synucleinopathy and a disease of aberrant vesicle trafficking. mRNAs and their regulatory miRNAs or other short/long noncoding RNAs are transported from the nucleus through the axon, and the membrane vesicles control the sorting of RNA populations, and even participate in mRNA translation [11]. The 1-L transcription of α-syn yields compatible amino acid sequences with AUUUA ARE (class I, 2DVFMK), PAS (98DQLgKNE/AAUgAAA), and polyA (130EEgYQDYE/AAgAAAA) (Fig. 3), supporting a protein-RNA regulatory model. It seems that α-syn, which is associated with vesicle transport, could also be involved in the post-transcriptional regulation of RNA and participate in the transport of RNA signals from the nucleus out of the neuron along the entire axon (Fig. 1). Expression of α-syn is regulated in a neuronal-cell-type-dependent manner, with some neurons expressing high levels of α-syn (DA-neurons) and other neurons or glia expressing the protein very poorly [5]. Accumulation of α-syn in filamentous inclusions (LBs) inside "α-syn producing" neurons leads to a situation in which "α-syn interacting" mRNAs, miRNAs, and other short/long non-coding RNAs are extremely deregulated, and post-transcriptional "protein-RNA" regulations by α-syn are extreme; this situation can ultimately lead to the death of neurons (see 4.1). Conversely, when α-syn accumulates in intracellular LBs and is not efficiently transferred to "α-syn accepting/non-producing" cells, the post-transcriptional regulations by α-syn in these cells are changed. The situation can lead to inflammatory reactions, cognitive decline, and motor circuit disturbances (see 4.2). The spectrum of identified genes suggests a role of α-syn in inflammation and immune responses (see 4.2.2).

4.1 Post-Transcriptional Dysregulation by α-Syn Inclusions (LBs)

4.1.1 Post-Transcriptional Dysregulation by LBs inside of α-Syn Producing Cells (DA-Neurons)

As discussed above, in PD individuals, α-syn accumulates inside α-syn-producing cells, and subtle post-transcriptional regulations by α-syn translate into extreme post-transcriptional repressive or promotive functions of α-syn. When SRPX2 mRNA is extremely sequestered into LBs, then SRPX2 protein level is reduced and DA-neuron synapses are not protected from microglial engulfment and elimination [26,27]. When TRPM1 mRNA is extremely sequestered into LBs, neuromelanin levels are reduced [31]. When SYTL2/SLP2 mRNA and SYTL4/SLP4 regulatory RNA (e.g., miRNA) are extremely sequestered into LBs, secretory vesicles are not docked at a single PIP2-enriched plasma membrane initiation site, but are directed to different sites in the PM, and vesicular secretion is enhanced [35]. It also increases the attachment of multivesicular bodies (MVBs) to the PM, which increases exosome secretion [36]. When the MYO5C regulatory RNA is extremely sequestered into intracellular LBs, the MYO5C molecular motor-driven transport of secretory vesicles [37] (e.g., melanosomes [38]) along actin cables to sites of secretion is promoted. Analogously, when a VAPA regulatory RNA is extremely sequestered into intracellular LBs, the VAPA-driven biogenesis of RNA/RBP-containing MVBs/EVs on the ER membrane [136] is extremely promoted. LB-sequestration of regulatory RNAs for TPTEN-family phosphatases post-transcriptionally promotes these membrane phosphatases (TPTE2, TPTE and TPTEP2-CSNK1E), then the PI3K-AKT pathway is down-regulated and subsequently GSK3β is activated and TAU is more phosphorylated and co-aggregated with α-syn (Fig. 5). In addition, ZNF800, which upregulates PTEN and inhibits AKT signaling activity [76], is over-promoted by α-syn LBs. CTCFL/BORIS, a transcription factor and RBP that promotes upstream initiators of the PI3K-AKT pathway [187], is over-repressed. IKBKE/IKKε, a serine/threonine protein kinase that directly, without the need for PI3K involvement, phosphorylates and activates AKT [125], is over-repressed (Fig. 6, group 1). In addition, RICTOR is over-repressed, then the assembly of mTORC2 complex is inhibited and GSK3β is activated, and TAU is more phosphorylated and co-aggregated with α-syn (Fig. 5, group 3). In PD-DA-neurons, consistent with findings in

PD, the PI3K-AKT pathway is extremely downregulated, neuromelanin is reduced, and vesicular transport is aberrantly modified/activated.

mTORC2-SGK1 signaling integrates external signals in order to regulate autophagic turnover of mitochondria through ROS; loss of RICTOR induces mitochondrial ROS and leads to mitophagy [79]. It is interesting that FXR1 and OXR1, which protect against oxidative stress-induced neurodegeneration [129,130], are repressed by α-syn, and CA5B (carbonic anhydrase 5B), the silencing of which protects against ROS production [141], is promoted by α-syn (Fig. 6, group 2). More importantly, the aforementioned MYO5C and SYTL4, which support vesicular transport and docking to the PM, along with post-transcriptionally promoted HKDC1 (Fig. 6, group 2), which is involved in mitolysosomal exocytosis in flunarizine-induced parkinsonism-like symptoms [143], support mitochondrial entry to lysosomes (HKDC1) and lysosome-transport-docking-exocytosis (MYO5C-SYTL4). The promoted gap-junction protein GJA1 could also support the transfer of mitochondria out of the cell [139]. Consistent with PD, α-syn post-transcriptionally promotes/represses genes for which deregulation promotes mitochondrial degradation/exocytosis, and mitochondrial loss ultimately leads to cell death (Fig. 6).

In PD, impaired autophagy significantly increases α-syn aggregation/accumulation and DA-neuron degeneration [124]. As shown in Fig. 6, IKBKE/IKKϵ, a positive regulator of autophagy [126], is over-repressed, but the membrane tethering and lipid transfer factor ATG2B [124] is over-promoted by α-syn LBs. In addition, the Hsp110 chaperone family member HSPA4L/Apgl, which suppresses α-syn aggregation and pathology *in vivo* [88], is post-transcriptionally repressed by LBs (Fig. 5, group 4). Recently, palmitoylated DNAJC5 was shown to form oligomers to accommodate and export soluble α-syn [188]. In the presented model, ZDHHC21-palmitoyltransferase is post-transcriptionally promoted and the SMG1 negative regulator of S129-phosphorylation of α-syn is repressed. However, α-syn DNAJC5 export or increased degradation, mediated by S129-phosphorylation, is only available for the soluble (non-aggregated) form of α-syn; when α-syn prion-like aggregates become resistant to solubilization, DNAJC5 does not export α-syn, S129-phosphorylation-mediated proteasomal targeting is ineffective, and phosphorylated α-syn protein remains stored in aggregates. Actually, phosphorylated α-syn co-aggregates with phosphorylated TAU (phosphorylated by activated GSK3β, Fig. 5). Neuroprotection by trehalose led to the hypothesis that trehalose promotes the clearance of α-syn aggregates through activation of autophagy, but the association of autophagy activation and trehalose is still controversial [189]. On the other hand, trehalose inhibits protein denaturation and aggregation, probably promoting a soluble form, and α-syn can be exported from DA-neurons (palmitoylated DNAJC5) and also be more accessible for proteasomal targeting mediated by S129-phosphorylation. α-Syn accumulated in LBs promotes ZDHHC21-palmitoyltransferase, represses SMG1 (a negative regulator of S129-phosphorylation), and represses the HSPA4L chaperone (anti-aggregation effect for α-syn). Therefore, the export and proteasomal targeting of soluble α-syn seems to be promoted, but anti-aggregation by HSPA4L/Apgl is repressed by LBs. Trehalose appears to help maintain the soluble form of α-syn so that α-syn is more exported and proteasomally degraded, and despite impaired autophagy, LBs grow more slowly in DA-neurons.

Intracellular accumulation of α-syn degradation-resistant aggregates, post-transcriptionally, over-promotes SEPTIN7 and VAPA, which limits Ca^{2+} entry via a fraction of STIM-Orai complexes (SEPTIN7) [94], and mediates pro-apoptotic potassium current enhancement through increased Kv2.1-VAPA association and insertion into the PM [100]. Disruption of intracellular Ca^{2+}-homeostasis/signaling (promoted SEPTIN7 limits Ca^{2+} entry; limited Ca^{2+} entry is caused by repressed TRPM1) and K^+-homeostasis/signaling (increased Kv2-VAPA association and K^+-efflux) alters action potential frequency and may mediate DA-neuron death in PD [190]. Repression of guanine monophosphate synthase (GMPS), which converts XMP (xanthosine 5′-phosphate) to GMP, reduces the level of guanine nucleotides/phosphates that are important for cell metabolism, proliferation, and signaling. Indeed, evidence has shown that purine metabolism is dysregulated in PD [70,71]. In contrast to GMPS, AK7 (adenylate kinase 7) and AMPD3 (adenosine monophosphate deaminase 3) are over-promoted (Fig. 5, group 3,2,7); adenylate kinase and downstream AMP-signaling act as an integrated metabolic monitoring system, and overexpression of AMPD3 and increased AMP-deamination significantly reduce mitochondrial protein synthesis [116].

Nrf2 (NFE2L2) is a key redox-regulated transcription factor. Its activation leads to the upregulation of cytoprotective and antioxidant enzymes/proteins [191]. GSK3β, which is activated by the downregulated PI3K-AKT, mTORC2-AKT (Fig. 5), and IKBKE-AKT (Fig. 6) pathways, phosphorylates Nrf2, which promotes the degradation of this transcription factor against oxidative stress. Another type of phosphorylation (mTORC2-PKC-Nrf2) promoting nuclear importation of Nrf2 [191] is reduced by over-repression of RICTOR (Fig. 5, group 3). In the nucleus, the NF-κB/p65 subunit competes with Nrf2 by binding to the antioxidant response element [191]. Intracellular accumulation of degradation-resistant α-syn aggregates, post-transcriptionally, over-promotes KPNB1 (Fig. 6, group 3), a key regulator for NF-κB/p65 nuclear importation [151]. In fact, a more than 70-fold higher proportion of PD-DA-neurons with NF-κB/p65 in their nuclei was observed in PD patients than in control subjects [150]. As a result of increased degradation of Nrf2, its limited nuclear transport, and increased NF-κB/p65 competition in the nu-

clei, PD-DA-neurons switch to ROS production/sensitivity and apoptosis. This is consistent with PD knowledge. Increased Nrf2 activity after NF-κB inhibition has already been evaluated; it reduced DA-neuron apoptosis in the rotenone-induced PD rat model, the lipopolysaccharide-induced PD rat model, and the MPTP-induced mouse model [191].

Inhibition of PARP1 energy-exhaustion-induced apoptosis is considered a relevant approach for the treatment of PD [192]. LBs post-transcriptionally over-promote GIT2 (Fig. 6, group 3), the positive regulator of poly (ADP-ribose)-polymerase-1 (PARP1). GIT2 appears to control multiple aspects of the complex ageing process and PARP1-mediated DNA repair capability contributes to mammalian longevity [155]. PARP1 catalyzes the covalent attachment of poly (ADP-ribose) (PAR) on acceptor proteins (PARylation), which affects DNA repair, chromatin remodeling, and gene transcription [192]. PARP1 protects neurons from cell death under mild oxidative stress as a result of DNA repair, but an excessive activation of PARP1 leads to mitochondria-related energy-exhaustion-induced apoptosis [192]. Intracellular accumulation of α-syn promotes ROS and GIT2 (Fig. 6, group 3), which activate PARP1. In addition α-syn represses ATPSCKMT (Fig. 6, group 1), a mitochondrial methyltransferase that trimethylates Lys-43 in the c-subunit of mitochondrial ATP synthase. A lack of this methylation results in decreased ATP-generating ability of the complex [132]. Over-activated PARP1 (ROS and GIT2) and increased ATP consumption, together with a reduced ability to generate ATP (repressed ATPSCKMT/promoted AMPD3), lead to mitochondrial energy exhaustion and neuronal death. LBs post-transcriptionally promote RNF146 (Fig. 5, group 7), a PAR-controlled E3 ligase that directly interacts with PAR and mediates the degradation of proteins PARylated by PARP1 [113]. This could enhance PARP1 activity and energy-exhaustion-induced apoptosis, but RNF146 appears to directly inhibit self-PARylated PARP1 by binding to PAR [115]. In PD, transcription of the *RNF146* gene is significantly reduced [115], and despite α-syn post-transcriptional promotion of RNF146 (Fig. 5, group 7), PARP1-mediated neuronal death can occur.

DAZL (deleted in azoospermia like) is post-transcriptionally over-promoted by LBs (Fig. 5, group 8). Like α-syn, DAZL is also able to form resistant aggregates (during gametogenesis in the testis), but is usually low in the brain and therefore does not form aggregates [19], but its increase in DA-neurons could promote further α-syn aggregation. Interestingly, germ lines produce characteristic cytoplasmic ribonucleoprotein complexes called "nuage" or "germinal granules" [171], and TDRD1 (Tudor domain containing 1) and TDRD4/RNF17 control the proper nuage formation and the piwi pathway [172]. They are post-transcriptionally dysregulated according to the presented PD model. Repressed TDRD1 acts as a molecular scaffold for piwi-proteins and piRNAs [172], and promoted RNF17/TDRD4 represses an adaptive amplification loop for secondary piRNA generation – the ping-pong cycle [168]. Piwi-interacting RNAs act as guides to identify piwi targets and have a role in post-transcriptional silencing/regulation [168]. Downregulation of these processes can be lethal to the neuronal cell. In addition, the model presented here identified post-transcriptional repression of MAMLD1. MAMLD1 likely plays a role in multiple steps of male development and increases testosterone biosynthesis [178]. Using transcriptome data from PD patients, *MAMLD1* was identified as the gene responsive to Braak stages in PD [179].

4.1.2 Post-Transcriptional Dysregulation by Phagocytosed LBs (Microglia)

As mentioned above, the neuronal protector of the neuronal synapse against microglial engulfment, SRPX2 (blocking the classical C1q-mediated complement cascade), is post-transcriptionally over-repressed in "infected" DA-neurons. Consequently, increased LB-phagocytosis may lead to the accumulation of these degradation-resistant α-syn aggregates in microglia and accelerate microglial inflammatory responses. Stimulation of microglia with aggregated α-syn has been shown to induce an inflammatory microglial phenotype/function associated with NF-κB activation and L-plastin downregulation [30]. According to the presented PD model, phagocytosed LBs post-transcriptionally promote KPNB1 (Fig. 6, group 3), a positive regulator for nuclear importation of NF-κB/p65 subunit, and repress LCP1/L-plastin, a critical regulator of immune cell function (Fig. 5, group 1). NRG1-ERBB4 signaling-dependent inhibition of NF-κB has anti-inflammatory effects in microglia [112], but phagocytosed LBs downregulate the ERBB4 receptor (Fig. 5, group 7), which downregulates NRG1 signaling. The transmembrane receptor TREM2 expressed on microglia, binds LPS and induces phagocytosis. It can be released from the cell surface by metalloproteases, and the resulting soluble form (sTREM2) induces NF-κB signaling and pro-inflammatory cytokine expression in microglia [97]. Specifically, the metalloproteinase meprin β (MEP1B) has been shown to release membrane-bound TREM2 and control phagocytic activity [97]. According to the protein-RNA regulatory model, phagocytosed LBs post-transcriptionally promote MEP1B (Fig. 5, group 5); as a result, they can induce NF-κB signaling and proinflammatory cytokine expression in infected microglia, and even, as recently reported, exosomes from microglia infected with LBs are fully capable of inducing "α-syn prion infection" in recipient neurons and spread the disease [193].

4.2 Post-Transcriptional Dysregulation in α-Syn Accepting Cells

α-Syn is produced/localized intracellularly and is a multifunction player in exocytosis, endocytosis, and vesicle transport/recycling (Fig. 1). However, as noted above, palmitoylated DNAJC5 forms oligomers to accommodate and export soluble α-syn to extracellular space [188], and α-syn bound/encapsulated in membrane vesicles is efficiently transported from α-syn-producing neurons. In light of this, α-syn-negative cells can acquire α-syn as free or membrane-vesicular from the extracellular space, and the protein subsequently performs protein-RNA regulation inside the cells.

4.2.1 Post-Transcriptional Dysregulation by Reducing Total and Soluble α-Syn

In all meta-analyses of cerebrospinal fluid (CSF), the evidence suggests that soluble and total α-syn is lower, and aggregated is higher, in PD patients than in healthy controls [194]. This CSF decrease in total and soluble α-syn can post-transcriptionally dysregulate the expression of various genes (Figs. 5,6) in the "accepting" cells. For example, α-syn post-transcriptionally promotes RAP1A (Fig. 5, group 8); the precise level of RAP1A is important in the dopamine pathway for DA-D1 receptor-PKA-RASGRP2-RAP1A-MAPK signaling for the excitability in medium spiny neurons [120]. The extracellular α-syn reduction will post-transcriptionally decrease the expression of RAP1A in medium spiny neurons that "accept" α-syn. Another example can be α-amylase, which has a glycogen degrading (energy) function within synapses. In PD patients, total salivary α-syn is significantly reduced [54], but amylase concentrations are increased [55]. According to the presented PD-model, α-syn post-transcriptionally represses AMY1A, AMY1B, AMY1C, AMY2A and AMY2B genes (Fig. 5, group 2), so that α-syn extracellular reduction post-transcriptionally increases the expression of these genes/proteins in α-syn-"accepting" cells. Astrocytes are critical for neuron protection; GJA1 promotes mitochondrial trafficking from astrocytes to neurons, which may be responsible for the protection [139]. α-syn post-transcriptionally promotes GJA1 (Fig. 6, group 2), so extracellular reduction of α-syn reduces GJA1 expression in α-syn-"accepting" astrocytes, and mitochondrial transmission from them to neurons is then less efficient. α-syn post-transcriptionally promotes GIT2 (Fig. 6, group 3), which appears to control multiple aspects of the complex aging process, so extracellular reduction of α-syn downregulates GIT2 and can induce anxiety-like behavior and advanced aging [155]. Similarly, extracellular α-syn reduction downregulates transcriptional activator LPP and co-receptor RGMB in α-syn-"accepting" cells. LPP translocates from the nucleus to the cell periphery, where it guides motor axons [165,166]. RGMB, mediating amplification of BMP2 signaling, has been identified as a gene related to motor progression of PD [49]. Similarly, down-regulation of SEPTIN7 in α-syn-"accepting" cells will disturb dendritic outgrowth and motility, which are crucial for synaptic plasticity [93].

4.2.2 Post-Transcriptional Dysregulation of Inflammatory and Immune Responses Leading to Stimulation of α-Syn Production/Aggregation Inside of α-Syn Producing Cells (DA-Neurons)

According to the PD model presented here, α-syn post-transcriptionally represses LCP1 and IL1RAP1 co-receptors and the inflammatory activator IKBKE/IKKϵ (Figs. 5,6), so that extracellular α-syn reduction upregulates these proteins in α-syn-"accepting" glia. LCP1, which can function downstream of FcγR [28], significantly increases the assembly of the NLRP3 inflammasome and promotes inflammatory responses [29]. IL1RAP (interleukin 1 receptor accessory protein)/IL1R3 forms a complex with receptors for IL1/(IL1-like) cytokines, and is essential for IL1-like cytokine signaling [85,86] (Fig. 5, group 4). The IKBKE/IKKϵ inflammatory activator phosphorylates various proteins to release NF-κB into the cytosol and activate inflammatory signaling [125]. It appears that tissue infection or excessive inflammatory responses may increase the demand for extracellular α-syn, and to accelerate neuronal α-syn synthesis to inhibit LCP1, IL1RAP1, and IKBKE/IKKϵ etc. in α-syn-"accepting" cells. This, in turn, may stimulate the aggregation of α-syn in neurons with subsequent spread to DA-neurons; then, eventually, LB-formation reduces the available α-syn for accepting cells, thereby perpetuating inflammation, LB-formation, and PD development. Recently, it has been suggested that α-syn produced by neuronal cells is required for proper regulation of inflammatory and immune responses for normal immune cell function [195].

5. Conclusions

The present bioinformatics study showed that α-syn could be an aggregation-prone RBP (Figs. 2,3), associated with intracellular and extracellular transport of RNA vesicles (endosomes/exosomes and microvesicles) that post-transcriptionally regulate a network of genes (Figs. 5,6).

In α-syn-producing neurons (e.g., DA-neurons), the identified genes/proteins explain the reasons for: (a) the intracellular accumulation of α-syn (extracellular requirement for α-syn as a regulator of inflammatory and immune responses - LCP1, IL1RAP1, IKBKE; impaired autophagy IKBKE, ATG2B, repression of chaperone HSPA4L); (b) aberrant vesicle transport (dysregulation of SYTL2, SYTL4, MYO5C, VAPA); (c) Nrf2-degradation and TAU-phosphorylation (activated GSK3β by dysregulation of IKBKE, TPTE2, ZNF800, RICTOR, CTCFL); (d) reduced protection of synapses from microglial uptake/elimination (SRPX2); (e) ROS production and mitochondrial loss (Nrf2-degradation and increased NF-κB/p65

in nucleus, OXR1-repression); and finally (f) the dysfunctionality and death of neurons (mitochondrial energy exhaustion, synapse energy exhaustion - repressed AMY1 and AMY2 genes). Accumulation of phagocytosed LBs in microglia induces NF-κB signaling (MEP1B, KPNB1, ERBB4) and the expression of pro-inflammatory cytokines; "α-syn prion-like infection" is subsequently transmitted by exosomes (aberrant vesicle transport) from infected microglia/neurons to recipient neurons. As a result, α-syn accumulates intracellularly in prion-like aggregates and "free" extracellular α-syn is reduced. Reduction of "free" α-syn can post-transcriptionally dysregulate the expression of various genes (Figs. 5,6) in "accepting" cells that express α-syn very poorly. This will lead to cognitive decline and progression of motor circuit disturbances.

Although the presented concept will need to be verified *in vivo*, this bioinformatic study revealed potentially "groundbreaking" findings that will, I hope, initiate the necessary experimental studies.

Availability of Data and Materials

The datasets generated and/or analysed during this study are listed in the **Supplementary Material**, further information is available from the corresponding author.

Author Contributions

The single author had the sole role in designing, data collecting, analyzing, and writing the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2811292.

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