

Protein family review

The synucleins

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Summary

Synucleins are small, soluble proteins expressed primarily in neural tissue and in certain tumors. The family includes three known proteins: α -synuclein, β -synuclein, and γ -synuclein. All synucleins have in common a highly conserved α -helical lipid-binding motif with similarity to the class-A₂ lipid-binding domains of the exchangeable apolipoproteins. Synuclein family members are not found outside vertebrates, although they have some conserved structural similarity with plant 'late-embryo-abundant' proteins. The α - and β -synuclein proteins are found primarily in brain tissue, where they are seen mainly in presynaptic terminals. The γ -synuclein protein is found primarily in the peripheral nervous system and retina, but its expression in breast tumors is a marker for tumor progression. Normal cellular functions have not been determined for any of the synuclein proteins, although some data suggest a role in the regulation of membrane stability and/or turnover. Mutations in α -synuclein are associated with rare familial cases of early-onset Parkinson's disease, and the protein accumulates abnormally in Parkinson's disease, Alzheimer's disease, and several other neurodegenerative illnesses. The current challenge is to understand the normal cellular function of these proteins and how they might contribute to the development of human disease.

Gene organization and evolutionary history

The synuclein family consists of three distinct genes, α -synuclein, β -synuclein, and γ -synuclein, which have so far been described only in vertebrates. Table 1 catalogs the unique members of the synuclein family that are currently listed in GenBank [1]; these 16 sequences encode the orthologs of each of the three synucleins in the species in which they have been described. The sequences are shown aligned in Figure 1a and their estimated relationships are indicated by the dendrogram in Figure 1b. The α -synuclein gene has been mapped to human chromosome 4q21.3-q22 [2], β -synuclein to human chromosome 5q35 [3], and γ -synuclein to human chromosome 10q23.2-q23.3 [4]. The α -synuclein gene is organized as 7 exons, 5 of which are protein-coding, while the β -synuclein gene has 6 exons (5 protein-coding) and the γ -synuclein gene has 5 exons (all protein-coding) (reviewed in [5]).

Characteristic structural features

All synuclein protein sequences consist of a highly conserved amino-terminal domain that includes a variable number of

11-residue repeats and a less-conserved carboxy-terminal domain that includes a preponderance of acidic residues. The only significant divergences within the repeat domain are the deletion of 11 amino acids (residues 53-63) in all β -synucleins and the addition of a repeat after residue 32 in the γ -synuclein of the electric ray *Torpedo californica* (Figure 1a). The 11-mer repeats make up a conserved apolipoprotein-like class-A₂ helix (Figure 2a,b), which mediates binding to phospholipid vesicles; lipid binding is accompanied by a large shift in protein secondary structure, from around 3% to over 70% α -helix [6].

Although no confirmed synuclein orthologs have been identified in non-vertebrates, a low-scoring BLAST 'hit' for similarity is obtained for LEA76, a plant protein belonging to the late embryo-abundant (LEA) group III protein family. Upon further examination, the sequence similarity is attributable to the presence of an 11-residue repeat encoding a similar class-A₂ lipid-binding motif (Figure 2c). Like synucleins, LEA group III proteins are relatively unordered in solution; upon fast drying, however, they shift to a largely α -helical

Table 1**Summary of known synuclein family members**

Gene type	Species	Other names	OMIM accession number*	GenBank accession number†
α	Human	NACP	163890	586087
α	Rat	SYN1, SYN2, SYN3 (splice variants)		9507125
α	Mouse	SYN2 (splice variant)		6678047
α	Chicken			7689260
α	Canary	Synelfin		2501104
β	Human		602569	4507111
β	Bovine	PNP14		464424
β	Rat	PNP14		2501106
β	Mouse			15809030
β	Chicken			7689264
γ	Human	BCSG1, persyn	602998	4507113
γ	Rat	Sensory neuron synuclein		13928954
γ	Mouse	Persyn		6755592
γ	Chicken	Persyn		7689262
γ	Bovine	Synoretin		6942174
γ	Electric ray	Synuclein		730882

*See OMIM [36]; †see GenBank [1].

conformation [7], and are hypothesized to associate with and stabilize cellular membranes against desiccation stress. A *Caenorhabditis elegans* LEA homolog has been reported [8] that also shares this structural motif (Figure 2d). Thus, despite the low degree of primary sequence similarity, further scrutiny of the LEA proteins' potential functional relationships to the synucleins is warranted.

Localization and function

The first synuclein was identified in 1988 by Maroteaux *et al.* [9], who screened an expression library with an antiserum raised against purified cholinergic vesicles from the electric organ of the Pacific electric ray *Torpedo californica*. This initial cDNA clone (encoding electric-ray γ -synuclein; Table 1) was used to isolate a rat clone encoding a 140-amino-acid protein (rat α -synuclein, Table 1). The product of the β -synuclein gene was first isolated as a bovine brain-specific phosphoprotein (phosphoneuroprotein 14 kDa or PNP14), and its sequence was first described in 1993 [10].

The α - and β -synuclein proteins are predominately expressed in brain, particularly in the neocortex, hippocampus, striatum, thalamus, and cerebellum; protein immunoreactivity is enriched at presynaptic terminals [11,12]. Although their normal physiological functions are unknown, several lines of evidence suggest a role in membrane-associated processes at the presynaptic terminal: α -synuclein is specifically upregulated in a discrete population of presynaptic terminals of the songbird brain during a period of song-acquisition-related synaptic rearrangement [13]; α - and β -synuclein proteins were biochemically

purified from bovine brain as constitutive inhibitors of phospholipase D2 [14], an enzyme that catalyzes the hydrolysis of phosphatidylcholine to phosphatidic acid and appears to play a role in cytoskeletal reorganization and/or endocytosis at the plasma membrane [15]; α -synuclein knockout mice have enhanced dopamine release at nigrostriatal terminals in response to paired electrical stimuli, suggesting that α -synuclein is an activity-dependent negative regulator of dopamine neurotransmission [16]; and, finally, depletion of α -synuclein from cultured primary hippocampal neurons by treatment with antisense oligonucleotides results in a decrease in the distal pool of presynaptic vesicles, as visualized by electron microscopy [17].

Mammalian γ -synuclein was first identified as breast cancer-specific gene 1 (*BCSG1*) in a high-throughput direct differential-cDNA-sequencing screen for markers of breast cancer [18]. The protein is expressed in the peripheral nervous system (in primary sensory neurons, sympathetic neurons, and motor neurons) [18] and is also detected in brain [19], ovarian tumors [20], and in the olfactory epithelium [21]. A sequence dubbed synoretin was independently isolated from ocular tissues in a screen for novel proteins regulating phototransduction and is now thought to represent the bovine ortholog of γ -synuclein [22]. The normal cellular function of γ -synuclein is likewise unknown, but exogenous expression of the protein increases the invasive and metastatic potential of breast tumors [23].

Synucleins in neurodegenerative disease

In 1993, Ueda *et al.* reported [24] that a short peptide (non-amyloid component, NAC) derived from purified amyloid

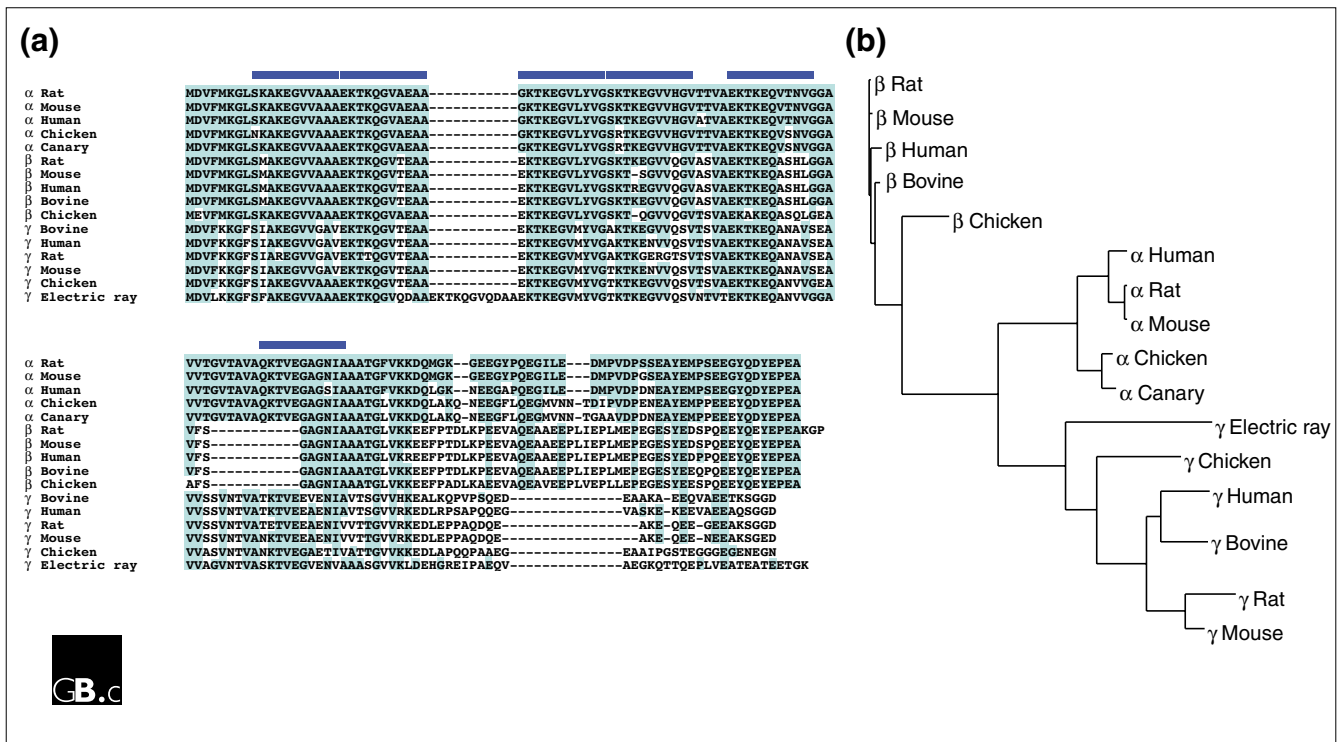


Figure 1 Alignment and relationships of the 16 known synuclein sequences. There are about 80 synuclein sequences in GenBank [1], which can be further sorted into 16 unique groups, each representing a single protein-coding sequence orthologous to one of the three synucleins (summarized in Table 1). (a) The resulting 16 synuclein sequences were aligned with the Multalin program [37]. Shading indicates identity with rat α -synuclein; blue bars represent the 11-residue repeats. (b) A dendrogram of synuclein relationships, generated with ClustalW [38] and displayed using TreeView [39].

plaques from the brains of people with Alzheimer's disease was derived from a larger precursor protein, non-amyloid component precursor (NACP), which is now known to be identical to human α -synuclein. Then, in 1997, Polymeropoulos and colleagues reported [25] that a missense mutation (A53T) in α -synuclein was genetically linked to early-onset, familial Parkinson's disease. Description of a second linked mutation (A30P) followed in 1998 [26]. Antibodies to α -synuclein protein were used to show that the protein accumulates in the ubiquitinated protein inclusions and dystrophic neurites (Lewy bodies and Lewy neurites) that are the hallmark pathological features of the disease; this localization was observed even in cases of sporadic Parkinson's disease, which are not associated with α -synuclein mutations [27]. Indeed, α -synuclein is the primary fibrillar component of Lewy bodies, and α -synuclein lesions are also observed in cases of dementia with Lewy bodies and multiple system atrophy, and in some cases of Alzheimer's disease, the parkinsonism-dementia complex of Guam, and Hallervorden-Spatz disease (reviewed in [28]). Although the accumulation of fibrillar α -synuclein in neurodegenerative disease can be interpreted as evidence that the fibrils are themselves toxic, an equally plausible view is that the fibrils are inert or even protective. Conway *et al.* [29] recently observed that the neurotransmitter dopamine forms adducts with α -synuclein that

stabilize a protofibrillar form of the protein (at the expense of fibril formation); the authors proposed that the accumulation of toxic α -synuclein protofibrils could account for the selective loss of dopamine-containing neurons in Parkinson's disease.

The detection of α -synuclein in ubiquitinated inclusions raises the issue of whether α -synuclein is normally targeted for turnover by the ubiquitin-proteasome machinery. Although the evidence for α -synuclein turnover by the proteasome is equivocal [30-32], proteasomal inhibitors do not appear to cause accumulation of poly-ubiquitinated α -synuclein. The α -synuclein binding partner synphilin-1 was, however, recently shown to be ubiquitinated and targeted for proteasomal turnover by parkin, a ubiquitin ligase, mutation of which is itself a risk factor for familial Parkinson's disease. This may provide a common pathological mechanism linking familial mutations in α -synuclein and parkin via their common interactions with synphilin-1 [33].

The β - and γ -synuclein proteins are not found in Lewy bodies, but both are associated with hippocampal axon pathology in Parkinson's disease and dementia with Lewy bodies [34]. A change in the expression of γ -synuclein has also been specifically observed in the retina of patients with Alzheimer's disease [22].



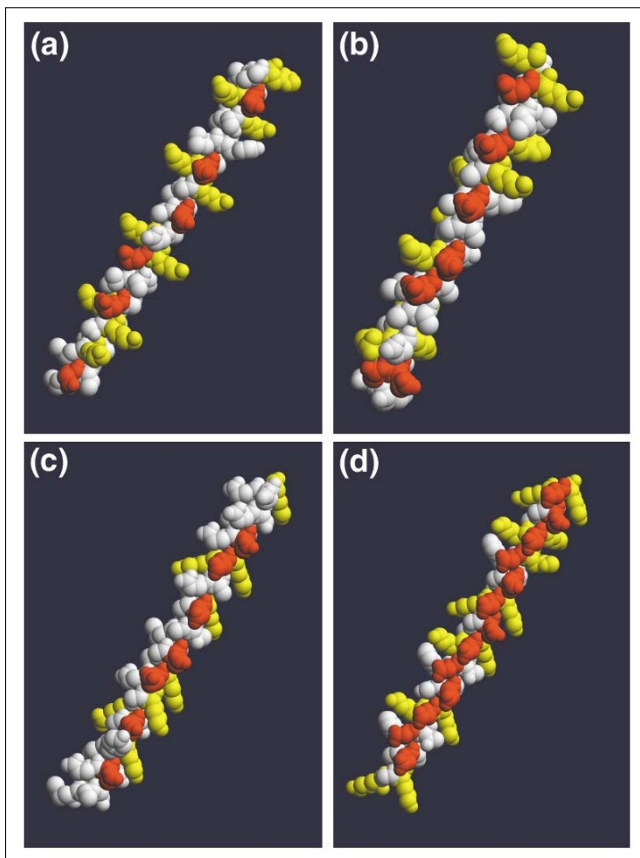


Figure 2
Comparison of the amphipathic α -helical domains of α -synuclein and related proteins. Sequences of interest were imported into Swiss-PdbViewer [40], assigned an ideal α -helical structure, and exported as .pdb files. Models were then formatted and exported with RASMOl [41], and animations (available with the complete version of this article, online) were compiled with QuickTime Pro. **(a)** Human α -synuclein residues 1-50, modeled as an α -helix. The initial frame shown here shows just the hydrophilic face of the helix, with acidic residues confined to the center (red) and basic residues at each interface (yellow); the opposite hydrophobic face (shown in the animation online) contains only uncharged residues (white). **(b)** Human apolipoprotein AI residues 190-231; **(c)** *Arabidopsis thaliana* LEA76 residues 1-50; **(d)** *C. elegans* LEA residues 351-400; all are modeled as in (a).

Frontiers

The association of synucleins with human disease has focused a great deal of interest on this protein family. The question of what the synucleins do still remains, however. Most of the experimental evidence available with regard to function is gleaned from experiments with α -synuclein, but the conservation of an extended, class-A₂ amphipathic α helix comprising more than half of each of the protein sequences indicates a common biochemical mechanism among all synucleins, probably involving lipid binding. Perrin *et al.* [35] report irreversible multimerization of α -, β -, and γ -synuclein upon exposure to polyunsaturated phospholipid species, cellular membrane components that are the most susceptible to oxidative damage. This specific interaction might serve to

protect these vulnerable lipids from damage or to scavenge damaged lipids and target them for turnover. Paxinou *et al.* [32] also noted recently that α -synuclein is degraded, at least in part, by the lysosome, suggesting a role for α -synuclein in the autophagocytic clearance of damaged cellular organelles. Thus, it is tempting to speculate that the synucleins help to maintain cellular membrane integrity. But much work remains to be done to elucidate the normal cellular functions of these unusually conserved proteins and to determine how they contribute to diverse disease processes spanning neurodegenerative disease and cancer.

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Additional data files

Additional data files available with the online version of this article include animated versions of Figure 2a, Figure 2b, Figure 2c and Figure 2d, which can be viewed with QuickTime Player.

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