

FIGURE 37.1 Neuropathological findings of two human brain disorders associated with synucleinopathy. Immunohistochemical (A,C,D) and immunoelectron microscopy (B) images were obtained from midbrain (A,B) and frontal cortex (C,D) sections from patients with Parkinson disease (A,B), a normal infant (C), and an infant with a fatal lysosomal storage disease (D). Sections were probed with anti- α -synuclein antibodies, developed and either counterstained with hematoxyline (blue; A,C,D), or developed with an immunogold particle-coated secondary antibody (B). In (A), a reduced number of dopamine neurons, reactive gliosis and the presence of a round, classical Lewy body inclusion (brown) located in the cytoplasm of a single remaining neuron can be seen. The α -synuclein-containing Lewy body (diameter, 6 μ m; arrow) is partially surrounded by clusters of physiological neuromelanin and located in proximity to the nucleus. In (B), round gold particles (black; diameter, 12 nm) decorate α -synuclein fibrils (gray) in an affinity-enriched Lewy body. Healthy human cortex shown in (C) contains high levels of soluble α -synuclein seen diffusely throughout the neuropil (brown). In the absence of cathepsin D expression (D), the neuronal architecture of the cortex is disrupted, α -synuclein signals are reduced in the neuropil and instead begin to aggregate (diameter, 1 to 6 μ m) within the cytoplasm and neurites. (Image (B) provided by Wei Ping Gai, Flinders University, Australia; image (D) provided by Jaana Tyynelae, Helsinki University, Finland; panels (C) and (D) from [80].)

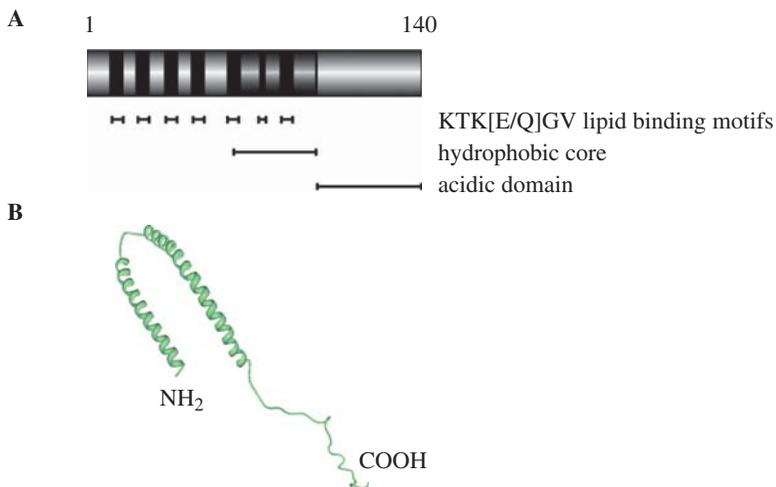


FIGURE 37.2 Graphic representation of primary sequence motifs in human α -synuclein and models of secondary and tertiary structure. (A) Schematic of primary structure of human α Syn, highlighting the six to seven lipid-binding motifs, the hydrophobic core, and the acid carboxyl terminus of the protein. In its native state, α Syn is unfolded, highly soluble, and cytoplasmic. (B) Ribbon diagrams representing the secondary structure of micelle-bound α Syn derived from solution NMR spectroscopy. (From the PDB database, accession number 1XQ8 [102].

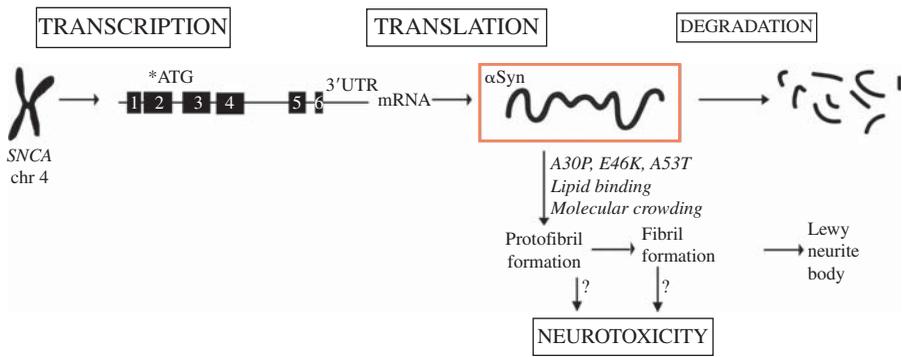


FIGURE 37.4 Schematic representation of α -synuclein metabolism. Steady-state levels of soluble α Syn are maintained through equilibrium between α Syn production (processes of transcription and translation), protein degradation, and the generation of insoluble oligomeric species. Our current understanding of the molecular mechanisms and pathways that regulate protein expression and degradation are discussed in the text. Soluble α Syn is prone to formation of oligomeric species mediated through its central hydrophobic core. The formation of higher-order structures is modulated by lipid binding and molecular crowding and is enhanced by point mutations that are linked to autosomal dominant heritable PD (A30P, E46K, A53T), and may be regulated by posttranslational modifications, such as Ser129 phosphorylation. The relative neurotoxicity of the insoluble protofibril and fibril species remains an important question in understanding the pathogenesis of synucleinopathies.