BBA - Biomembranes xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

BBA - Biomembranes

journal homepage: www.elsevier.com/locate/bbamem

Review

Electrostatic and hydrophobic interactions of lipid-associated α-synuclein: The role of a water-limited interfaces in amyloid fibrillation

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ARTICLE INFO

Keywords:
Lipid-associated α-synuclein
Lipid membrane-water interface
Water-limited environment
Intrinsically disordered protein structures
Electrostatic and hydrophobic interactions
Amyloid fibrillation

ABSTRACT

Human α-synuclein (αSyn) is an intrinsically disordered protein (IDP) whose biological and pathological functions in brain neuronal cells have not yet been fully elucidated. αSyn intrinsically participates in aiding neurotransmitter trafficking through αSyn the association with lipid membranes. However, lipid-associated states of αSyn also induce amyloid self-assembly that is linked to the pathogenesis of various synucleinopathies. These contradicting actions arise from the limited water content near lipid-water interfaces that controls αSyn electrostatic and hydrophobic interactions. Thus, understanding the molecular interactions between αSyn and lipid membranes in the presence of water molecules is critical in elucidating the pivotal role of lipid-associated αSyn in amyloid self-assembly. In this review, we describe how the membrane interface controls electrostatic and hydrophobic interactions of lipid-associated αSyn. Moreover, membrane amyloid self-assembly of αSyn will be further discussed with regards to the structural dynamics of lipid-associated αSyn and water molecules near the interface.

1. Introduction

α-Synuclein (αSyn) is an intrinsically disordered protein (IDP), comprising 140 amino acid residues, that is expressed in neuronal cells of the human brain [1]. αSyn is mainly present near the synaptic terminals of neuronal cells [2] and it maintains a dynamic equilibrium between its cytosolic and lipid-associated states [3,4]. Cytosolic native αSyn is present in a disordered conformation [5], whereas lipid-associated αSyn undergoes large structural transitions to form an α-helix with highly dynamic and partially disordered conformations [6]. Lipid-associated αSyn, whose binding is reversible, is mainly found in synaptic vesicles and plasma membranes of synaptic terminals [7,8] and promotes neurotransmitter trafficking—in cooperation with soluble *N*-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE) proteins [9–11]—and remodeling of membranes to attain distinct morphologies [11–14]. However, lipid-associated states in the cellular environment also enable misfolding events of αSyn, resulting in the formation of β-sheet rich, fibrillar αSyn aggregates [15]. Fibrillar αSyn aggregates are found as the main components of Lewy bodies (LBs) or Lewy neurites (LNs), which are pathological hallmarks of various synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLBs), and multiple system atrophy (MSA) [16–18]. Lipids were coaccumulated with αSyn aggregates in postmortem tissues of PD patients and *in vitro* αSyn fibrillation, indicating that lipid-associated αSyn directly participates in the pathology of synucleinopathies through fibrillation [19–22]. Furthermore, lipid compositions are altered in parkinsonian brains [23,24] and various lipidoses have been linked with parkinsonism [25]; however, it is unclear if the metabolic pathways involved in the compositional variation of lipids are the cause or result of αSyn-lipid associations and amyloid fibrillation. Thus, unraveling the physicochemical nature of lipid-associated αSyn is critical to understanding how biological events between αSyn and the lipid membrane are linked to pathological amyloid self-assembly inside neuronal cells.

The membrane-binding properties of αSyn originate from its primary structure that is conventionally categorized into three regions, N-terminal (residues 1–60), non-amyloid-β component (NAC; 61–95), and C-terminal (96–140) regions (Fig. 1A) [26]. N-terminal and NAC regions contain seven imperfect 11 residue-repeated motifs with highly conserved KTKEGV sequences (Fig. 1B) that are classified as amphipathic class A_2 lipid-binding α-helical segments [27]. N-terminal and NAC regions interact with the lipid membrane through structural transitions from random coil to α-helix, whereas C-terminal regions remain largely unstructured and water solvated [28]. The amphipathic

Abbreviations: αSyn, α-synuclein; IDP, intrinsically disordered protein; LBs, Lewy bodies; LNs, Lewy neurites; ER, endoplasmic reticulum; NAC, non-amyloid-β component; PC, phosphatidylcholine; PS, phosphatidylserine; PUFA, polyunsaturated fatty acid; ε_r, relative permittivity

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https://doi.org/10.1016/j.bbamem.2018.02.007
Received 28 December 2017; Received in revised form 5 February 2018; Accepted 5 February 2018

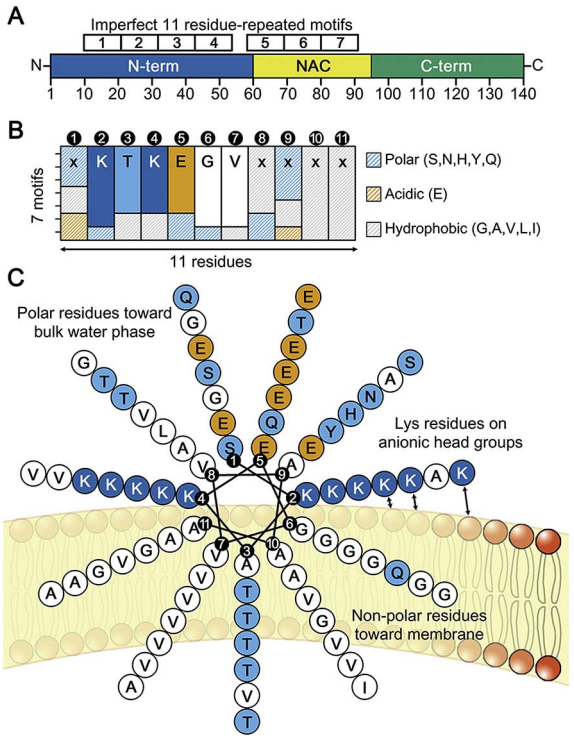

Fig. 1. (A) Schematic representation of αSyn structure with seven imperfect 11 residue-repeated motifs. N-terminal and NAC regions directly participate in lipid membrane associations. (B) Distribution of amino acids in the KTKEGV-repeated motifs. (C) Helical wheel projection of lipid-associated αSyn. αSyn mainly interacts through electrostatic interactions between Lys residues and lipid head groups, as well as hydrophobic interactions between non-polar residues and aliphatic acyl chains.

N-terminal and NAC regions form a long 11/3 α-helical structure in which polar and non-polar residues are arranged toward the bulk water phase and the lipid membrane, respectively, while lysine (Lys) residues are oriented for contact with anionic head groups (Fig. 1C) [29,30]. Consequently, the membrane-bound α-helical structures are stabilized by intermolecular electrostatic interactions of Lys residues with anionic lipid head groups and hydrophobic interactions of non-polar residues with lipid acyl chains [31–33].

The lipid membrane is a system separated from the bulk water phase [34], providing a water-limited environment for N-terminal and NAC regions of αSyn [35]. This unique property enhances electrostatic interactions by lowering relative permittivity (ε_r) around αSyn [36] and solvates the hydrophobic residues of αSyn with aliphatic acyl chains of lipids in membrane packing defects [37], thereby stabilizing α-helical structures on the lipid membrane. Notably, depending on the lipid composition, α-helical structures of lipid-associated αSyn are converted to partially folded intermediates involved in the misfolding events of αSyn [38]. These conformational transitions increase the probability of exposing hydrophobic NAC regions to water molecules in the bulk phase, triggering the intermolecular hydrophobic interactions of αSyn [15]. Thus, the structural transitions of αSyn in the lipid-water interface are correlated with its pathological role. However, despite numerous studies on lipid-associated αSyn, the water-limited lipid environment that controls the reversibility of αSyn conformations and amyloid self-assembly has not yet been fully elucidated.

In this review, we aim to update our understanding of the role of water molecules in αSyn amyloid self-assembly near lipid-water interfaces based on current findings. We will discuss the cellular membranes that are relevant to lipid-associated states of *in vivo* αSyn and the physicochemical features regulating membrane-binding properties of αSyn. Furthermore, the driving force behind the lipid-association of αSyn in cell-membrane mimicking systems will be discussed based on

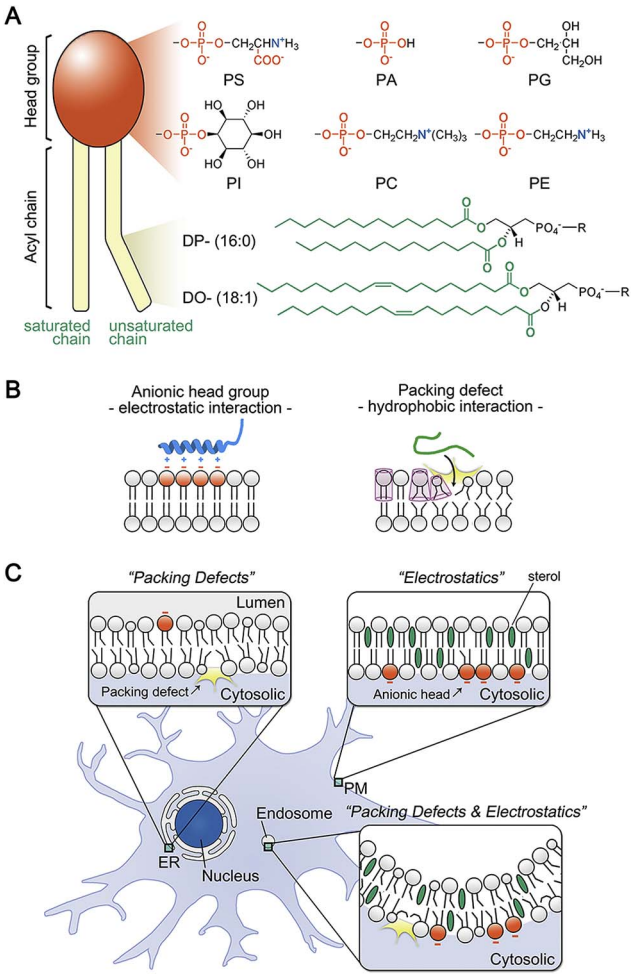

Fig. 2. (A) Molecular structure of amphiphilic lipids with polar head groups and aliphatic acyl chains. (B) Schematic representation of electrostatic and hydrophobic interactions with the lipid membrane. (C) Intracellular lipid territories of eukaryotic cells regulating physicochemical properties of the membrane of each organelle. Plasma membrane and endoplasmic reticulum (ER) regulate the lipid-association of amphipathic IDPs through their own lipid compositional characteristics. Electrostatic interactions in plasma membranes and hydrophobic interactions in the ER mainly induce lipid associations of IDPs. Endosomes, like synaptic vesicles, possess characteristics of both plasma membranes and ER and are optimized for αSyn-lipid association.

the role of water-limited lipid environments. Finally, consequences of αSyn structural transitions will be discussed together with the αSyn self-assembly mechanisms on lipid membranes.

2. Electrostatic and hydrophobic interactions based on lipid territories in cellular organelles

2.1. Electrostatic interactions and localization of anionic phospholipids in synaptic vesicles and plasma membranes

Phospholipids are abundant in the cellular membranes interacting with αSyn. They are unique amphiphiles that construct the various types of lipid-water interfaces enclosing each cellular organelle [39,40]. The molecular structure of phospholipids consists of polar head groups and aliphatic acyl chains (Fig. 2A). These components confer physicochemical properties to the membrane, such as negative charges and lipid packing defects that control electrostatic and hydrophobic interactions, respectively, between lipid-associated proteins and the lipid membrane (Fig. 2B) [41]. Anionic head groups, including phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylglycerol (PG), phosphatidylinositol (PI), and PI derivatives with a variable number of