Journal of Magnetic Resonance 280 (2017) 127–139

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

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

Membrane remodeling by amyloidogenic and non-amyloidogenic proteins studied by EPR

Jobin Varkey, Ralf Langen

Zilkha Neurogenetic Institute, University of Southern California, Los Angeles, CA 90033, United States

ARTICLE INFO

Article history:
Received 4 January 2017
Revised 18 February 2017
Accepted 18 February 2017

Keywords:
Membrane protein
Membrane curvature
Phospholipids
Electron paramagnetic resonance
Protein structure

ABSTRACT

The advancement in site-directed spin labeling of proteins has enabled EPR studies to expand into newer research areas within the umbrella of protein-membrane interactions. Recently, membrane remodeling by amyloidogenic and non-amyloidogenic proteins has gained a substantial interest in relation to driving and controlling vital cellular processes such as endocytosis, exocytosis, shaping of organelles like endoplasmic reticulum, Golgi and mitochondria, intracellular vesicular trafficking, formation of filopedia and multivesicular bodies, mitochondrial fusion and fission, and synaptic vesicle fusion and recycling in neurotransmission. Misregulation in any of these processes due to an aberrant protein (mutation or misfolding) or alteration of lipid metabolism can be detrimental to the cell and cause disease. Dissection of the structural basis of membrane remodeling by proteins is thus quite necessary for an understanding of the underlying mechanisms, but it remains a formidable task due to the difficulties of various common biophysical tools in monitoring the dynamic process of membrane binding and bending by proteins. This is largely since membranes generally complicate protein structure analysis and this problem is amplified for structural analysis in the presence of different types of membrane curvatures. Recent EPR studies on membrane remodeling by proteins show that a significant structural information can be generated to delineate the role of different protein modules, domains and individual amino acids in the generation of membrane curvature. These studies also show how EPR can complement the data obtained by high resolution techniques such as X-ray and NMR. This perspective covers the application of EPR in recent studies for understanding membrane remodeling by amyloidogenic and non-amyloidogenic proteins that is useful for researchers interested in using or complimenting EPR to gain better understanding of membrane remodeling. We also discuss how a single protein can generate different type of membrane curvatures using specific conformations for specific membrane structures and how EPR is a versatile tool well-suited to analyze subtle alterations in structures under such modifying conditions which otherwise would have been difficult using other biophysical tools.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Protein-membrane interactions are pivotal to many cellular processes [1–4]. Understanding the molecular mechanisms of these interactions is, therefore, of great importance. In the recent past, many proteins have been identified that can remodel membranes by their interplay with various cellular membranes [4,5]. These include protein families like BIN/Amphiphysin/Rvs (BAR) [6–8], Eps 15-homology [9,10], epsin [11], synaptotagmins [12] and synucleins [13–15].

Membrane remodeling proteins are involved in a plethora of cellular events within the cell like endocytosis, exocytosis, shaping of organelles such as endoplasmic reticulum, Golgi and mitochondria, intracellular vesicular trafficking, formation of filopedia and multivesicular bodies, mitochondrial fusion and fission, and synaptic vesicle fusion and recycling in neurotransmission. In these highly dynamic processes, interplay between proteins and lipids give rise to highly curved membrane structures which are not thermodynamically favored, unless stabilized by the curvature stabilizing proteins and lipids.

Processes requiring generation of membrane curvature are crucial to the survival and normal functional activity of the cell. For example, endocytosis is an energy-requiring process that is constantly used by cells to selectively move materials to the inside of the cell by forming an invagination in plasma membrane and then pinching-off into the cell internal. It is used for movement of solutes, microorganisms, cell debris, signaling molecules and fluid. The mechanism(s) underlying endocytosis is not completely

E-mail addresses: jvarkey@usc.edu (J. Varkey), langen@usc.edu (R. Langen)

http://dx.doi.org/10.1016/j.jmr.2017.02.014
1090-7807/© 2017 Elsevier Inc. All rights reserved.

understood due to the intrinsic complexity of the process requiring involvement of multiple protein and lipid players. It is a multistep process involving membrane bending, invagination, enlargement of the invaginated area, constriction of the plasma membrane, fusion of the membrane leaflets followed by excision or separation of the newly formed vesicle from the plasma membrane [4]. Different proteins are involved in the different steps and dysfunction of any one of these steps can lead to failure of the endocytic process. In addition, aberrant control of membrane curvature can compromise the activity of membrane remodeling proteins in various other membrane remodeling processes, leading to a diseased state. For example, some point mutations in the BAR (Bin1/amphiphysin/RVS167) domain-containing amphiphysin inhibit its ability to tubulate membranes *in vitro* and cause centronuclear myopathy. This disease causes muscle weakness and skeletal muscle atrophy and is characterized by a pronounced disruption of the membranous T tubule network. [16]. Mutation in dynamin-2 (*DNM2*), another membrane remodeling protein, also causes centronuclear myopathy further illustrating the importance of membrane curvature generation in the pathogenesis of this disease [17].

Various mechanisms have been proposed to explain how proteins can bend membranes (Fig. 1) [18–20]. One of these mechanisms is scaffolding where proteins directly impart their own intrinsic curvature onto the membrane. For example, amphiphysin contains a 'banana-shaped' BAR domain that directly molds the membrane into a curved shape. The specific alignment of multiple such BAR domains can generate a unidirectional membrane curvature that stabilizes membrane tubules [21,22]. Another mechanism is wedging, where the asymmetric insertion of protein regions, often amphipathic helices, pushes the headgroups apart in a manner akin to the generation of membrane curvature by lipids with spontaneous positive curvature. Many proteins, including epsin, α-synuclein, IAPP and some BAR-domain containing proteins, called N-BAR proteins have such helical wedges. Non-helical wedges can also be found and are present in some BAR proteins such as pacsin [23]. In addition to pushing headgroups apart and affecting the spontaneous curvature of the membrane, wedges also add mass to the leaflet they insert into. This asymmetric addition of material to one leaflet could further promote membrane curvature by the bilayer couple mechanism. This mechanism arises from the expansion of the total area of one membrane leaflet compared to the other [4,5,18,19,24]. Using these and/or quite possibly other mechanisms such as molecular crowding of protein on membrane, partitioning of shaped transmembrane domains, and cytoskeleton-mediated 'pulling and pushing' of membrane, a variety of membrane morphologies like small vesicles, tubular structures, membrane protrusions and lipoprotein particles are generated and have been observed *in vivo* [4,5,18,19,24,25]. Interestingly, a single protein, for example α-synuclein, can also generate different lipid morphologies *in vitro*, even by just modulating the protein-to-lipid ratio (Fig. 2) [13,14]. Understanding the structure of a protein in membrane-bound form is difficult using techniques like X-ray

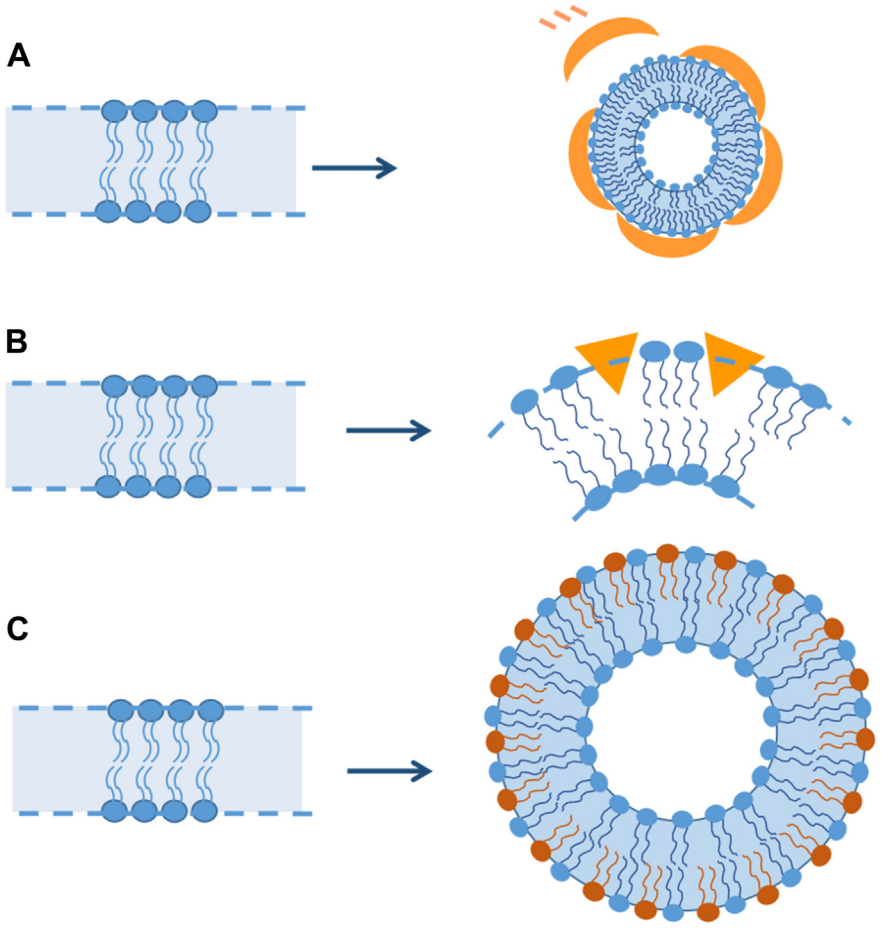

Fig. 1. Mechanisms of membrane bending. (A) Scaffolding mechanism – Membranes are bent by the scaffolding of intrinsically curved protein domains (Orange curved structures) on the membrane surface; (B) Wedging mechanism – Membrane bending occurs by insertion of protein (Orange triangles) on the membrane surface that acts like a wedge pushing apart the phospholipid headgroups; and (C) Bilayer couple mechanism – By asymmetric addition of material on one side of the bilayer, for example, small unilamellar vesicles are able to able to retain high curvature due to presence of ~twice the amount of lipid molecules in outer monolayer as compared to inner monolayer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Download English Version:

https://daneshyari.com/en/article/5404528

Download Persian Version:

https://daneshyari.com/article/5404528

Daneshyari.com