Progress in Neurobiology 97 (2012) 127–141

Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

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

The recycling endosome and its role in neurological disorders

Xueyi Li, Marian DiFiglia *

Laboratory of Cellular Neurobiology and Department of Neurology, Massachusetts General Hospital, 114, 16th Street, Charlestown, MA 02129, USA

ARTICLE INFO

Article history:
Received 3 August 2011
Received in revised form 14 October 2011
Accepted 17 October 2011
Available online 20 October 2011

Keywords:
Membrane traffic
The recycling endosome
Rab11
Neurological disorders
Huntington's disease

ABSTRACT

The recycling endosome (RE) is an organelle in the endocytic pathway where plasma membranes (proteins and lipids) internalized by endocytosis are processed back to the cell surface for reuse. Endocytic recycling is the primary way for the cell to maintain constituents of the plasma membrane (Griffiths et al., 1989), i.e., to maintain the abundance of receptors and transporters on cell surfaces. Membrane traffic through the RE is crucial for several key cellular processes including cytokinesis and cell migration. In polarized cells, including neurons, the RE is vital for the generation and maintenance of the polarity of the plasma membrane. Many RE dependent cargo molecules are known to be important for neuronal function and there is evidence that improper function of key proteins in RE-associated pathways may contribute to the pathogenesis of neurological disorders, including Huntington's disease. The function of the RE in neurons is poorly understood. Therefore, there is need to understand how membrane dynamics in RE-associated pathways are affected or participate in the development or progression of neurological diseases. This review summarizes advances in understanding endocytic recycling associated with the RE, challenges in elucidating molecular mechanisms underlying RE function, and evidence for RE dysfunction in neurological disorders.

Contents

Abbreviations: AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, amyloid precursor protein; CHO, Chinese hamster ovary; EAAC1, excitatory amino acid carrier 1; EAAT3, excitatory amino acid transporter 3; EE, early endosome; EHD, Eps15 homology (EH) domain containing protein (EHD); ER, endoplasmic reticulum; ES, embryonic stem; GAP, GTPase-activating protein; GDF, GDI-displacement factor; GEF, guanine nucleotide exchange factor; HD, Huntington's disease; HRP, horseradish peroxidase; Htt, huntingtin; LE, late endosome; α2-M, α2-microglobulin; MDCK, Madin–Darby canine kidney; PrP, prion protein; Rab11FIP, Rab11 family interacting protein; rabGDI, rabGDP dissociation inhibitor; RE, recycling endosome; SE, sorting endosome; SH3TC2, Src homology 3 domain and tetratricopeptide repeat 2; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; Tfn, transferrin; TfnR, transferrin receptor; TNFα, tumor necrosis factor α; tTGase, tissue transglutaminase; VAMP, vesicle-associated membrane protein.

* Corresponding author. Tel.: +1 617 726 8446; fax: +1 617 726 1264.
E-mail address: difiglia@helix.mgh.harvard.edu (M. DiFiglia).

0301-0082/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.pneurobio.2011.10.002

1. Introduction

The endocytic pathway of mammalian cells is composed of a series of heterogeneous and highly dynamic membrane-enclosed tubulo-vesicular structures called endosomes, which lie at the crossroad between the plasma membrane, the entry portal of the cell, and the lysosome, the clearance station of the cell. In mammalian cells, endocytosis can occur by various mechanisms, including a clathrin-dependent process (often called receptor-mediated endocytosis) that has been well characterized. All endocytosis is initiated by sequestering cargo into curved structures, which eventually mature into primary endocytic vesicles through cooperative actions of a cohort of macromolecules including lipids. Although traditionally viewed as two major components – the early endosome (EE) and the late endosome (LE), the realization that endocytosed ligands and their receptors are processed differently has led to use of the term sorting endosome (SE) as an operational term for the EE (Maxfield and McGraw, 2004). Newly formed endocytic vesicles fuse with each other to form the SE or with pre-existing SE, where the fate of endocytosed cargoes is determined. The absorption of plasma membranes by endocytosis is counterbalanced by the return of membrane cargo to the cell surface through endosomal recycling. The recycling process maintains the homeostatic composition of the plasma membrane. In mammalian cells, two intracellular pathways – a short loop and a long loop pathway handle endocytosed plasma membrane constituents (proteins and lipids) for return to the cell surface (Dunn and Maxfield, 1992; Hopkins, 1983; Salzman and Maxfield, 1989). The "short-loop" or fast recycling pathway retrieves endocytosed proteins and lipids directly from the SE within 2–3 min. In the "long loop" or slow recycling pathway endocytosed proteins and lipids travel from the SE to the pericentriolar RE in about 10 min from where they are then transferred back to the cell surface. The factors in mammalian cells that determine which recycling route is selected for transport of particular cargoes are not fully understood (Daro et al., 1996). Membrane trafficking and sorting along the endocytic pathway involves the Rab family of small guanosine triphophatases (GTPases), which are frequently used as markers for identifying their host organelles (Grosshans et al., 2006; Zerial and McBride, 2001). Fig. 1 illustrates the endosomal organelles and their corresponding Rab proteins based on studies of the clathrin-dependent endocytic pathway.

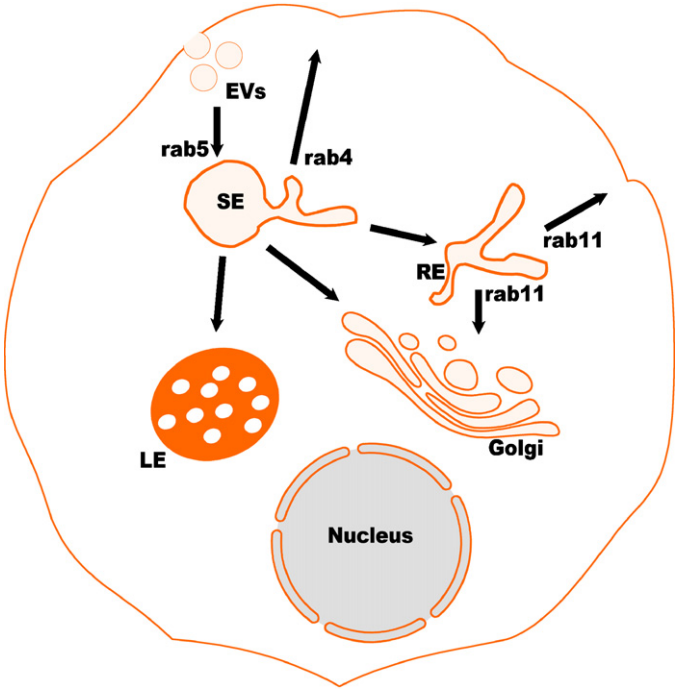

Fig. 1. The endosomal system and the corresponding Rab proteins in non-polarized cells. Schematic shows the path of internalized membranes through the endocytic pathway. Cell surface receptors and their ligands are sequestered into pits that bud into the cells to form endocytic vesicles (EVs). EVs fuse with each other or with the preexisting sorting endosome (SE) using Rab5. At the SE internalized ligands and other solutes are retained in the central vacuole which matures into the late endosome (LE); receptors and the majority of lipids segregate in narrow-diameter tubules of SE for recycling back to the cell surface. The recycling of cargo back to the plasma membrane occurs by a short-loop under control of Rab4, or by a long-loop from the juxtanuclear recycling endosome (RE) that is controlled by Rab11. Certain internalized cargo is transferred from either the SE or the RE to the trans-Golgi network. The transfer of cargo from RE is regulated by Rab11.

Continuous membrane flow through the endosomal system is a fundamental mechanism for regulating plasma membrane plasticity and is the basis for control of a range of cellular events, including nutrient uptake, signal termination and propagation, cytokinesis, antigen presentation and immune surveillance. During embryogenesis, membrane traffic through the endosomal system manages tissue remodeling, polarity biogenesis and cell fate specification. Pathogens such as viruses exploit the endocytic pathway to enter the cell and to hijack molecular machinery of the endosomal system. Thus, aberrant function in the endosomal system may lead to developmental problems and severe cellular dysfunction.

Because it maintains plasma membrane homeostasis in mammalian cells, membrane recycling through the endosomal system has been a topic of intensive interest. Numerous factors that regulate the recycling of endocytosed membranes have been discussed in excellent reviews (Grant and Donaldson, 2009; Jones et al., 2006; Maxfield and McGraw, 2004). Neurons more than other cell types possess an architecture and systems of signaling that require tightly controlled regulation of endocytic and secretory pathways to ensure their normal function. Most knowledge about membrane trafficking in neurons pertains to the biogenesis and recycling of synaptic vesicles. The RE is not well understood in neurons. However, emerging data suggests that dysfunction at the level of the RE underlies the pathogenesis of human diseases, including those affecting the nervous system. Here, we summarize factors that are crucial for RE function, discuss challenges in elucidating mechanisms of RE membrane dynamics, and review evidence for involvement of RE dysfunction in neurological disorders.

2. Delineating the recycling endosome (RE)

2.1. RE biogenesis

Understanding RE biogenesis requires knowledge of cargo sorting at the SE where endocytosed cargoes destined for the RE or