Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

The formation and function of ER-endosome membrane contact sites

Emily R. Eden

UCL Institute of Ophthalmology, London, UK

ARTICLE INFO

Article history:
Received 25 September 2015
Received in revised form 27 January 2016
Accepted 29 January 2016
Available online xxxx

Keywords:
Endosome
Endoplasmic reticulum
Membrane contact site
Lipid transport

ABSTRACT

Recent advances in membrane contact site (MCS) biology have revealed key roles for MCSs in inter-organellar exchange, the importance of which is becoming increasingly apparent. Roles for MCSs in many essential physiological processes including lipid transfer, calcium exchange, receptor tyrosine kinase signalling, lipid droplet formation, autophagosome formation, organelle dynamics and neurite outgrowth have been reported. The ER forms an extensive and dynamic network of MCSs with a diverse range of functionally distinct organelles. MCSs between the ER and endocytic pathway are particularly abundant, suggesting important physiological roles. Here, our current knowledge of the formation and function of ER contact sites with endocytic organelles from studies in mammalian systems is reviewed. Their relatively poorly defined molecular composition and recently identified functions are discussed. In addition, likely, but yet to be established, roles for these contacts in lipid transfer and calcium signalling are considered. This article is part of a Special Issue entitled: The cellular lipid landscape edited by Tim Levine and Anant K. Menon.

1. Introduction

Membrane contact sites (MCSs) are regions of close apposition (≤30 nm) between two organelles, establishing microdomains for interorganellar exchange. The ER network forms extensive MCSs with multiple organelles within the cell, including the plasma membrane, mitochondria and Golgi apparatus. The first indication that the ER might make functional contact sites with endocytic organelles came from studies in yeast that identified a junction between the nucleus and vacuole formed by direct interaction between the ER protein Nvj1 and the vacuole protein Vac8 [1]. Although extremely abundant, ER contacts with the endocytic pathway (Fig. 1) in mammalian cells were only recently described [2,3]. Membrane contact sites are stabilized by tethering complexes that maintain close proximity between the apposing membranes without membrane fusion. These tethers can often be discerned by electron microscopy, as multiple strands between the apposing membranes of the two organelles (Fig. 1). While our understanding of the composition of tethering complexes remains incomplete, with recent advances in membrane contact site biology, many organelle-specific tethering proteins have been identified [4–6]. The ER-localized Vesicle associated membrane protein (VAMP)-Associated Proteins (VAPs) have been implicated in tethering numerous different MCSs. For example, ER:mitochondrial MCSs are promoted by VAPB:PTPIP51 interaction [7],while ER:Golgi MCSs are promoted by VAP interaction with OSBP, CERT and Nir2 FFAT (diphenylalanine in an acidic tract) motifs [8]. A VAP homologue in yeast (Scs2) has been implicated in MCSs between the ER and the plasma membrane that are important in the regulation of phosphoinositide lipid turnover [9]. Moreover, VAP interaction with the FFAT motifs of the sterol binding proteins ORP1L [3] and STARD3 [10] on late endosomes/lysosomes have been implicated in MCS formation between the ER and the endocytic pathway, as will be discussed in more detail below.

2. ER-endosome contact site formation

The regulation and molecular composition of ER-endocytic organelle MCSs remains poorly characterized, but three independent studies implicate VAPs in tethering these contacts (Fig. 2), either by direct interaction with the FFAT motifs of endosomal sterol-binding proteins ORP1L and STARD3, or indirectly, by interaction with another integral ER membrane protein, protrudin, which interacts with Rab7 and phosphatidylinositol 3-phosphate (PI3P) at the endosome [11].

ORP1L is a sterol and oxysterol binding protein [12] that is recruited to a population of endosomes that are positive for the Neimann-Pick type C (NPC) protein NPC1[13] by interaction with Rab7 [14]. Under conditions of low cholesterol in the endocytic pathway, ORP1L undergoes a conformational change that promotes VAP interaction [3]. Overexpression of an ORP1L mutant (ΔORD) in which the c-terminal oxysterol-binding domain had been removed to mimic ORP1L conformation under cholesterol-free conditions (thereby favouring VAP interaction) increased both the number and size of ER-endosome contact sites [3]. Similarly, over-expression of STARD3 or STARD3NL, which localize to a different population of earlier endosomes that contain the cholesterol transporter ABCA3 [13], resulted in a striking extension of ER-endosome contacts [10]. These data signal a role for VAP interactions with

E-mail address: e.eden@ucl.ac.uk.

http://dx.doi.org/10.1016/j.bbalip.2016.01.020
1388-1981/

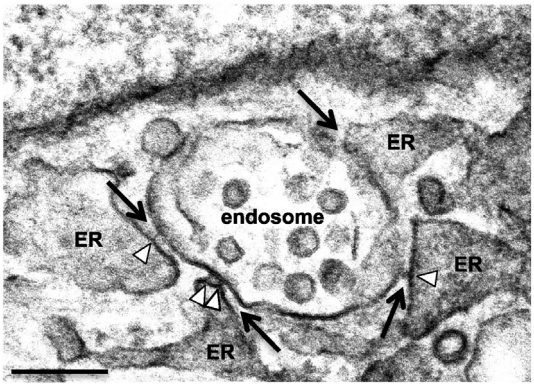

Fig. 1. Electron micrograph of an ER-endosome membrane contact site. Hela cells were prepared for transmission electron microscopy. The image shows membrane contact sites (black arrows) between the ER and an endosome. Tethers (white arrowheads) between the two organelles are often visible at the contact site. Scale bar, 200 nm.

endosomal sterol-binding proteins in the formation of these contact sites, but it should be noted that while the increase in contact sites mediated by STARD3 overexpression was VAP-dependent, neither study reported a reduction in basal contact site formation on depletion of VAP/ORP1L/STARD3. It is therefore possible that VAP interactions might function at and/or stabilize existing ER-endosome contacts rather than initiating contact site formation.

As mentioned above, in addition to the interactions with endosomal FFAT-motif-containing proteins, VAPA also binds the FFAT motif of an integral ER membrane protein, protrudin [11]. Protrudin also contains a PI3P-interacting FYVE domain and a low complexity region through which it interacts with Rab7. Coincident interaction of ER-localized protrudin with endosomal PI3P and RAB7 promotes the formation of ER-endosome contact sites and the recruitment of VAPA to the contact [11]. Overexpression of protrudin results in rearrangement of the ER to form multiple and extended contacts, demonstrating a role in recruiting the ER to the contact site, but whether protrudin stabilizes pre-existing contacts or initiates contact site formation remains unclear.

Another interaction reported to stabilize ER-endosome contact sites is that between the ER localized protein tyrosine phosphatase 1B (PTP1B) with endocytosed EGFR (Fig. 3). Depletion of PTP1B reduced contact sites and EGF stimulation increased the size of contacts, but these contact sites still formed in the absence of PTP1B or EGF [2], suggesting that existing contact sites provide platforms for PTP1B-EGFR interactions, which stabilize what would otherwise be extremely transient sites of contact. As yet there is no evidence for recruitment of VAPs to these contact sites, but as key regulators are identified, a role for VAPs might also become apparent.

Interestingly, in addition to binding Rab7, ORP1L, like protrudin, also binds phosphoinositides, through its PH domain [14], but the significance of this in its role at contact sites has not been established. Rab7 interactions are required for both protrudin- and ORP1L-regulated ER-endosome contact sites, suggesting a central role for this small GTPase in the regulation of ER-endosome contact sites. A Rab exchange from Rab5 to Rab7 marks the maturation of an early, sorting endosome, to a late endosome [15]. That PTP1B-EGFR interactions occur at early (Rab5-positive) as well as mature (Rab7-positive) endosomes, suggests that the regulation of ER-endosomes MCSs might involve several key tethering complexes specific to different endosome populations, possibly defined by the Rab5–Rab7 switch.

3. Functions of ER-endosome contact sites

3.1. Endosome fission and positioning

Endocytic organelles are extremely dynamic, continuously moving as they progress from initial endocytosed vesicles at the plasma membrane to sites of fusion with the predominantly perinuclear lysosomal compartment. However, not all cargo is destined for lysosomal degradation and many sorting, fusion and fission events occur along the pathway mediating alternative fates, notably recycling to the plasma membrane or retrograde transport to the trans-Golgi network [16].

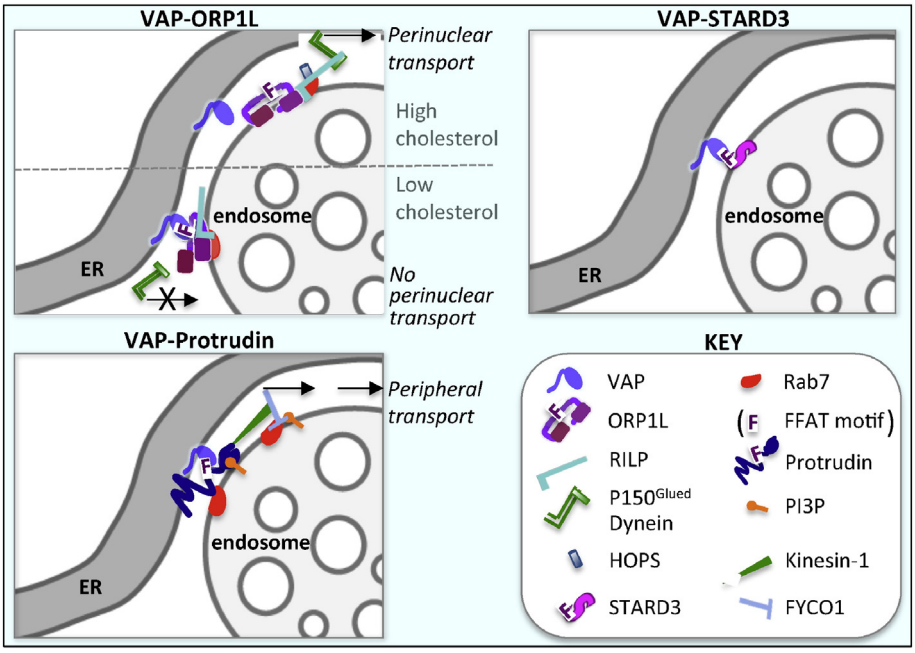

Fig. 2. VAP interactions with FFAT motif-containing proteins at ER-endosome contact sites. VAP interacts with the FFAT motif of ORP1L when LDL-cholesterol is low, terminating ORP1L/RILP/dynein-mediated minus-end directed transport towards the perinuclear compartment. VAP also interacts with the FFAT motif of STARD3, another endosomal sterol-binding protein, promoting contact site formation. VAP additionally binds the FFAT motif of an ER-anchored protein, protrudin, which, through coincident binding of Rab7 and PI3P, mediates kinesin1-dependent, plus-end directed, transport towards the periphery of the cell.

Please cite this article as: E.R. Eden, The formation and function of ER-endosome membrane contact sites, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.01.020