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DOI: https://doi.org/10.1093/femsml/uqad018

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Journal Article
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Originally published at:
Vormittag, Simone; Ende, Rachel J; Derré, Isabelle; Hilbi, Hubert (2023). Pathogen vacuole membrane contact sites – close encounters of the fifth kind. microLife, 4:uqad018.
DOI: https://doi.org/10.1093/femsml/uqad018

microLife, 2023, **4**, 1–16
DOI: 10.1093/femsml/uqad018
Advance access publication date: 7 April 2023
Short Review

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Pathogen vacuole membrane contact sites – close encounters of the fifth kind

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Abstract

Vesicular trafficking and membrane fusion are well-characterized, versatile, and sophisticated means of ‘long range’ intracellular protein and lipid delivery. Membrane contact sites (MCS) have been studied in far less detail, but are crucial for ‘short range’ (10–30 nm) communication between organelles, as well as between pathogen vacuoles and organelles. MCS are specialized in the non-vesicular trafficking of small molecules such as calcium and lipids. Pivotal MCS components important for lipid transfer are the VAP receptor/tether protein, oxysterol binding proteins (OSBPs), the ceramide transport protein CERT, the phosphoinositide phosphatase Sac1, and the lipid phosphatidylinositol 4-phosphate (PtdIns(4)*P*). In this review, we discuss how these MCS components are subverted by bacterial pathogens and their secreted effector proteins to promote intracellular survival and replication.

Keywords: *Chlamydia*, *Coxiella*, *Dictyostelium discoideum*, endoplasmic reticulum, FFAT motif, *Legionella*, Legionnaires’ disease, lipid transfer proteins, membrane contact site, oxysterol binding proteins, pathogen vacuole, phosphoinositide, Sac1 phosphoinositide phosphatase, *Salmonella*, VAP

Membrane contact sites in health and disease

The ability for organelles to interact and communicate is essential for maintaining cellular homeostasis. One of the major means of intracellular communication, and the focus of research for many years, is vesicular trafficking. In general, vesicular trafficking involves two distinct membranes or membrane-bound organelles and occurs via three highly regulated steps: vesicle budding, transport, and fusion (Fig. 1A). During vesicle budding, coat proteins are recruited from the cytosol to the membrane surface and cause the deformation of the membrane to form a rounded bud (Springer et al. 1999, Kirchhausen 2000, Bonifacino and Lippincott-Schwartz 2003, McMahon and Mills 2004). After budding off from the membrane, vesicles are trafficked along cytoskeletal elements (actin and microtubules) by molecular motors such as dynein and kinesin to their target membrane (Hammer and Wu 2002, Matanis et al. 2002, Short et al. 2002). Upon arrival at the target membrane, the vesicle fuses with the target membrane through the presence of cognate SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) proteins on the vesicle and target membrane (Jahn and Scheller 2006).

Another important means of inter-organelle communication is the direct interaction of two closely associated organelles, referred to as membrane contact sites (MCS) (Fig. 1B). Studies describing associations between organelles were first published in the 1950 s (Bernhard and Rouiller 1956, Copeland and Dalton 1959). However, a lack of functional significance for these associations at the time delayed further advances until the 1990 s, when associations between the ER and mitochondria were identified as sites of phospholipid synthesis and calcium transfer (Vance 1990, Rizzuto et al. 1998). MCS have since gained recognition due to their important implications in cell homeostasis, and several human diseases have been linked to MCS dysfunction (Area-Gomez et al. 2012, Stoica et al. 2014, Castro et al. 2018).

Specifically, MCS are zones of close apposition between the membranes of two organelles (10–30 nm) without membrane fusion (Prinz 2014, Scorrano et al. 2019). Functional inter-organellar contact is ubiquitous, with organelles forming MCS with at least one other organelle (Valm et al. 2017, Shai et al. 2018). MCS can be either homotypic, occurring between two identical organelles, or heterotypic, occurring between two different membranes or organelles. Similar contacts can also occur between membrane-bound organelles and non-membrane-bound organelles (Ma and Mayr 2018); however, these contacts are likely divergent from other cellular MCS and are not included in this review. The majority of cellular MCS include the ER, thus ER-containing MCS are the most well studied. For example, the ER forms membrane contact sites with mitochondria, endosomes, the Golgi, and the plasma membrane (PM) (Phillips and Voeltz 2016, Wu et al. 2018) (Fig. 1B). Membrane contacts sites not involving the ER have also been identified in recent years, such as mitochondria-PM, mitochondria-peroxisome, and lipid droplet (LD)-peroxisome MCS (Eisenberg-Bord et al. 2016).

The formation and function of MCS are dependent on the unique molecular composition of the two membranes involved. However, there are several general classes of MCS components:

Received: February 14, 2023. **Revised:** March 30, 2023. **Accepted:** April 6, 2023
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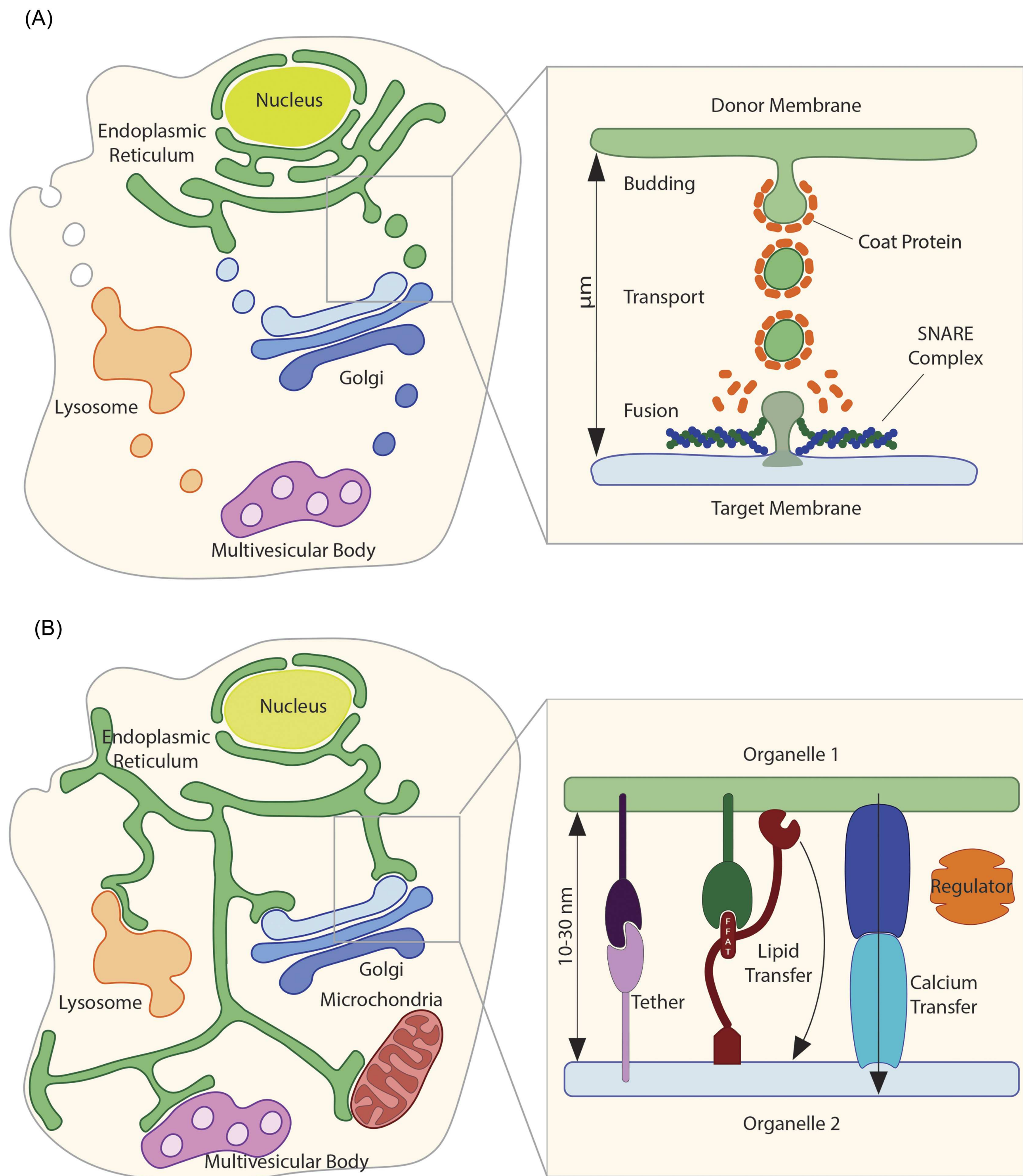

Figure 1. Vesicle trafficking and MCS formation. (**A**) Representation of the major vesicular trafficking events occurring between the ER, the Golgi, the plasma membrane, endosomes and multivesicular bodies. Inset: Representation of vesicle budding assisted by a coat protein from the donor membrane, long-range (µm scale) trafficking of the coated vesicle, and coat disassembly prior to SNARE-mediated fusion to the recipient membrane. (**B**) Representation of MCS occurring between the ER and the PM, the Golgi, mitochondria, endosomes and multivesicular bodies. Please note that additional MCS exist but are not represented here. Inset: Representation of the short-range (nm scale) transfer of small molecules at MCS, which is facilitated by structural (tether), functional (lipid/ion transfer) and regulatory components.

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structural components, functional components, and the newly emerging class of regulatory components (Scorrano et al. 2019) (Fig. 1B). Structural components often act as tethers between the two membranes, maintaining them in close proximity (Scorrano et al. 2019). Functional components include lipid transfer proteins, ion channels, and metabolite channels/transporters, and these components have direct roles in ion, lipid, or metabolite exchange (Scorrano et al. 2019). Regulatory components act dynamically to regulate the formation of MCS and the activity of other MCS components (Honscher and Ungermann 2014, Honscher et al. 2014, Giorgi et al. 2015). Post-translational modification plays a major role in the regulation of protein interactions; thus, kinases and phosphatases often act as regulators at MCS (Kumagai et al. 2014, Duan and Walther 2015, Wu et al. 2018, Kors et al. 2022). It is important to note that these component classifications are not mutually exclusive, and many components can be placed in multiple classes.

MCS play diverse roles throughout the cell, some of the most notable being the regulation of intracellular calcium and non-vesicular lipid trafficking (Srikanth and Gwack 2012, Prakriya 2013, Hanada 2018, Wu et al. 2018). Although the bulk of lipid transfer likely occurs via vesicular trafficking, the non-vesicular lipid transfer occurring at ER-containing MCS plays an important role in maintaining lipid homeostasis in the absence of vesicular transport (Funato et al. 2020). MCS also play additional roles in organelle fission, such as the regulation of mitochondrial and endosomal fission at ER-mitochondria and ER-endosome MCS, respectively (Friedman et al. 2011, Murley et al. 2013, Rowland et al. 2014, Lewis et al. 2016). Additionally, MCS also have roles in organelle positioning (Friedman et al. 2010, Valm et al. 2017). For example, low levels of cellular cholesterol can result in endosomes forming MCS with the ER rather than continuing to be trafficked along microtubules (Rocha et al. 2009). Important for this review, there is increasing evidence that MCS play crucial roles in host pathogen interactions, with both viral (Amako et al. 2009, Roulin et al. 2014, McCune et al. 2017, Ishikawa-Sasaki et al. 2018) and bacterial pathogens (Auweter et al. 2012, Elwell and Engel 2012, Derré 2017, Justis et al. 2017, Stanhope and Derré 2018, Ende et al. 2022, Vormittag et al. 2023) using MCS to establish and maintain infection.

In this review we will introduce several MCS components, focusing on those most relevant to host pathogen interactions, as there are excellent reviews that cover additional MCS components (Scorrano et al. 2019, Prinz et al. 2020). We will also discuss how bacterial pathogens exploit these components and MCS formation to promote and support their intracellular survival.

Components of membrane contact sites

The VAP receptor

VAP (Vesicle-associated membrane protein (VAMP)-associated) proteins are a family of ER-resident receptor/tether proteins that commonly play a role in the formation of ER-containing MCS through interaction with partner proteins on the opposing organelle (Murphy and Levine 2016) (Fig. 2). Two of the VAP family proteins, VAPA and VAPB, are highly homologous and are commonly referred to together as VAP (Murphy and Levine 2016). VAP proteins contain a globular domain with homology to major sperm protein (MSP domain), a predicted coiled-coil domain, and a transmembrane domain that anchors it in the ER (Kaiser et al. 2005). The formation of ER-MCS in the absence of VAP indicated that additional VAP variants or other proteins play a role in ER-MCS formation (Eden et al. 2016, Dong et al. 2016b). In fact, recent studies have identified three new homologs of VAP, motile sperm domain-containing proteins MOSPD1, MOSPD2, and MOSPD3, thus adding to the list of VAP-family proteins (Di Mattia et al. 2018, Cabukusta et al. 2020).

FFAT motif containing protein partners of the VAP receptor

VAP family proteins form tethering complexes through the interaction of the MSP domain with FFAT motifs in partnering proteins such as oxysterol-binding protein (OSBP) (Loewen et al. 2003, Murphy and Levine 2016) (Fig. 2). FFAT (two phenylalanines (FF) in an Acidic Tract) motifs are linear peptide motifs with an E_1-F_2-F_3-D_4-A_5-X_6-E_7 consensus core sequence flanked by adjacent acidic residues that create an acidic tract (Loewen et al. 2003, Loewen and Levine 2005). While deviation from the consensus core sequence is shown to be well tolerated, the residue in position two is considered essential and must be either a phenylalanine (F) or a tyrosine (Y) (Loewen and Levine 2005, Murphy and Levine 2016). Significant variation in the core FFAT motif sequence has become increasingly reported (Slee and Levine 2019, James and Kehlenbach 2021). Recent work identified phospho-FFAT motifs, where the residue in the fourth position of the motif core is a phosphorylatable serine or threonine, which upon phosphorylation favored the interaction with VAP (Di Mattia et al. 2020). Additionally, MOSPD1 and MOSPD3 favor interactions with proteins containing FFAT motifs referred to as FFNT (two phenylalanines (FF) in a Neutral Tract) motifs, where the residues flanking the core of the FFAT motif are neutral amino acids rather than acidic (Cabukusta et al. 2020).

The diversity of FFAT motif containing proteins contributes to the wide range of VAP-interacting partners, including soluble lipid transfer proteins as well as transmembrane proteins (James and Kehlenbach 2021). Thus, the role of VAP-FFAT interactions at MCS goes beyond tethering, especially during non-vesicular lipid transfer as discussed in the next section.

Oxysterol binding and related proteins

In 1985 OSBP was identified as a receptor for oxysterols (Taylor and Kandutsch 1985) (Fig. 2A). Since then, a multitude of OSBP-related proteins (ORP) have been identified. OSBP and ORPs are conserved in mammalian cells, the yeast *Saccharomyces cerevisiae* (de Saint-Jean et al. 2011, Tong et al. 2013) and the social amoeba *Dictyostelium discoideum* (Fukuzawa and Williams 2002, Vormittag et al. 2023)—the evolutionary relationship among these proteins is outlined in Vormittag et al. 2023. Most of our knowledge about OSBP and ORPs structure and function comes from characterization of the mammalian proteins.

OSBP and the 11 human ORPs were classified into six subfamilies based on DNA sequence similarity and gene structure: family I (OSBP and ORP4), II (ORP1 and ORP2), III (ORP3, ORP6 and ORP7), IV (ORP5 and ORP8), V (ORP9) and VI (ORP10 and ORP11). All proteins contain multiple domains that are critical for membrane anchoring. With the exception of ORP5 and ORP8, which have transmembrane domains, most of the mammalian ORPs contain a pleckstrin homology (PH) domain (Fig. 2A) that interacts with phosphoinositide (PI) lipids and/or proteins in non-ER organelle membranes (Lemmon 2004, Olkkonen and Li 2013). Additionally, OSBP, ORP1-4, ORP6, ORP7, and ORP9 contain a FFAT motif (Fig. 2A), which is necessary for ER anchoring via binding to VAP (Wyles et al. 2002, Lehto et al. 2004, Wyles and Ridgway 2004, Lehto et al. 2005).

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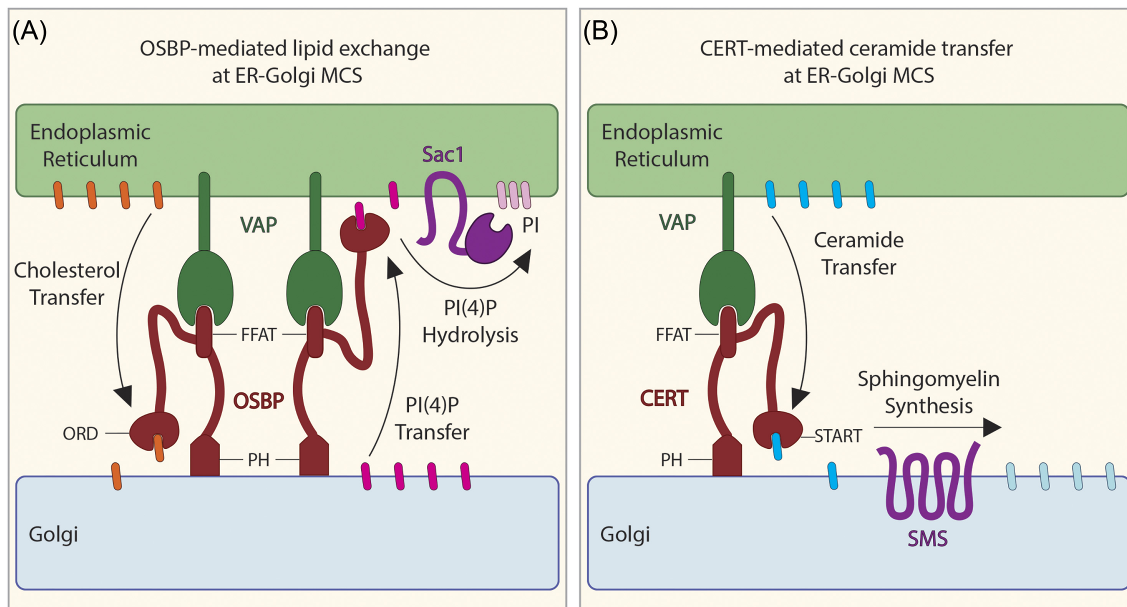

Figure 2. OSBP- and CERT-mediated lipid exchange at ER-Golgi MCS. (**A**) OSBP-meditated lipid exchange at ER-Golgi MCS implicates the FFAT motif and the ORD domain of OSBP, which binds to VAP and promotes lipid exchange, respectively. The Sac1 PI(4)*P* phosphatase maintains a PI(4)*P* lipid gradient between the two adjacent membranes. (**B**) CERT-mediated lipid exchange at ER-Golgi MCS implicates the FFAT motif and the START domain of CERT, which binds to VAP and promotes ceramide transfer, respectively. The sphingomyelin synthase SMS maintains a ceramide gradient between the two adjacent membranes.

The primary known function of OSBP and ORPs is lipid transfer, which is mediated by core lipid binding domains (ORD) sharing 70% identify within each ORP family (Laitinen et al. 1999, Jaworski et al. 2001, Lehto et al. 2001), as well as the ORP signature motif EQVSHHPP. In addition to lipid binding, some ORD domains have been shown to interact with specific protein partners (Olkkonen et al. 2012, Pietrangelo and Ridgway 2019, D'Ambrosio et al. 2020). The ORD domains are also flanked by conserved regions of unknown functions. Several ORPs exist as long (L) and short variants (S), which differ in their cellular localization and interaction partners.

The long variant of ORP1, ORP1L, localizes to ER-late endosome (LE)/lysosome contact sites by interaction of its N-terminal ankyrin repeat domain (ARD) with the late endosome small GTPase Rab7 (Johansson et al. 2005). ORP1L also interacts with VAP through its FFAT motif after a conformational change due to low cholesterol conditions (Johansson et al. 2003, Johansson et al. 2005, Rocha et al. 2009, Vihervaara et al. 2011). The short variant of ORP1, ORP1S, lacks the PH domain as well as the FFAT motif and the ARD (Lehto et al. 2001, Loewen et al. 2003, Jansen et al. 2011). ORP1S localizes in the cytoplasm and in the nucleus and acts at ER-PM and LD-PM contact sites as well as at LE/lysosome-PM contact sites (Jansen et al. 2011, Zhao et al. 2020). Both ORP1 variants bind cholesterol or phosphatidylinositol 4-phosphate (PtdIns(4)*P*) through their ORD (Suchanek et al. 2007, Vihervaara et al. 2011, Zhao and Ridgway 2017, Dong et al. 2019).

ORP2 binds cholesterol, oxysterols, PtdIns(4)*P*, and PtdIns (4,5)P_2 through its ORD (Wang et al. 2019). ORP2 only exists as a short variant consisting of an ORD and a FFAT motif (Lehto et al. 2001) and might act at ER-PM, LD-ER and endosome-PM contact sites (Laitinen et al. 2002, Hynynen et al. 2005, Hynynen et al. 2009, Wang et al. 2019).

ORP3 localizes to ER-PM contact sites after phosphorylation by protein kinase C (Lehto et al. 2008, Weber-Boyvat et al. 2015, Gulyas et al. 2020). ORP3 contains a FFAT motif, a PH domain, and an ORD that binds sterol, PtdIns(4)*P* and possibly phosphatidylcholine (PC) (Suchanek et al. 2007, D'Souza et al. 2020, Gulyas et al. 2020). Furthermore, ORP3 recruits the small GTPase R-Ras and thus contributes to the control of cell adhesion and migration (Lehto et al. 2008, Weber-Boyvat et al. 2015).

The long form of ORP4, ORP4L, localizes to ER-Golgi and ER-PM-contact sites (Zhong et al. 2016a, Zhong et al. 2016b, Pietrangelo and Ridgway 2018). The short variant, ORP4S, lacks the FFAT motif and interacts with vimentin intermediate filaments (Wang et al. 2002). An additional variant, ORPM, lacks a functional PH domain (Wyles et al. 2007, Charman et al. 2014). All ORP4 variants bind sterols or PtdIns(4)*P* through their ORD (Wyles et al. 2007, Goto et al. 2012, Charman et al. 2014).

ORP5 harbours a C-terminal transmembrane domain, thereby being constitutively anchored to the ER (Yan et al. 2008, Du et al. 2011). ORP5 acts at ER-PM contact sites (Maeda et al. 2013, Chung et al. 2015). OPR5 ORD binds phosphatidylserine (PS) and PtdIns(4)*P*, and its PH domain recognizes PtdIns(4)*P* as well as PtdIns(4,5)P_2 (Ghai et al. 2017, Lee and Fairn 2018, Sohn et al. 2018). ORP5 also localizes to ER-mitochondria (Galmes et al. 2016), and ER-LD contact sites by interaction of its ORD with the LD monolayer (Du et al. 2020).

ORP6-11 have been studied in less detail. ORP6 localizes to ER-PM contact sites, its ORD likely binds PtdIns(4)*P* and it associates with ORP3 or itself (Lehto et al. 2004). Little is known about ORP7, except that it localizes to ER-PM contact sites (Lehto et al. 2004). ORP8 displays ER localization and acts at ER-mitochondria and ER-PM contact sites exchanging PS for PtdIns(4,5)P_2 (Yan et al. 2008, Galmes et al. 2016, Ghai et al. 2017, Sohn et al. 2018). The long variant of ORP9, ORP9L, localizes to ER-Golgi contact sites and binds sterols and PtdIns(4)*P* through its ORD (Wyles and Ridgway 2004, Ngo and Ridgway 2009, Liu and Ridgway 2014). The short variant, ORP9S, lacks a PH domain and also localizes to ER-Golgi contact sites (Liu and Ridgway 2014). ORP10 acts at ER-Golgi contact sites, lacks a FFAT motif and binds PS as well as PtdIns(4)*P*

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through its ORD (Maeda et al. 2013, Venditti et al. 2019). ORP10 possibly heterodimerizes with ORP9 to overcome its inability to bind VAP (Nissila et al. 2012). ORP11 acts at ER-Golgi contact sites, lacks a FFAT motif and can interact with ORP9L. ORP11 ORD likely binds PtdIns(4)*P* and possibly sterols and PS (Suchanek et al. 2007, Maeda et al. 2013).

Unicellular eukaryotic fungi and protists, such as *S. cerevisiae* and *D. discoideum*, respectively, have also contributed to OSBP and ORPs characterization. In addition to elucidating their function at MCS, studies of the *S. cerevisiae* oxysterol-binding protein homolog (Osh) proteins were critical in providing structural insights into the mechanisms of lipid binding. The structure of the ORD domain of Osh4p revealed that it is comprised of a conserved β-barrel capped with a N-terminal lid (de Saint-Jean et al. 2011, Tong et al. 2013), in which cholesterol is bound in a 'head-first' orientation where the iso-octyl side chain interacts with the lid. In comparison, PtdIns(4)*P* is bound in a 'tail-first' orientation, where the inositol 4-phosphate headgroup interacts with two histidine residues close to the entrance (de Saint-Jean et al. 2011). *D. discoideum* produces short OSBPs, termed OSBP1-12, which contain ORD with the signature motif EQVSHHPP, but lack PH domains and FFAT motifs (Fukuzawa and Williams 2002, Vormittag et al. 2023).

Another important MCS lipid transport protein in mammalian cells is the ceramide transfer protein (CERT). CERT localizes to ER-Golgi contact sites (Hanada et al. 2003) (Fig. 2B). CERT interacts with VAP on the ER via its FFAT motif and with PtdIns(4)*P* at the Golgi through its PH domain. Once anchored at ER-Golgi MCS, the START domain of CERT binds, extracts, and transfers ceramide from the ER to the Golgi (Hanada et al. 2003, Kawano et al. 2006, Kudo et al. 2008). At the Golgi, a sphingomyelin synthase converts ceramide into sphingomyelin and thus maintains a ceramide gradient between the two adjacent membranes (Hanada 2018).

The phosphoinositide phosphatase Sac1

Sac1 is an integral membrane protein, which anchors to the ER through two C-terminal transmembrane helices (Whitters et al. 1993, Nemoto et al. 2000, Konrad et al. 2002) (Fig. 2A). Sac1 is a phosphoinositide (PI) lipid phosphatase that contains the catalytical motif $CX_5R(T/S)$ (Nemoto et al. 2000). Sac1 binds the coat protein complex I and II (COPI and COPII, respectively), thereby cycling between the ER and the Golgi (Rohde et al. 2003, Weixel et al. 2005, Blagoveshchenskaya et al. 2008, Cheong et al. 2010). Human Sac1 preferentially dephosphorylates PtdIns(4)*P* and to a lesser extent also PtdIns(3)*P* (Rohde et al. 2003). Importantly, the hydrolysis of PtdIns(4)*P* results in a PI lipid concentration gradient between two membranes and is the driving force for the lipid exchange activity of OSBP (Mesmin et al. 2013) (Fig. 2A).

Lipid transport at membrane contact sites

Various lipids, including sterols, ceramide, PS, and PIs are transported by lipid transfer proteins at MCS (Fig. 2). The precursor of PIs, phosphatidylinositol (PtdIns), is primarily synthesized in the ER and transported by vesicular trafficking or via lipid transfer proteins to distinct membranes (Di Paolo and De Camilli 2006). Phosphoinositide lipids contain a hydrophobic membrane anchor and a D-*myo*-inositol head group, which can be phosphorylated at position 3, 4, and/or 5 resulting in seven different PIs (De Matteis and Godi 2004, Behnia and Munro 2005, Raiborg et al. 2016). PI lipids can be modified by kinases, phosphatases, and lipases, which are recruited by small GTPases (Christoforidis et al. 1999, Godi et al. 1999, Jones et al. 2000, Murray et al. 2002).

The different PI lipids are spatially organized in the cell and show distinct subcellular localizations (Balla 2013). The PM contains PtdIns(4,5)P_2, PtdIns(4)*P*, PtdIns(3)*P*, PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3, while the Golgi is rich in PtdIns(4)*P* and to a lesser extent also harbours PtdIns(4,5)P_2. Early endosomes are rich in PtdIns(3)*P*, late endosomes accumulate PtdIns(3,4)P_2, and PtdIns(5)*P* is found on the nuclear membrane (De Matteis and Godi 2004, Behnia and Munro 2005, Di Paolo and De Camilli 2006, Weber et al. 2009b, Balla 2013). Sterols and PtdIns(4)*P* are synthesized at different membranes in the cell, giving rise to lipid gradients upon close contact of membranes of different lipid composition. Further in agreement with a counter exchange model of lipid transfer, reconstitution experiments with proteoliposomes showed that sterol and PtdIns(4)*P* are exchanged only when present on different membranes (*in trans*), but not on the same membrane (*in cis*) (de Saint-Jean et al. 2011, Mesmin et al. 2013, Moser von Filseck et al. 2015, Mesmin et al. 2017) (Fig. 2A).

Sterols comprise up to 40 mol% of lipids in the trans-Golgi and PM but only low levels (<5 mol%) in the ER (Radhakrishnan et al. 2008, van Meer et al. 2008, Mesmin and Maxfield 2009). This distribution arises in part from the presence of lipid components stabilizing cholesterol in the PM, like sphingolipids and phospholipids with saturated acyl chains, while the ER is rich in unsaturated lipids (van Meer et al. 2008, Holthuis and Menon 2014). Sterols increase the membrane thickness and decrease permeability to solutes. If present in excess, cholesterol is modified to cholesteryl ester by acyl coenzyme A and stored in the ER or LDs (Kreutzberger et al. 2015, Stratton et al. 2016).

Ceramide is synthesized in the ER and converted at the Golgi to sphingomyelin by the sphingomyelin synthase SMS (Fig. 2B), or to glycoceramides by various other enzymes (Jeckel et al. 1990, Wang et al. 2021). PS accumulates in the PM inner leaflets and in lower concentrations in the membranes of many other organelles (Leventis and Grinstein 2010). Upon undergoing apoptosis, cells flip PS to the outer leaflet, and the exposed PS is recognized by phagocytes (Brouckaert et al. 2004, Birge et al. 2016).

Subversion of membrane contact sites by bacterial pathogens

A vast majority of intracellular bacterial pathogens create distinct replication-permissive compartments termed pathogen vacuoles. Although, the composition and features of these pathogen-derived vacuoles are specific to each pathogen, interactions with cellular membranes are a commonality. While the interception of host vesicular trafficking is a well-documented and characterized process, the formation of MCS, in particular with the ER, is emerging as a novel mechanism by which bacterial pathogens establish their replicative niche. In the following chapters, we review how the bacterial pathogens *Chlamydia*, *Legionella*, *Coxiella,* and possibly *Salmonella*, use secreted effector proteins to redirect cellular components of ER-Golgi, ER-PM, or ER-endosome contact sites to their distinct vacuoles, thereby assembling MCS between the pathogen vacuole and the ER.

Membrane contact sites of the *Chlamydia* inclusion with the ER

The Gram-negative, obligate intracellular pathogen *Chlamydia trachomatis* is the causative agent of the most common sexually transmitted infection of bacterial origin in the United States and leading cause of infectious blindness worldwide (Wright et al. 2008, Mishori et al. 2012, Malhotra et al. 2013, Cheong et al. 2019).

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Upon entering the host cell, *Chlamydia* resides within a vacuole termed the inclusion (Moulder 1991, Abdelrahman and Belland 2005, Moore and Ouellette 2014, Gitsels et al. 2019) (Fig. 3). To establish and maintain its intracellular niche, *Chlamydia* interacts with host cell factors and organelles. These interactions, as well as maturation of the inclusion, are facilitated by *Chlamydia* type III secretion system (T3SS)-translocated effectors (Lara-Tejero and Galan 2019). A subset of these effectors, called inclusion membrane (Inc) proteins are embedded within the inclusion membrane and are characterized by the presence of two or more bilobed transmembrane domains and cytosolic tails that enable interactions with host factors (Bannantine et al. 2000, Dehoux et al. 2011, Lutter et al. 2012, Moore and Ouellette 2014, Bugalhao and Mota 2019).

Inc proteins have been shown to play a role in the direct interaction of the *Chlamydia* inclusion membrane with the ER (Fig. 3). This direct interaction was first observed by electron microscopy showing smooth and rough ER vesicles in close contact with the inclusion (Peterson and de la Maza 1988). Additional studies have identified patches of the ER maintained in close proximity (10-20 nm) to the inclusion in the absence of membrane fusion (Giles and Wyrick 2008, Derré et al. 2011, Elwell et al. 2011, Dumoux et al. 2012, Dumoux et al. 2015). Due to the morphological and molecular similarities with cellular MCS, these sites of direct contact have been referred to as ER-Inclusion MCS (Derré et al. 2011, Agaisse and Derré 2015).

Studies designed to characterize the molecular composition of ER-Inclusion MCS have identified several *Chlamydia* Inc proteins and host factors enriched at these sites. The Inc protein IncD interacts with the host lipid transfer protein CERT, which in turn binds VAP on the ER (Derré et al. 2011, Agaisse and Derré 2014) (Fig. 3). Depletion of CERT or VAP resulted in a significant decrease in inclusion size and infectious progeny production (Derré et al. 2011, Elwell et al. 2011). Based on the role of CERT and VAP at ER-Golgi MCS, the IncD-CERT-VAP complex is proposed to function in the non-vesicular trafficking of host lipids to the inclusion, a process essential for intracellular growth (Derré et al. 2011, Elwell et al. 2011, Agaisse and Derré 2014).

The host ER calcium sensor STIM1, a known component of ER-PM MCS, has also been shown to localize to ER-Inclusion MCS (Agaisse and Derré 2015). While its role at ER-Inclusion MCS remains unclear, STIM1 has been proposed to play a role in extrusion of the *Chlamydia* inclusion from the host cell (Nguyen et al. 2018). Recently STIM1 has also been implicated in preventing store-operated, calcium entry-dependent NFAT (nuclear factor of activated T cells) nuclear translocation in *C. trachomatis*-infected cells (Chamberlain et al. 2022). Finally, as this manuscript was under review, Cortina *et al*. reported the inclusion membrane protein IncS as STIM1-interacting partner at ER-Inclusion MCS (Cortina and Derré 2023), although the role of the IncS-STIM1 complex remains elusive.

The *Chlamydia* Inc protein IncV is also enriched at ER-Inclusion MCS (Stanhope et al. 2017) (Fig. 3). Work by Stanhope et al. demonstrated that IncV directly interacts with VAP through the presence of two FFAT motif cores in the C-terminal cytosolic tail of IncV (Stanhope et al. 2017). One of the FFAT motif cores is similar to the canonical sequence of eukaryotic FFAT motif cores, whereas the second motif diverges from the canonical sequence and was originally termed a non-canonical FFAT (Stanhope et al. 2017). Overexpression of IncV resulted in a dramatic increase in VAP and ER recruitment to the inclusion. Mutation of the essential position two of the IncV FFAT motifs disrupted the IncV-VAP interaction, supporting the notion that the IncV-VAP interaction functions as a tether between the inclusion and the ER (Stanhope et al. 2017). The IncV-VAP interaction serves as a prime example of molecular mimicry, where a bacterial pathogen displays eukaryotic motifs on the surface of its vacuole to allow for MCS formation.

Recently, Ende *et al*. showed that multiple layers of host cell kinase-mediated phosphorylation regulate the assembly of the IncV-VAP tethering complex and ER-Inclusion MCS formation (Ende et al. 2022). Previous work by Mirrashidi *et al*. predicted that IncV interacted with multiple host kinases, including all three subunits of the host kinase CK2 (Mirrashidi et al. 2015) (Fig. 3). Mutation of predicted CK2 phosphorylation motifs in the C-terminal region of IncV indicated that CK2 is recruited to the inclusion by IncV (Ende et al. 2022). Co-immunoprecipitation and electron microscopy further revealed that the phosphorylation of IncV by CK2 was required for establishing the IncV-VAP interaction at the inclusion (Ende et al. 2022). Phosphomimetic mutations in IncV indicated that phosphorylation of IncV by CK2 occurs within one of the FFAT motif cores and serine-rich tracts immediately upstream of IncV FFAT motif cores (Ende et al. 2022). Interestingly, IncV possesses phosphorylatable serine tracts, rather than acidic tracts, upstream of the two FFAT motif cores (Ende et al. 2022). Phosphomimetic mutation of these serine tracts to aspartic acid residues resulted in IncV remaining trapped within the bacteria and failing to be properly translocated, suggesting that the serine tracts allow for the mimicry of eukaryotic FFAT motifs while ensuring T3SS-mediated translocation of IncV to the inclusion membrane (Ende et al. 2022).

Overall, ER-Inclusion MCS resemble cellular MCS. The two membranes are tethered through VAP-FFAT interactions, and the presence of the IncD-CERT-VAP complex suggests that these MCS most likely play a role in non-vesicular lipid transfer. However, ER-Inclusion MCS do notably differ from cellular MCS. For example, in naïve cells, CERT and STIM1 localize to distinct MCS, namely ER-Golgi and ER-PM MCS, respectively. However, during *Chlamydia* infection these seemingly unrelated MCS components are both redirected to ER-Inclusion MCS, highlighting the capacity of the pathogen to bypass cellular ‘rules’. Additionally, unlike most eukaryotic FFAT motifs that contain tracts of acidic residues, the IncV FFAT motifs contain tracts of phosphorylatable serine residues, presumably to accommodate IncV secretion, further highlighting how pathogens have evolved to successfully hijack cellular molecules and pathways beneficial to their intracellular replication. Including these features in current FFAT motif identification algorithms could potentially identify additional FFAT motif containing proteins. Importantly, because pathogens often mimic cellular processes, the regulatory role of host kinase CK2 at ER-Inclusion MCS may indicate a role for CK2 at cellular MCS as well.

The *Legionella*-containing vacuole-ER membrane contact sites

Legionella pneumophila is a Gram-negative, rod-shaped, non-encapsulated, and flagellated bacterium, which upon inhalation of contaminated aerosols replicates in alveolar macrophages and can cause a severe pneumonia called Legionnaires’ disease (Newton et al. 2010, Hilbi et al. 2011, Mondino et al. 2020). *L. pneumophila* is a facultative intracellular bacterium that replicates in environmental free-living protozoa, such as *Acanthamoeba*, *Hartmannella*, *Vahlkampfia* and *Tetrahymena* species, as well as in the social amoeba *D. discoideum* (Steinert and Heuner 2005, Hoffmann et al. 2014a, Boamah et al. 2017, Swart et al. 2018). In mammalian and protozoan host cells, transmissive (virulent and motile) *L.*

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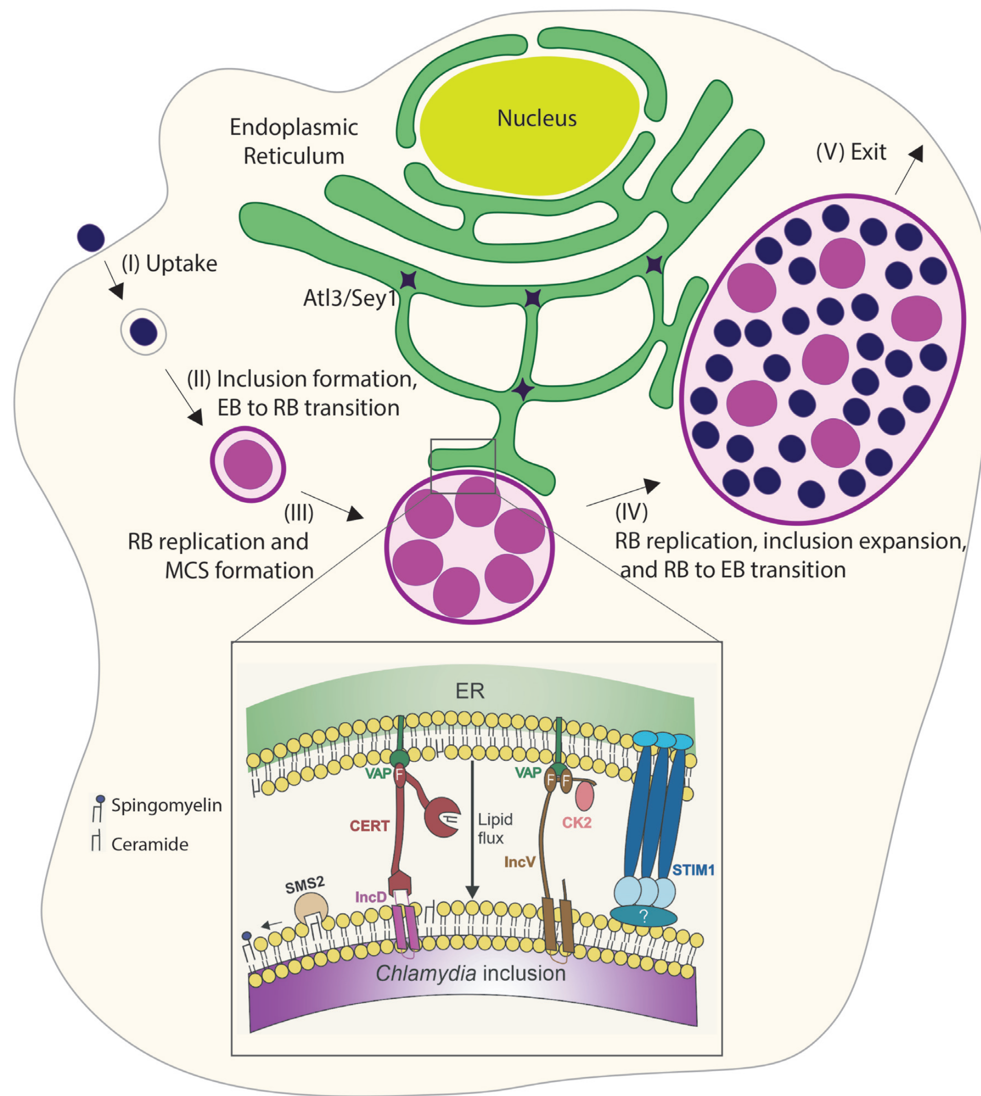

Figure 3. Formation of the *Chlamydia* ER-Inclusion MCS. Intracellular replication of *C. trachomatis* comprises the following steps: (I) uptake, (II) formation of the *Chlamydia* inclusion and transition of *Chlamydia* elementary bodies (EBs) to reticulate bodies (RBs), (III) RB replication and ER-Inclusion MCS formation, (IV) further RB replication, inclusion expansion and transition of RBs to EBs, and (V) bacterial exit through lytic or non-lytic (extrusion) pathways. The ER associates with the inclusion throughout the infection cycle. Several protein complexes localize to ER-Inclusion MCS. The T3SS-translocated *Chlamydia* Inc protein IncD recruits CERT to the inclusion membrane by binding to the PH domain of CERT. IncD bound CERT associates with the ER by binding to VAP via its FFAT motif. The IncD-CERT-VAP complex most likely functions in lipid transfer from the ER to the inclusion. The T3SS-translocated *Chlamydia* Inc protein IncV, which contains two FFAT motifs, directly associates with VAP. The IncV-VAP complex functions as a tether. The assembly of the IncV-VAP tether is positively regulated by IncV phosphorylation by the host kinase CK2. Through an unknown mechanism, the ER calcium sensor STIM1 also localizes to ER-Inclusion MCS.

pneumophila establishes a unique compartment, the *Legionella*-containing vacuole (LCV), wherein which the bacteria switch to a replicative form (Isberg et al. 2009, Hubber and Roy 2010, Hilbi and Buchrieser 2022) (Fig. 4). As replication ceases, the bacteria switch back to the virulent form, and a transmissive bacterial subpopulation escapes the LCV and lyses the host cell (Striednig et al. 2021).

LCV formation is controlled by the bacterial Icm/Dot type IVB secretion system (T4BSS) (Segal et al. 2005, Kubori and Nagai 2016). The Icm/Dot T4BSS translocates approximately 330 different 'effector' proteins into host cells, where they subvert pivotal processes, including the endocytic, secretory, retrograde and autophagy pathways, cytoskeleton dynamics, metabolism, transcription, translation, and apoptosis (Ge and Shao 2011, Hilbi and Haas 2012, Finsel and Hilbi 2015, Escoll et al. 2016, Personnic et al. 2016, Bärlocher et al. 2017, Qiu and Luo 2017, Swart et al. 2020). A decisive step during LCV maturation is the diversion from the endocytic pathway and the interception of the secretory pathway, along with a PI lipid conversion from endosomal PtdIns(3)*P* to secretory PtdIns(4)*P* (Weber et al. 2006, Weber et al. 2014, Steiner et al. 2018, Swart and Hilbi 2020) (Fig. 4).

PI lipid conversion of the LCV is catalysed by several Icm/Dot-translocated effectors: the PtdIns 3-kinase MavQ (Li et al. 2021), the PtdIns(3)*P* 4-kinase LepB (Dong et al. 2016a), and the PtdIns(3,4)P_2 3-phosphatase SidF (Hsu et al. 2012), as well as possibly by host PI-metabolizing enzymes: the PtdIns 4-kinases PI4KIIIβ (Brombacher et al. 2009) and PI4KIIIα (Hubber et al. 2014), and the PtdIns(4,5)*P* 5-phosphatase OCRL (Weber et al. 2009a, Choi et al. 2021). A number of Icm/Dot-translocated effectors also anchor to the LCV membrane by binding to distinct PI lipids (Swart

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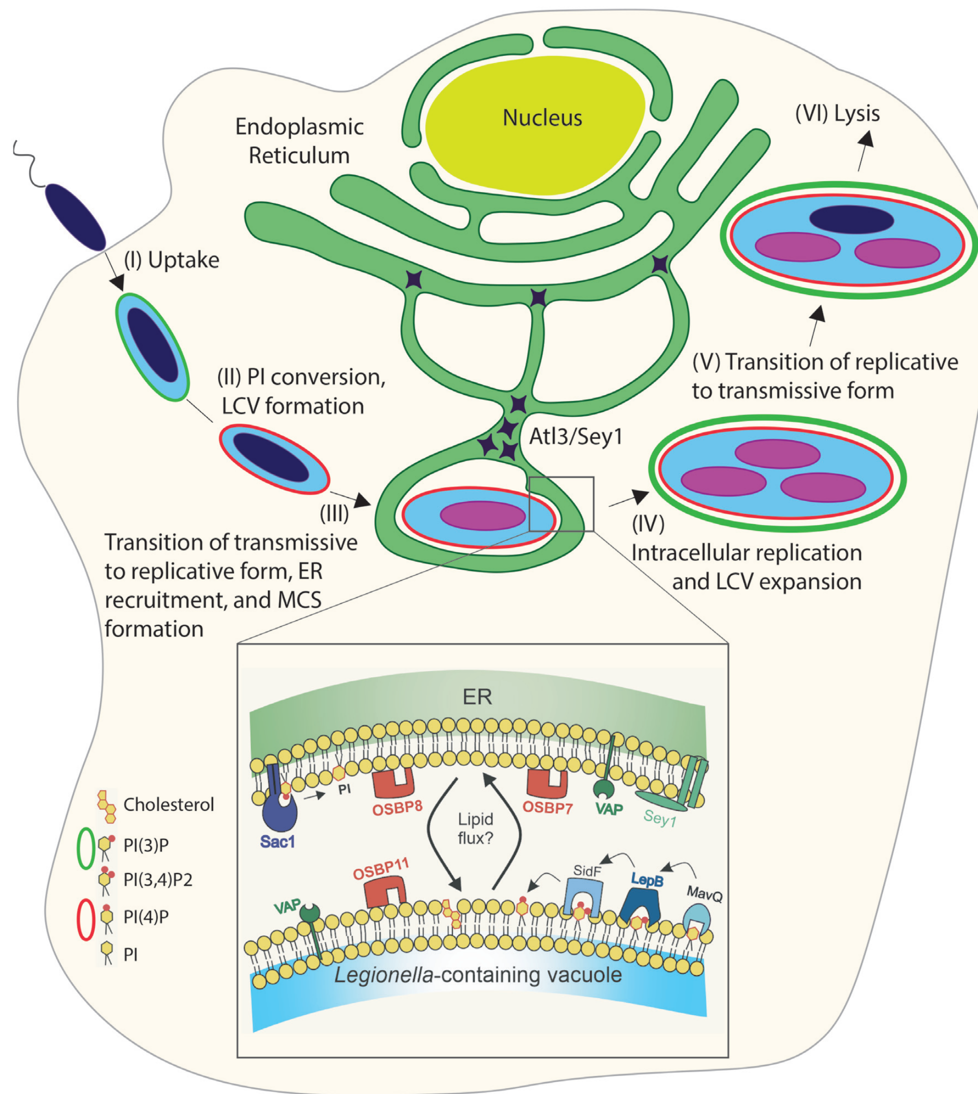

Figure 4. Formation of the *Legionella*-containing vacuole-ER MCS. Intracellular replication of *L. pneumophila* comprises the following steps: (I) uptake, (II) PI conversion and formation of the *Legionella*-containing vacuole (LCV), (III) transition of virulent/transmissive to replicative *L. pneumophila*, ER recruitment, and LCV-ER MCS formation, (IV) intracellular bacterial replication and LCV expansion, (V) transition of replicative to virulent/transmissive *L. pneumophila*, and (VI) host cell lysis and bacterial exit. At the LCV-ER MCS the VAP protein localizes to the LCV membrane as well as to the ER. OSBP7, OSBP8, the PI lipid phosphatase Sac1, and the large fusion GTPase Sey1 localize to the ER, while OSBP11 and T4BSS-translocated *L. pneumophila* effector proteins localize to the LCV.

and Hilbi 2020). Accordingly, the ubiquitin ligase SidC (Weber et al. 2006, Ragaz et al. 2008, Dolinsky et al. 2014, Luo et al. 2015), the Rab1 GEF/AMPylase SidM (Brombacher et al. 2009, Schoebel et al. 2010, Del Campo et al. 2014) and the phytate-activated protein kinase Lpg2603 (Hubber et al. 2014, Sreelatha et al. 2020) bind to PtdIns(4)*P*. On the other hand, the retromer interactor RidL (Finsel et al. 2013), the Atg8 phosphatidylethanolamine deconjugase RavC (Choy et al. 2012, Horenkamp et al. 2015), and the glycosyltransferases SetA (Jank et al. 2012) and LtpM (Levanova et al. 2019) bind to PtdIns(3)*P*.

Upon maturation, the LCV undergoes a conversion from a tight to a spacious compartment (Lu and Clarke 2005, Ragaz et al. 2008, Case et al. 2016) and intimately associates with the ER (Swanson and Isberg 1995, Abu Kwaik 1996, Solomon and Isberg 2000, Lu and Clarke 2005, Robinson and Roy 2006). The ER does not fuse with the PtdIns(4)*P*-positive LCV membrane for at least 8 h post infection (Weber et al. 2014) (Fig. 4). Intriguingly, the contact sites of the LCV with the ER are connected by periodic 'hair-like' structures (Tilney et al. 2001), and ER elements remain attached to LCVs even after immuno-affinity purification of intact pathogen vacuoles (Urwyler et al. 2009, Hoffmann et al. 2014b, Schmölders et al. 2017). Taken together, these findings suggested that the LCV forms MCS with the ER.

Using a proteomics approach and dually fluorescence-labelled *D. discoideum* amoeba, Vormittag *et al.* recently analysed the role of selected MCS proteins for LCV-ER MCS formation and vacuole remodelling (Vormittag et al. 2023). Comparative proteomics analysis of LCVs purified from a *D. discoideum* parental strain or from a strain lacking the ER-residing large fusion GTPase Sey1/atlastin (Steiner et al. 2017, Hüsler et al. 2021) indicated the presence of the MCS proteins OSBP7, OSBP8 and the PtdIns(4)*P* 4-phosphatase Sac1 (Vormittag et al. 2023). The study also revealed that at LCV-ER MCS VAP localized to both the ER and the LCV membrane, while Sac1, OSBP7, and OSBP8 preferentially localized to

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the ER, and OSBP11 preferentially localized to the LCV membrane (Fig. 4).

VAP, Sac1 and OSBP11 promoted initial LCV expansion and intracellular replication of *L. pneumophila*, whereas OSBP8 restricted these processes (Vormittag et al. 2023). Furthermore, staining with the sterol probes filipin and GFP-D4H* (Tweten 1988, Shatursky et al. 1999) revealed that sterols are depleted from the LCV within 2 h post infection in the parental *D. discoideum* strain, as well as in mutant strains lacking VAP, OSBP7, OSBP8 or OSBP11, while PtdIns(4)*P* accumulated in parallel (Vormittag et al. 2023). In addition to Sac1, the *L. pneumophila* PtdIns 4-kinase LepB and the PtdIns(4)*P*-binding effector SidC also promoted initial LCV expansion, since *L. pneumophila* mutant strains lacking these effectors were impaired for this process (Fig. 4). In summary, the study indicated that a *Legionella*- and host cell-driven PtdIns(4)*P* gradient generated at LCV-ER MCS promotes VAP-, OSBP- and Sac1-dependent LCV maturation (Vormittag et al. 2023).

Finally, *L. pneumophila* effectors not only localize to LCV-ER MCS but also target mitochondria-ER contact sites (Murata et al. 2022). Mitochondria-ER-associated membranes (MAMs) are implicated in various cellular functions, including lipid synthesis and trafficking, mitochondrial morphology, inflammasome activation, autophagosome formation, and apoptosis (Escoll et al. 2017). The *L. pneumophila* effector Lpg1137 binds the MAM- and mitochondria-enriched phospholipid phosphatidic acid and proteolytically degrades the MAM-localizing SNARE syntaxin 17 (Murata et al. 2022).

Membrane contact sites of the *Coxiella*-containing vacuole

Coxiella burnetii is a Gram-negative, coccobacillary, obligate intracellular bacterium and the causative agent of Q fever (Delsing et al. 2011). After uptake, *C. burnetii* resides within a replication-permissive compartment, the *Coxiella*-containing vacuole (CCV) (Heinzen et al. 1999, Voth and Heinzen 2007). The nascent CCV fuses with early and late endosomes, lysosomes and autophagosomes and adopts an acidic pH of ~4.5, which activates the Icm/Dot T4BSS (Voth and Heinzen 2007, Newton et al. 2013) and the translocation of over 130 effector proteins into the host cytoplasm (Segal et al. 2005, Beare et al. 2011, Qiu and Luo 2017).

ORP1L is recruited to the CCV in a T4BSS-dependent manner prior to pathogen vacuole expansion (Justis et al. 2017). The association of ORP1L with the CCV occurs through its N-terminal ARD domain, which interacts with active Rab7 localized at the CCV (Beron et al. 2002, Johansson et al. 2005, Justis et al. 2017). Because ORP1L contains a FFAT motif and binds to VAP on the ER, it is possible that ORP1L is part of a protein complex that mediates lipid transfer and/or tethering of the CCV to the ER, leading to the formation of CCV-ER MCS.

The role of ORP1L in lipid transfer to the CCV is supported by the fact that the CCV is rich in sterols, as determined by filipin staining, and by the reduction of CCV size upon depletion of ORP1L, although bacterial growth was not affected (Justis et al. 2017). The reduction of *C. burnetii* growth observed upon knockdown of the cholesterol transporter NPC-1 or pharmacological depletion of cholesterol, does however support the importance of sterols for bacterial growth (Howe and Heinzen 2006, Czyz et al. 2014).

It is not known if *Coxiella* effectors plays a role in ORP1L recruitment to the CCV or in CCV-ER MCS biology at wide. Of the many *Coxiella* effectors only a few have been characterized (Qiu and Luo 2017). Of interest, the Icm/Dot substrate ElpA (ER-localizing protein A) is present in most *C. burnetii* strains and disrupts ER structure and function during infection (Graham et al. 2015). Additionally, the *C. burnetii* effector *Coxiella* vacuolar protein B (CvpB) binds PtdIns(3)*P* and PS on CCVs and early endosomal compartments (Martinez et al. 2016). CvpB also inhibits the activity of the PtdIns 5-kinase PIKfyve to manipulate PtdIns(3)*P* metabolism and to promote CCV expansion. Based on the preliminary characterization of ElpA and CvpB, it will be interesting to investigate their potential role in CCV-ER interactions.

Modulation of the *Salmonella*-containing vacuole by OSBP and VAP

Salmonella enterica serovar Typhimurium (S. Typhimurium) is a Gram-negative, facultative intracellular bacterial pathogen and the cause of gastroenteritis and diarrhea (Hohmann 2001). During infection, S. Typhimurium forms a replication-permissive compartment, the *Salmonella*-containing vacuole (SCV) in phagocytic and epithelial cells (Knodler and Steele-Mortimer 2003, Bakowski et al. 2008, LaRock et al. 2015). SCV formation is controlled by two type III secretion systems (T3SSs), located on *Salmonella* pathogenicity island (SPI)1 and SPI2 (Jennings et al. 2017, Galan and Waksman 2018). SPI1 is required for the initial invasion, and SPI2 is produced after internalization. SPI2 translocates approximately 30 different effector proteins into the host cytoplasm (LaRock et al. 2015, Jennings et al. 2017).

Bacterial growth in the SCV is promoted by effectors translocated by the SPI2 T3SS. These effectors prevent fusion with bactericidal lysosomes, direct the SCV to close proximity with the Golgi apparatus and trigger the formation of membrane tubules (*Salmonella*-induced filaments, Sifs), a process, which requires the effectors SseF and SseG (Kuhle et al. 2004, Deiwick et al. 2006). SseF and SseG as well as SifA have been shown to intercept secretory trafficking from the Golgi to the PM (Kuhle et al. 2006, Bakowski et al. 2008). SifA, SseJ and to a lesser extend SseL are also necessary for cholesterol accumulation at the SCV (McEwan et al. 2015, Walch et al. 2021). SseJ esterifies cholesterol due to its deacylase activity and increases the formation of LDs (Ohlson et al. 2005, Nawabi et al. 2008). This enzymatic activity and the localization of SseJ to the SCV requires binding to active RhoA GTPase (LaRock et al. 2012).

OSBP localizes to the SCV in a process mediated by SseJ and SseL (Auweter et al. 2012, Kolodziejek et al. 2019). SseJ binds OSBP at the coiled-coil domain independent of RhoA (Kolodziejek et al. 2019), and SseL binds OSBP at the coiled-coil domain as well as at the FFAT motif (Rytkonen et al. 2007, Auweter et al. 2012). OSBP has been shown to support intracellular replication of S. Typhimurium (Auweter et al. 2012). Additionally, infection of OSBP-depleted, or VAPA/B double knockout cells resulted in increased cytoplasmic S. Typhimurium, suggesting a stabilization role of OSBP and VAPA/B for the SCV (Kolodziejek et al. 2019). While these findings suggest the formation of SCV-ER MCS, they could also reflect indirect effects via ER-Golgi MCS disruption, calling for future studies to further characterize SCV-ER interactions.

Conclusions

MCS are characterized by discrete stretches of membrane contact between two apposing organelles to facilitate the non-vesicular trafficking of small molecules such as calcium and lipids. The extensive characterization of a multitude of MCS in mammalian cells and yeast that occurred over the past decade, resulted in a comprehensive, yet constantly evolving, structural, molecular, and functional landscape of the MCS. Lipid transfer at MCS is a

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complex and highly regulated process. By anchoring to each of the contacting organelles, via binding to receptors (e.g. VAP) on one organelle, and specific PI lipids on the other, specific lipid transfer proteins (e.g. OSBP, ORPs, CERT) mediate the transfer of lipids (e.g. sterols, PtdIns(4)*P*, PE, ceramide, etc) from one organelle to another. Phosphoinositide phosphatases such as Sac1 further modify the lipid composition of the donor or recipient membrane. The short range (10-30 nm) lipid exchange that establishes along a gradient is key to membrane remodelling and organelle maturation to adopt specific functions.

Intravacuolar bacterial pathogens such as *Chlamydia*, *Legionella*, *Coxiella*, and *Salmonella*, have evolved to mimic and/or hijack these non-vesicular trafficking processes to establish their distinct replication-permissive compartments. The mechanisms reported so far include the formation of MCS between the pathogen vacuole and the ER, the recruitment of specific cellular MCS components to pathogen vacuoles aided by the translocation of bacterial effector proteins, and/or the establishment of a lipid gradient between the pathogen vacuole and the ER.

Future studies will continue to investigate the complex composition and architecture of MCS in naïve or infected cells, using proteomics approaches as well as high-resolution fluorescence microscopy and cryo-EM technology. To assess functional aspects of MCS, bacterial effectors targeting MCS components might serve as versatile tools. Hence, in addition to generating cell biological insights into MCS components, architecture and function, the sophisticated ways bacterial pathogens subvert MCS will also be elucidated.

Acknowledgements

Work in the group of HH was supported by the Swiss National Science Foundation (SNF; 31003A_175557, 310030_207826). Work in the group of ID was supported by the National Institute of Health (NIH; AI166237 and AI162758).

Conflict of interest. The authors declare no conflicts of interest.

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