Membrane Contact Sites in Autophagy

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Membrane contact sites (MCSs) are formed by stable association between regions of the limiting membrane of two or more organelles, which are physically tethered together and exert specific functions. MCSs are very dynamic; they can rapidly assemble and disassemble, according to their function, and the gap between the adjacent membranes is highly variable. The term autophagy entails all those transport pathways that deliver intracellular components to vacuoles/lysosomes for turnover. Three main autophagic processes have been described: (1) macroautophagy, which is characterized by the sequestration of the cargoes by double-membrane autophagosomes that fuse with vacuoles or lysosomes; (2) microautophagy, which involves the direct engulfment of the cargo by the endosomes or vacuoles/lysosomes; and (3) chaperone-mediated autophagy (CMA), in which single polypeptides with a specific recognition sequence are recognized by HSP70 and translocated into the mammalian lysosomes via a channel formed by LAMP2A.

phagophore autophagosome endoplasmic reticulum mitochondria MAMs vacuole plasma membrane nucleus-vacuole junctions

1. ER-Phagophore Membrane Contact Sites (MCSs)

The ER plays a key role in the lipid biosynthesis as it serves as a central cellular hub for intracellular communication, organelle trafficking and macromolecule synthesis. Therefore, it forms MCSs with all intracellular organelles, including the phagophore whose extremities are tethered with the ER in both yeast and mammalian cells [1][2][3][4][5][6][7][8]. In mammals, it appears that the phagophores also have some MCSs with the ER distributed elsewhere on their surface [9][10]. While these latter MCSs remain to be characterized, work in yeast has identified some of the components and the mechanism establishing the MCSs between the extremities of the phagophore and the ER. This association seems to be less strong than the one with other contacts (e.g., the nucleus) since the level of visible deformation on both organelles is much lower [1]. The fact that the phagophore is very frequently tethered via part of its rim to the ER or the nucleus is consistent with ongoing lipid transfer at these MCSs [1][11]. In those contacts, Atg9-Atg2-Atg18 complex is positioned at the phagophore tips, while ER exit sites (ERES) are present on the ER side [2][3]. ER-phagophore MCSs are probably tethered by Atg2-Atg18 and ATG2A-WIPI4 [12][13]. Structural studies suggest in vitro that ATG2A, which has a rod-like structure shared by all ATG2 proteins [13], tethers a liposome by binding with one of its edges the membranes containing PtdIns3P and WIPI4, the mammalian Atg18 counterpart [14][15][16], and with the other opposite membrane [17][18][19].

In vivo, Atg2 is recruited to the phagophore via coincidence binding to PtdIns3P and Atg9, which concentrates on high curvature membrane regions such as the extremities of the phagophore [7]. Atg2 binding (via its C-terminal region) to Atg9 induces the subsequent recruitment of Atg18, which bind to both Atg2 and PtdIns3P [7][20][21]. The N-terminal domain of Atg2, in contrast, appears to be responsible for its interaction with the ER [12], but it remains enigmatic which ERES components bind to ATG2 proteins. In addition to acting as a tether, in vitro experiments have revealed that ATG2 proteins act as functional proteins as they are able to transfer lipids at the phagophore-ER MCSs [13][19][22]. Together with the VPS13 proteins, which associate with several MCSs [23][24], ATG2 proteins belong to the chorein_N family of lipid transporters. The rod-like structure of ATG2 proteins possess a N-terminally chorein_N motif that allows the binding and extraction of multiple glycerolipids from the donor membrane in vitro [13][19][25]. The subsequent phospholipid transfer occurs through a hydrophobic cavity that spans their entire length and can accommodate several glycerolipids [19][25]. Atg18 and WIPI4 binding accelerate the lipid transfer by ATG2 proteins, indicating that those proteins may act as MCSs regulators [18][22]. The lipid transfer by ATG2 proteins could lead to an amassment of phospholipids on the external lipid layer of the phagophore membrane, disrupting its expansion into an autophagosome. This potential problem, however, is very likely avoided by Atg9/ATG9A proteins, which, beside their role in phagophore nucleation, also have intrinsic lipid scramblase activity shown in in vitro experiments [26][27] and directly interact with at least two regions of ATG2 proteins [7][20][21]. Consistent with this notion, Atg9/ATG9A lipid scramblase mutants show a defect in phagophore expansion [26][27], and recent in vitro experiments have revealed that Atg9 stimulates the Atg2-Atg18 complex-mediated lipid transfer to the acceptor membrane [28]. Moreover, evidence suggests that ATG9-ATG13-ATG101 is central to the formation of a super-complex with the ULK kinase and PI3K complexes, which enhances the action of the ATG2-WIPI4 complex as a tether and lipid transfer protein at the phagophore-ER MCSs [29].

Extraction of lipids from the external leaflet of the ER could also create an unbalanced lipid distribution in the limiting membrane of this organelle, which would need to be dissipated to guarantee an uninterrupted flux of lipids. Interestingly, two redundant ER-localized mammalian lipid scramblases, i.e., VMP1 and TMEM41B, are essential for autophagy [11][30][31][32]. In line with this idea, it has been observed that Atg9, here acting as regulatory protein, also enhances Atg2 lipid transfer when localized at the donor membrane [28].

The VMP1 scramblase—which localizes to specific mitochondria-ER MCSs, ER-lipid droplets and ER-endosome MCSs—plays an important role in mammalian autophagy because when depleted, it leads to an autophagic flux block and concomitant high levels of PtdIns3P (see also below) [33][34]. VMP1 activity appears to be a MCS regulator that ensures the appropriate size of the MAMs, since its depletion results in abnormal MAM phenotypes [31]. VMP1 also directly modulates ER-phagophore MCSs, preventing SERCA-pump inactivation by blocking binding of phospholamban (PLN)/sarcolipin (SLN), two micropeptide proteins, to SERCA [35]. Dysregulated SERCA activity disrupts calcium homeostasis and leads to an induction of autophagy [36][37]. VMP1 depletion, on the other hand, results in the failure of the phagophore to mature, which is accompanied by an increased interaction at omegasomes between the VAPs, acting here as regulatory proteins, with the autophagy proteins FIP200, a subunit of the ULK kinase complex, and WIPI2, a component of the ubiquitin-like conjugation systems [35][38]. VAPs are involved in the establishment of several MCSs between the ER and other organelles, including the phagophore [4][39]. Consequently, depletion of VAPs also results in impaired autophagy because, together with WIPI2, they tether

phagophores with the ER [38]. Interestingly, mutations in VAPB are associated with amyloid lateral sclerosis, and one of them, $VAPB^{P56S}$, leads to a reduced autophagic flux [38]. However, it cannot currently be excluded whether the autophagy defect of the $VAPB^{P56S}$-expressing cells is indirectly due to a defect in the correct localization of the endolysosomal degradative enzymes caused by an alteration of the ER-Golgi MCSs [40]. VAP proteins participate together with the ER integral membrane proteins ATLASTIN 2 (ATL2) and 3 (ATL3) in recruiting the ULK kinase complex onto the ER by interacting with ULK1 and ATG13, and this event enhance MCSs formation [41].

2. ER-Mitochondria MCSs and Mitochondria-Associated ER Membranes (MAMs)

ER-mitochondria MCSs and MAMs are ubiquitous, with about 5 to 20% of the mitochondrial network linked to the ER, and even more under specific stress conditions, such as nutrient starvation or tunicamycin treatment [42][43][44]. Mitochondria have a long-standing history as potential suppliers for autophagosomal membranes [9][10][45][46][47]. Initially, it was proposed that mitochondria are the main membrane source for the lipids composing autophagosomes [46]. However, later it was shown that not mitochondria, but rather MAMs are involved in autophagosome biogenesis by promoting the recruitment of ATG14 to the ULK kinase complex already present at the phagophore nucleation sites [48]. ATG14 recruitment to the MAMs depends on the SNARE protein STX17, and it enhances the assembly of the autophagy-specific PI3K complex as well as its lipid kinase activity [48]. In line with this, depletion of STX17 through bacterial proteases results in decreased autophagy [49]. However, STX17 is also required for fusion between autophagosomes and lysosomes [50][51][52]. Consequently, the autophagy flux block observed upon inactivation of STX17 is probably due to an impairment of at least two autophagy steps. Furthermore, ER-mitochondria MCSs and MAMs may contribute to autophagosome biogenesis through their function in lipid metabolism and synthesis [53][54][55][56].

MAMs can be formed by several tether pairs, which are characterized by specific predominant functions. The MAMs composed by the tether pair VAPB (in the ER) and PTPiP51 (in mitochondria) influence autophagy initiation through calcium signalling [57]. Dissolving these MCSs by ablating VAPB or PTPiP51 leads to an enhancement in autophagosome formation. These MAMs are relevant for calcium transfer from ER to mitochondria [39], and impairment of this function appears to lower mTORC1-mediated autophagy inhibition. The full connection between calcium signalling and autophagy needs further elucidation, although it has recently been shown that SERCA interacts with STX17, which is required for early and late autophagy steps [58].

The ER transmembrane proteins EI24 and IP3R, together with GRP75 and outer mitochondrial membrane protein VDAC1, form another set of MAMs [59]. Depletion of EI24 causes an impairment of autophagosome biogenesis and autophagic flux [60][61], suggesting that those MCSs also play a key role in autophagy.

Moreover, inhibition of oxidative phosphorylation (OXPHOS) or nutrient starvation results in enhanced MAMs formation with MFN2 as a tether [62]. Increased MAM formation is regulated by AMPK, which phosphorylates MFN2 upon the decrease of cellular energy levels. How this affects the cell remains unclear, since together with MFN1, MFN2 is a mitochondrial fusion factor [63]. MFN2 appears to have an impact on glycolysis and OXPHOS because

energetic stress in MFN2 knockout cells leads to a reduced glycolysis and OXPHOS capacity. Interestingly, MFN2 forms a complex with ERLIN1, AMBRA1 and GD3 in MAMs-specific lipid microdomains [44]. These microdomains participate in the initial steps of autophagy in several ways [44][64][65]. ERLIN1, but also ERLIN2, specifically accumulate in MAMs-associated ER lipid microdomains during lowering of the cellular energy [44][66]. ERLIN1 interacts with AMBRA1 [64], which is a well-known regulator of autophagy that is phosphorylated by ULK1 during starvation and promotes autophagy by connecting the autophagy-specific PI3K complex to dynein for its transport to omegasomes [67][68]. The ganglioside GD3 is a component of the MAM's lipid raft that interacts with PtdIns3P and is also present at sites of autophagosome formation [65]. Depletion of GD3-synthetase results in an impaired autophagic flux.

In yeast, MAMs have been implicated in basal mitophagy, but not in bulk autophagy [69]. In particular, it appears that the phagophore forms at the ER-mitochondria MCSs called ER mitochondria encounter structure (ERMES) and composed by Mmm1 and Mdm12 at the ER membrane and Mdm10 and Mdm34 at the mitochondrial membrane [69]. In mammals, MAMs that contain BECN1 and PTEN-induced kinase 1 (PINK1) are also required for ER-mitochondria MCS formation, both promoting membrane tethering and mitophagosome biogenesis, although it remains to be determined whether they represent the counterpart of the yeast ERMES [70]. The PINK1 kinase, together with E3 ubiquitin ligase PARKIN, modulates certain types of mitophagy, especially those induced by mitochondrial depolarization [71]. During the early steps of mitophagy, ER-mitochondria MCSs must be dissolved [72][73] and this seems to require the phospho-ubiquitination of their tether MFN2 by PINK1 and PARKIN, which triggers p97-mediated MFN2 degradation by the proteasome [73][74][75]. This finding is in contrast with the above-mentioned one in which the conclusion was that mitophagy induction increases MAM formation in a PINK1-dependent way. The reason for this apparent discrepancy between studies is unknown.

In conclusion, it appears that multiple different types of ER-mitochondria MCSs are important for the normal progression of autophagy. Their functional interconnection, however, remains a question to be addressed. Nonetheless, at the cytosol-ER interface, a very recent study seems to functionally connect EI24, FIP200 and calcium signalling [60], and, thus, also some of the MAMs/ER-mitochondria MCSs and phagophore-ER MCSs that have been described.

3. ER-PM MCSs

The ER also forms MCSs with the PM, which are involved in lipid trafficking and calcium homeostasis, but autophagy regulation, as well [76][77]. ER-PM MCSs may contribute to one or more steps necessary for the generation of the phagophores [78]. In particular, the mammalian ER-PM MCSs composed by the tethers ESYT1 at the ER, and ESYT2 and ESYT3 at the PM, appear to have a central role in modulating autophagosome biogenesis; consequently, autophagy inducers enhance the expression of ESYT2, as well [78]. ESYT proteins are required for autophagosome formation at the ER-PM MCSs by locally promoting the interaction between VMP1 and BECN1, which leads to an enhancement of the PI3K complex activity [78]. While VMP1 and ESYT2 form a stable complex, the well-known interaction between VMP1 and BECN1 appears to be induced by stress conditions

[78][79][80]. Since ESYTs colocalize with LC3 and other autophagy marker proteins, this evidence points to the ESYT protein-containing MCSs being a platform to enable PtdIns3P synthesis [78].

4. Phagophore-Vacuole MCSs

The interaction of the yeast Atg machinery with the vacuole is not only important for the fusion of the mature autophagosomes with vacuoles, but also for the early steps of autophagy. The PAS is formed adjacently to the vacuole [81][82], and its formation involves the initial recruitment of the Atg1 kinase complex via binding to the vacuolar surface protein Vac8 via Atg13 [83][84][85][86][87]. The subsequent local generation of the phagophore probably leads to the establishment of the so-called vacuole-isolation membrane contact sites (VICS). This single MCS is present over the course of the entire phagophore elongation [2][3]. Electron tomographic analyses have revealed that the phagophore is associated with the vacuole with the side or the back, such that the elongation occurs toward the vacuolar membrane [1]. The distance and area of contact between the vacuole and the phagophore is very variable, indicating that this MCS is not specifically structured through for instance spacers [1]. In the absence of Vac8, the PAS is no longer associated with the vacuole, and autophagosome biogenesis only takes place proximal to the ER [84]. The resulting autophagosomes are smaller and formed at lower frequency, leading to an overall reduced autophagic flux [83][84][87][88]. Vac8 is also important for the progression of different types of selective autophagy, including the cytoplasm to vacuole targeting (Cvt) pathway, mitophagy, pexophagy and ribophagy [86][89][90]. In the context of selective types of autophagy, it has been postulated that Vac8 organises the PAS by binding to Atg11, which allows both the recruitment of the cargo near the vacuole and Atg1 kinase complex activation, thereby promoting the sequestration of the targeted cargo into the nascent autophagosome [91]. Vac8 also interacts with its armadillo repeat (ARM) domains within the Vps15-Vps34 subcomplex that is part of the autophagy-specific PI3K complex [89][91]. This interaction is important for recruiting the autophagy-specific PI3K complex to the PAS for the synthesis of PtdIns3P and the mobilization of downstream PtsIns3P-binding Atg factors [89][91]. It still remains to be determined when exactly the VICSs are formed, i.e., with the vesicles initially at the PAS or with the phagophore nucleated at this location. Nonetheless, VICS are also characterized by the presence of Atg21 and the absence of the vacuolar membrane protein Vph1 [87]. Atg21 is recruited to the phagophore via binding to PtdIns3P and is required to guide Atg8 lipidation [14][15][16][87]. The mechanism leading to the preferential concentration of Atg21 at the VICS is unknown. ARMC3, a mammalian ortholog of Vac8 with spatiotemporal expression in testis tissues, is implicated in ribophagy during spermatogenesis, but its involvement in MCSs remains to be elucidated [89][90].

5. Nucleus-Vacuole Junction MCSs

Nucleus-vacuole junctions (NVJs) are an extended MCSs between the yeast vacuole and its nucleus [92]. They play a central role in nucleophagy, the selective degradation of nuclear material, which includes RNA, nuclear envelope and lamina and/or parts of the spindle apparatus by autophagy [93]. Two mechanisms of nucleophagy have been described in yeast; selective microautophagy, or piecemeal nucleophagy (PMN), and macroautophagy [94]. Both mechanisms result in the destruction of non-required nuclear parts [95][96]. NVJs are required for PMN, and their

inward invagination into the vacuole followed by pinching off leads to the degradation of small parts of the nucleus, i.e., micronuclei [95]. The NVJ tethers are the nuclear membrane protein Nvj1 and vacuolar Vac8 [97][98][99]. Nvj1 is also degraded during PMN [94]. Although NVJs are constitutively formed, NVJ1 is equipped with a promoter with two stress response elements (STRE), and upon stress-inducing conditions, such as nutrient deprivation or hypoxia, the elevated amounts of Nvj1 correlates with an enhanced number of NVJs [95][96][97]. The binding domain between Vac8 and Nvj1 seems to be similar to the one mediating the Vac8-Atg13 association [100]; how the two interactions are reciprocally regulated remains to be determined.

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