Membrane contact sites (MCSs) allow the exchange of molecules and information between organelles, even when their membranes cannot fuse directly. In recent years, a number of functions have been attributed to these contacts, highlighting their critical role in cell homeostasis. Although inter-organellar connections typically involve the endoplasmic reticulum (ER), we recently reported the presence of a novel MCSs between melanosomes and mitochondria. Melanosome–mitochondrion contacts appear mediated by fibrillar bridges resembling the protein tethers linking mitochondria and the ER, both for their ultrastructural features and the involvement of Mitofusin 2. The frequency of these connections correlates spatially and timely with melanosome biogenesis, suggesting a functional link between the 2 processes and in general that organelle biogenesis in the secretory pathway requires interorganellar crosstalks at multiple steps. Here, we summarize the different functions attributed to MCSs, and discuss their possible relevance for the newly identified melanosome–mitochondrion liaison.

Eukaryotic cells contain numerous membrane-bound organelles, necessary to accomplish and segregate specialized functions. However, this partitioning also raises the problem of how subcellular organelles communicate. One way is by vesicular traffic, typically working within the secretory/endocytic pathway. This kind of transport requires that the membranes of interacting organelles can fuse with each other, either directly or by means of intermediate compartments. For instance, the endoplasmic reticulum (ER) and the plasma membrane (PM) cannot fuse directly, but they are functionally connected through multiple membrane traffic steps, a time-consuming process. Alternatively, organelles may rapidly connect one to another by means of membrane contact sites (MCSs), where their membranes become closely juxtaposed (10–30 nm). In this way, even organelles belonging to “independent” compartments, such as the ER and mitochondria, can exchange or share molecules, functions, and information. In recent years, MCSs have been shown to be required for a variety of functions on many organelles, emerging as a widespread mechanism operating in cell physiology and pathology.

The ER represents the largest membrane-bound compartment, and plays critical roles in protein and lipid synthesis and in the regulation of calcium signaling. Therefore, it is not surprising that this organelle, besides being functionally connected to the secretory/endocytic pathway via vesicular transport, is also able to directly interact by means of MCSs with virtually all other subcellular organelles, including Golgi apparatus, endosomes, lysosomes, plasma membrane, lipid droplets, mitochondria, and peroxisomes (Fig. 1). Although the main functions attributed to the interorganellar interactions regard the transfer and metabolism of lipids and the modulation of calcium fluxes and homeostasis, more recent evidence points to several additional roles, including sharing of enzymatic activities or control of organelle dynamics (Fig. 1).

We now identified a novel ER-independent interorganellar connection, involving mitochondria and melanosomes, lysosome-related organelles (LROs) of pigment cells devoted to the synthesis, transport, and transfer of melanin pigments. Indeed, quantitative ultrastructural analysis and tomographic reconstruction showed that a significant fraction of melanosomes is located in direct contact with mitochondria, that these interorganellar connections are mediated by fibrillar bridges, and that they are labeled by and require Mitofusin (Mfn) 2, similarly to the ER-mitochondria juxtaposition. Moreover, melanosome–mitochondrion contacts were associated to the melanogenesis process, since they were more abundant where and when active melanosome biogenesis takes place, while they were reduced in conditions of abnormal melanosome biogenesis. These findings reveal the presence of a physical and functional connection between mitochondria and the secretory/endocytic pathway that for the first time does not involve the ER and is implicated in physiological and pathological organelle biogenesis.
Nevertheless, the molecular players and physiological function of melanosome-mitochondrion connections remain to be uncovered, and can be hypothesized based on the role of other better-characterized MCSs.

**MCSs regulate calcium fluxes and signaling**

Calcium concentrations in the millimolar range are found in the extracellular space and in the lumen of the ER, the Golgi apparatus, and acidic organelles, whereas the cytosolic concentration of the ion is kept low (typically 100 nM).6 MCSs, in particular between the ER and PM, or the ER and mitochondria, have been implicated in the regulation of direct calcium transfer between organelles. This mechanism has the advantage of maximizing the efficiency of calcium signaling and interorganellar exchange, while avoiding excessive or prolonged changes in the overall concentration of cytosolic calcium, which in turn could be detrimental for the cell.7,7

In all cells, a store-operated calcium entry pathway (SOCE) functions at ER-PM MCSs to efficiently refill ER stores upon calcium release, typically caused by opening of inositol-1,4,5-triphosphate receptors (Ins(1,4,5)P3Rs). The transmembrane ER proteins STIM sense the depletion of calcium in the ER and oligomerize, translocating to ER-PM contact sites and activating the CRAC/Orai1 Ca2+ channels on the PM.8,10 In this manner, calcium depletion in the ER recalls the ion available in the extracellular space, which enters the cytosol and can reload the ER stores via the Sarcoplasmic/Endoplasmic Reticulum Ca2+ ATPases. In muscle cells an additional ER-PM MCSs is found that comprises voltage-gated calcium channels on the PM, functionally connected with Ryanodine Receptors (RyRs) on the ER, so that opening of the former also results in activation of the latter to maximize cytosolic calcium influx during excitation-contraction coupling.7,11

On the other hand, MCSs between the ER and mitochondria, also known as mitochondria-associated-membranes (MAMs)12 are mainly implicated in spatially restricting and buffering the calcium fluxes triggered by opening of Ins(1,4,5)P3Rs or RyRs on the ER membrane. Indeed, close juxtaposition between the 2 compartments generates cytosolic microdomains, where high calcium concentrations are achieved.13-15 and is required for the ability of mitochondria to efficiently uptake the calcium released from the ER by the low affinity mitochondrial calcium uniporter (MCU).16,17 The correct functioning of this system and the interorganelar distance are crucial for mitochondrial calcium homeostasis and appear necessary both to regulate ATP production, which depends on several Ca2+ dependent metabolic enzymes in the mitochondrial matrix, and to avoid Ca2+ overload in the mitochondria, which instead promotes apoptosis.18,19

A role in the modulation of calcium fluxes and/or signaling has also been postulated for MCSs between ER and late endosomes/lysosomes (LE/LYS). Indeed, both lysosomes and LROs are acidic calcium stores and lysosomes have been shown to release calcium upon different stimuli, by means of Ca2+ permeable channels, including 2 pore channels (TPC), transient receptor potential mucolipin (TRPML) channels, and Ins(1,4,5)P3Rs/RyRs.6,20-22 This in turn can evoke and/or amplify ER-dependent Ca2+ release, with implications for calcium oscillations in different systems.23,24 Moreover, defective lysosomal calcium homeostasis has been associated to endocytic and lysosomal dysfunction, abnormalities in membrane traffic, and lysosomal storage diseases.25,26 Among LROs, melanosomes contain high calcium concentrations and are thought to participate in calcium homeostasis and/or signaling, since melanin is able to bind and buffer the ion, likely functioning as an intracellular calcium reservoir.27-29 The melanosome-mitochondrion juxtaposition could be involved in buffering and/or sensing of calcium possibly released by melanosomes during maturation, controlling the local concentration of the ion and evoking further signals between the 2 organelles, required for proper melanosome biogenesis.

**MCSs mediate lipid transfer and metabolism**

The synthesis of membrane lipids takes place primarily in the ER; however, specific biosynthetic reactions are performed on other organelles, such as the Golgi apparatus and the mitochondria.30,31 Thus, either vesicular or non-vesicular transport is necessary to appropriately distribute lipids to the different subcellular compartments. MCSs play an important role in the regulation of lipid homeostasis by their ability to mediate non-vesicular lipid transfer among distinct compartments through the action of lipid-transport proteins (LTPs).1-2 A number of LTPs and their modes of action have been identified, including oxysterol-binding protein (OSBP) and OSBP-related proteins (ORP),32 operating at the ER-Golgi and ER-PM interface, and implicated in the exchange and metabolism of sterols and phosphoinositides;11,30,33 the ceramide-transfer protein CERT34,35 and the glucosylceramide-transfer protein FAPP2,36,37 operating non-vesicular transport at the ER-Golgi and intra-Golgi (cis-trans) contact sites, respectively; the extended synaptotagmins (known as tricalbins in yeast), functioning as ER–PM tether and most likely implicated in (glycerophospho) lipid transfer;38,39 and possibly in yeast the ER-mitochondrion encounter structure (ERMES) complex, an ER–mitochondrial tether, comprising several subunits containing lipid-binding domains.2,40

Sterol-binding proteins have been identified on LE/LYS as well, however at this location they appear to function mostly as lipid sensors and scaffold proteins, rather than lipid transfer effectors (see below). Nevertheless, melanosome-mitochondrion contacts may serve to control the quality and quantity of lipids on maturing melanosomes, regulating physical properties and abundance of their membranes, and the formation of specialized domains necessary for membrane traffic processes, such as the intralumenal sorting and processing of the structural protein Pmel17.41,42 Along the same line, mitochondria have been reported to supply membranes to forming autophagosomes,43 which could originate from the ER at MAMs.44 Melanosome biogenesis might share molecular mechanisms with autophagy, since genes involved in the autophagic process were identified in a screen for novel pathways involved in melanosogenesis.45 Thus, by means of MCSs, mitochondria could provide melanosomes with membranes or other components required for the shape and size changes occurring during their maturation. Interestingly, the small GTPase Rab32, which localizes to both the ER and mitochondria, and regulates the properties of MAMs,46,47 is also involved in the formation of autophagosomes,48 and in
melanosomal biogenesis and transport,49,50 thus representing a potential candidate regulator of this crosstalk.

MCSs promote protein-protein interactions and cell signaling

It is becoming evident that at least some MCSs function as signaling hubs, by facilitating the scaffolding of signaling protein complexes and allowing the carry out of catalytic reactions, either in cis or in trans, with enzyme and substrate located on the same or on juxtaposed organelles, respectively. For instance, some ORPs have been shown to act as protein scaffolds, coordinating lipid sensing and metabolism with cell signaling and membrane traffic events,51 and the protein kinase mTORC2 and the lipid/protein phosphatase PTEN localize to the ER and operate in cis at MAMs.52,53 Moreover, internalized EGFR on endosomes, and in particular on the limiting membrane of multivesicular bodies (MVB), becomes dephosphorylated in trans, by means of the protein tyrosine phosphatase 1B (PTP1B) located on ER membranes at MCSs between the 2 compartments.54 Close juxtaposition between the ER and MVBs allows enzyme and substrate to interact and might also be implicated in the subsequent fate of the receptor, such as sequestration in intra-luminal vesicles (ILV) and lysosomal degradation.34,55 Likewise, the ER-PM juxtaposition may allow the regulation of phosphoryl inositol 4-phosphate (PI4P) levels at the cell surface, by means of the ER-localized PIP phosphatase Sac1, although recent evidence supports an alternative mechanism.11,33,56

Similarly, the melanosome-mitochondrion interaction might play a role in the assembly and modulation of signaling pathways and membrane traffic events necessary for melanogenesis. Of note, melanosomal membranes carry a peculiar type of intracellular G-protein-coupled receptor (GPCR), named OA1, which is involved in melanosome biogenesis and transport,57-59 and appears functionally associated to melanosome-mitochondrion contacts.5 Thus, the OA1 GPCR might promote the formation of MCSs between the 2 organelles, either directly acting as a tether or, most likely, indirectly by means of its signaling cascade or by its ability to stimulate the melanogenic process.

MCSs control organelle dynamics and distribution

ER-mitochondria MCSs have been shown to play a role in mitochondrial fusion-fission and overall motility.60 These processes are crucial for mitochondrial biogenesis, distribution, and function, and their alteration results in inherited or age-related neurodegenerative diseases.61 Mitochondria continuously fuse and divide, by means of pro-fusion (Mfn 1 and 2, and OPA1, on the mitochondrial outer and inner membrane, respectively) and pro-fission (DRP1) proteins.64 They are also highly dynamic and move bidirectionally along microtubules, by exploiting the mitochondrial GTP-ase MIRO and its effector MILTON to recruit kinesin 1 and determine the prevalence of peripheral vs. centripetal organelle transport.62 The ER-mitochondria juxtaposition appears intertwined with these processes, since the pro-fission machinery is recruited and operates at sites where ER tubules contact mitochondria,63 and components of the pro-fusion machinery, namely Mfn 1 or 2 on the mitochondrial side and Mfn 2 on the ER, have been implicated in the interorganellar tethering.64 Moreover, Mfn 2 appears directly required for transport of axonal mitochondria by interacting with the MIRO/ MILTON complex and affecting both kinesin and dynein-based transport.65

Despite both mitochondria and the ER are highly motile organelles, they remain linked even as they move along microtubules.66 The maintenance of interorganellar contacts during microtubule-based motility is also a feature of endosomes, which mature and move while they remain bound to the ER.66,67 In the latter case, LTPs appear implicated in orchestrating membrane lipid content with organelle motility and connection with other compartments. On LE, the Rab7 effector ORPL1 is required for dynein activity upon recruitment by the RILP/dynactin complex.68 ORPL1 is also a cholesterol sensor, and in low cholesterol conditions it undergoes a conformational change that induces ER-LE MCSs, displacing the dynein/dynactin complex from RILP and leading to peripheral LE distribution.69 Similarly, the endosomal cholesterol-transfer proteins STARD3 and STARD3NL generate MCSs between LEs and the ER and appear implicated in endosome morphology and dynamics.
independently on ORPL1 and PTP1B. In either case, it is not known whether sterol exchange occurs at the interorganelar junctions.

As mitochondria, the ER, and endosomes, melanosomes are highly motile organelles, traveling along microtubules and actin filaments. Mitochondria and melanosomes might cope with their interactions during movement by means of dynamic, transient contacts, in a “stop-and-go” or in a “kiss-and-run” fashion. Alternatively, the organelles might be joined by more persistent and stable contacts, allowing coordinated motility and distribution. The latter possibility would be more compatible with the generation of cytosolic microdomains, allowing the localized exchange of small molecules between the 2 organelles, as in the case of calcium at the ER-mitochondria juxtaposition. In addition to the regulation of calcium fluxes, another main function of mitochondria is to produce ATP and both their biogenesis and transport certainly represent other physiological processes requiring energy. Thus, mitochondria juxtaposition might be required to timely and locally supply melanosomes with the ATP needed either for their movement along microtubule and actin tracks, or for melanin synthesis, or for controlling the melanosomal pH and membrane composition.

The compartmentalization of biochemical functions requires the reciprocal crosstalk between organelles to maintain the cellular homeostasis and to guarantee an efficient and coordinated response to environmental changes. Interorganelar MCs allow virtually any combination of membrane-bound compartments to establish a communication. The newly identified contacts between melanosomes and mitochondria demonstrate that the 2 compartments not only are coordinated at the transcriptional level, but also interact at the physical level. Given the characteristics of melanosomes as models of secretory organelles, it is possible that secretory granules in neuroendocrine cells or other LROs in hematopoietic cells connect with mitochondria during their biogenesis and transport. Understanding the structural and functional features of these interactions is critical not only by a biological point of view, but also for the possibility that organelle biogenesis could be pharmacologically modulated by exploiting and targeting MCs.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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