Published in final edited form as:
Curr Opin Cell Biol. 2014 February ; 0: 79–86. doi:10.1016/j.ceb.2013.10.006.

Morphology and Function of Membrane-bound Organelles

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Abstract

The cell interior is a busy and crowded place. A large fraction of the cell volume is taken up by organelles that come in a variety of shapes and sizes. These organelles are surrounded by membrane that not only acts as a diffusion barrier, but also provides each organelle with its unique morphology that contributes to its function, often in ways that are poorly understood. Here we discuss recent discoveries on the relationship between organelle structure and function.

Introduction

Organelles are dynamic, changing size and shape to maintain homeostasis and adjusting to the various needs of the cell. Some changes occur as part of the normal cell cycle, for example during cell division [1–3]. Other changes happen in response to challenges or stress and reflect a modification in organelle function, such as a change in protein folding capacity of the endoplasmic reticulum (ER) or ATP production in mitochondria [4, 5]. It is assumed that alterations to organelle morphology reflect an underlying functional optimization. Yet, this relationship is often poorly understood: for example, does the peripheral endoplasmic reticulum (ER) have to be in the shape of tubules in order to carry out its function? Does mitochondrial size matter? In this review we discuss recent advances in our understanding of the relationship between organelle structure and function, focusing primarily on the ER, nucleus and mitochondria. The reader is referred to excellent reviews that cover earlier work on Golgi [1], peroxosime [6] and endosome [7] structure.

Shaping a membrane-bound organelle

How are organelles shaped? The morphology of most organelles is characterized by a combination of flat and curved membrane, such as in the ER (Figure 1a). Cellular membranes are lipid bilayers made predominantly of phospholipids and proteins, both of which can contribute to membrane curvature. A difference in lipid composition between the two bilayers can itself lead to membrane curvature, and this likely drives the formation of the rims of Golgi cisternae and the tubular structures that connect the Golgi stack to form the ribbon [8]. Recently, a novel ER structure made of a helicoidal surface was shown to connect adjacent ER sheets [9••] (Figure 1b). This configuration, which is akin to the ramps of a parking garage, appears to be an energetically favorable structure that allows the dense

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packing of ER sheets to accommodate maximum protein synthesis in secretory cells. Thus, inherent properties of membranes contribute to their degree of curvature.

Proteins also contribute to membrane curvature, as in the case of the ER [10] (Figure 1c). Proteins called reticulons and DP1/Yop1/REEPs contain hydrophobic domains that form wedges on one side of the lipid bilayer, forcing it to bend towards the opposite side. These proteins are essential for maintaining ER tubules and are also involved in the highly curved regions of the NE where nuclear pore complexes are embedded. The tubular ER network is also shaped by the formation of three-way junctions, generated by homotypic membrane fusion between the tip of one ER tubule and the side of another in a process mediated by a conserved family of proteins called atlastin/Sey1 [11•, 12•]. Other proteins that contribute to membrane curvature are the BAR domain proteins, which form a rigid crescent-shaped structure and force membrane bending through electrostatic interactions between the concave surface of the protein dimer and the membrane [13]. Proteins also contribute to the constant luminal width of low curvature double-membrane structures, such as ER cisternae and the nuclear envelope, by acting as spacers within the luminal space [14•, 15]. Thus, organelle morphology is driven, in part, by dedicated proteins that affect membrane curvature and geometry.

Proteins that are not dedicated to altering membrane shape may also contribute to organelle structure. For example, the curvature of the cristae of the mitochondrial inner membrane is stabilized by the presence of ATP synthase [16, 17], and the ER sheets are likely stabilized by attached ribosomes [18]. Finally, membrane shape can be affected by external cytoskeletal forces. One such example is the formation of ER tubules through the attachment of the ER to microtubule associated proteins and the pulling forces exerted by microtubule elongation and microtubule motors [19–21]. The combination of lipid and protein composition, along with external forces, provides each organelle with its unique morphology.

Complex shapes allow for distinct functions within a single organelle

While some organelles, such as the nucleus or the vacuole, are simple in shape, other organelles, such as the Golgi and the ER, have complex shapes made up of a network of cisternae and tubules. This complexity allows for segregation of biochemical processes within the organelle: for example, ribosomes are preferentially associated with the flat ER membrane that forms the rough ER [14, 18]. In contrast, ER tubules are engaged in processes such as lipid synthesis and they are responsible for the majority of contacts between the ER and other organelles. Indeed, when the tubular structure of the ER is disrupted in yeast, the efficiency of lipid transfer between the ER and mitochondria is reduced [22•]. The ER forms membrane contact sites (MCS) with virtually all organelles in the cell; the juxtaposed membranes are typically 20 nm apart and they are held together by protein complexes that are unique to each organelle [23]. Traditionally, MCS were thought of as sites for inter-organelle communication, such as exchange of Ca^{+2} and the transfer of lipids, which are synthesized predominantly in the ER but are needed by all membrane-bound organelles. More recently, MCS between the ER and the mitochondria were shown to affect mitochondrial fission [24••]: ER tubules wrap around mitochondria at future fission sites and can constrict mitochondria even in the absence of the mitochondrial fission machinery, such as the dynamin related protein Dnm1/Drp1. The mechanism by which this constriction occurs, and whether ER tubules affect the structure of other organelles, remain to be determined.

Unlike the ER, the metazoan nucleus is usually a round or oval structure with limited membrane curvature, except where the inner and outer nuclear membranes meet at nuclear

pores. Thus, distinct domains within the nucleus, if they exist, are not defined by nuclear membrane-derived compartments. The budding yeast nucleus, however, changes shape during the cell cycle: while the metazoan nucleus disassembles in mitosis, the budding yeast nucleus remains intact, and in anaphase it forms an hourglass shape with only a narrow opening connecting the nuclear compartments within the mother and daughter cells. This opening is sufficiently small to form a diffusion barrier between the two nuclear halves, allowing the asymmetric accumulation of a transcription factor only in the daughter nuclear compartment [25•]. Widening of the opening connecting the mother and daughter nuclear halves by genetic manipulations allowed diffusion of proteins between the two compartments, indicating that yeast cells take advantage of cell cycle changes in nuclear shape to compartmentalize the nucleus.

Organelle shape and cell function

It is likely that organelle shape, and in particular the membrane configuration, has evolved to suit not only the organelle's biological activity, but also overall cell function. The formation of MCS discussed above is one such example, and recent studies suggest that the reticular nature of the peripheral ER is also important to allow passage of macromolecules from the cytosol to the plasma membrane. In fission yeast, for example, the localization of a plasma membrane protein, Mid1, which usually localizes in a sharp band at the cell midzone, was altered to a more dispersed pattern in a mutant harboring peripheral ER that was in the form of sheets rather than tubules [26]. The subsequent identification of proteins that link the ER to the plasma membrane in budding yeast helped explain this result [27, 28•]: when these ER- plasma membrane tethering proteins were absent, the peripheral ER collapsed to the center of the cell. Interestingly, when these tethering proteins were removed from the fission yeast mutant containing ER sheets described above, the ER sheets detached from the plasma membrane and Mid1 resumed its normal localization pattern [29]. The authors interpreted this result to mean that extensive ER sheets at the cell periphery may obstruct proper protein localization at the plasma membrane, and that the peripheral ER is in the form of tubules in part to allow access of proteins like Mid1 to the plasma membrane. Interestingly, sites of endocytosis do not overlap with plasma membrane regions that are associated with the ER [30], again suggesting that ER presence may limit the accessibility of cytosolic proteins to the plasma membrane. Taken together, these studies suggest that the ER can both facilitate access to the plasma membrane for ER components, through MCSs, but can block plasma membrane accessibility of cytosolic factors.

Another example of organelle shape adapting to the cell's needs is seen in mitosis. Most organelles must change shape and/or size (e.g. undergo fragmentation) during cell division to ensure their own proper segregation to the daughter cells. Less appreciated, until recently, was the need to change shape in order to get out of the way of the mitotic apparatus. Under certain pathological conditions that lead to abnormal cellular structure, chromosome segregation or nuclear division can be obstructed. For example, the *FAB1* gene, which is required to regulate vacuole morphology, was initially identified in a screen for chromosome segregation mutants in budding yeast because the grossly enlarged vacuole in *fab1* mutants prevented nuclear elongation [31]. But do organelles remodel to avoid obstructing the mitotic apparatus under non-pathological conditions?

Following NE break down in vertebrate cells, many NE components are resorbed into the ER. The ER itself is conspicuously absent from the area of the mitotic spindle and becomes enriched at spindle poles [18]. Two recent papers describe microtubule-dependent mechanisms that serve to keep the ER clear of the mitotic spindle, and in one case this is essential for proper NE architecture (Figure 2). Smyth et al. [32••] showed that phosphorylation of Stromal interaction molecule 1 (STIM1) keeps ER off of spindle

microtubules by dissociating it from the microtubule plus end binding protein 1 (EB1). Schlaitz et al. [33••] identified REEP4 in a proteomic screen for membrane proteins that bind microtubules in *Xenopus* egg extracts, and showed that depletion of REEP4 and its close homolog REEP3 caused ER membrane to accumulate on mitotic chromosomes and become trapped inside reforming daughter nuclei. Whereas expression of wild-type REEP4 rescued the phenotype, a REEP4 mutant defective in microtubule binding could not. Thus, while phosphorylation of STIM1 prevents association of ER membranes with microtubule plus ends, REEP3/4 function to concentrate these membranes near microtubule minus ends at spindle poles, away from the chromosomes, through an uncharacterized mechanism.

Changing shape in adaptation to stress

In addition to changes associated with the cell cycle, cells may experience a need to increase the functional capacity of an organelle, either due to specialization following differentiation or under stress conditions, when the activity of a certain cellular compartment must be increased in order achieve homeostasis. A well-documented case is the unfolded protein response (UPR), which is activated due to the accumulation of unfolded proteins in the ER and leads to increased phospholipid synthesis that drives ER expansion [34]. In a more recent example, a pathway linking mitochondria shape changes to stress in the form of nutrient deprivation has been identified [35••, 36••]. A catabolic process termed autophagy is induced by starvation and proceeds through the formation of a double-membrane vesicle, the autophagosome. Organelle and cytosolic components engulfed by the autophagosome are recycled following fusion with lysosomes, thereby prolonging cell survival when nutrients are scarce. In separate studies, Gomes et al. and Rambold et al. observed that mitochondria elongate during autophagy, which spares their degradation (Figure 3). Starvation-induced mitochondrial elongation is mediated by down regulation of dynamin-related protein 1 (Drp1), which prevents mitochondrial fission, leading to unopposed fusion. It is unclear whether elongated mitochondria cannot be targeted to autophagosomes because of their size or because they are not recognized in their fused form. Why mitochondria are spared is another question. Elongated mitochondria have a higher density of cristae and increased ATP production, which could spare amino acids for protein synthesis rather than catabolism thereby promoting cell survival under starvation conditions. In addition, mitochondria may also provide membrane to autophagosomes during starvation [37••].

The importance of organelle size

In addition to having a distinct shape, organelles also have a specific size. Organelle size may scale with cell size as was shown in yeast for the nucleus [38, 39] and more recently for mitochondria [40•]. Organelle size may also expand to accommodate the cell's changing needs, as in the case of ER expansion during the UPR or when mitochondria fuse to evade autophagy, described above. Thus, the size of an organelle undoubtedly affects its function, but in only very few cases has organelle size been manipulated to evaluate the consequences.

A recent study addressed the effects of assembling a very small nucleus [41••]. Micronuclei form around an individual or broken chromosome when it segregates improperly during mitosis and becomes separated from the main chromatin mass. Hetzer and colleagues showed that although micronuclei appear to be structurally normal, their nuclear envelopes frequently collapse due to defects in assembly of the underlying network of intermediate filaments, the nuclear lamina. Nuclear envelope collapse is accompanied by chromatin compaction, invasion of the ER, and loss of nuclear functions including transcription and DNA replication, and can trigger massive DNA damage, termed chromothripsis (Figure 4). Indeed, Pellman and colleagues [42] showed that DNA subjected to fragmentation within

micronuclei can be re-integrated into the genome in subsequent cell divisions. Although it is not currently known that size, per se, caused micronuclei-dependent damage, the underlying causes of micronucleus instability are likely to shed light on nuclear function.

It is also the case that not all small nuclei are defective. In certain large and rapidly dividing embryos, such as fish [43] and frog [44], nuclear envelopes form around individual or groups of chromosomes, rather than around the entire DNA mass, likely so that DNA replication can commence quickly. These micronuclei, termed karyomeres, fuse to form a mononucleus prior to the next division. Abrams et al. identified a protein in zebrafish, brambleberry, which is required for karyomere fusion [45•]. Brambleberry mutants fail to fuse their karyomeres but still develop normally, indicating that unlike micronuclei in differentiated cells, these karyomeres are functional. One possible explanation is that the embryonic nuclear lamina stabilizes micronuclei during embryogenesis, since expression of a B-type lamin largely rescued collapse of micronuclei in somatic cells. Or, perhaps embryonic karyomere nuclear envelopes avoid collapse because they need only persist for 30 minutes prior to the next division, compared to the many hours of a typical somatic cell interphase. The potential instability of micronuclei highlights how nuclear morphology can dramatically affect nuclear function. The many diseases associated with defects in nuclear structure, such as laminopathies, further illustrate that less dramatic structural defects than nuclear envelope collapse nevertheless have strong negative consequences.

Conclusions

In this review we presented examples of the relationship between organelles, their surrounding membranes and morphology, and their function. In describing recent studies, we highlighted some of the possible mechanisms determining organelle shape, as well as the functional consequences of altering their structure. Organelles differ in shape because the lipid and protein building blocks involved in determining membrane shape are distinct, resulting in the prototypical organelle shape we see by light and electron microscopy. While textbooks typically present a canonical set of organelle shapes, it is important to remember that most organelles are dynamic, displaying a rather wide range of possible shapes in different cell types, under different conditions and among different organisms.

There is still a lot that we don't understand about organelle morphology, and in particular how organelle size is determined and how morphology contributes to organelle function. For example, at membrane contact sites, the curved nature of ER tubules along with their specific lipid composition [46] may provide an energetically favorable conformation for the detachment of proteins or lipids that move between adjacent membranes. Another example is organelle fragmentation, which may have dual roles: it likely increases the odds of equitable partitioning to daughter cells during mitosis, but it may also serve to increase the surface area to volume ratio under conditions where surface-associated processes need to be up-regulated. Finally, a fascinating question is the reason for a constant nuclear/cell volume ratio: it could simply be a byproduct of protein synthesis rate, which may provide a proportional amount of building blocks for the cell and the nucleus (i.e. both are controlled by the same upstream machinery). Alternatively, this ratio could be kept constant by a dedicated, yet unknown, regulatory mechanism that scales nuclear size to cell size in order to regulate the intra-nuclear concentration of signaling and chromatin associated factors, thereby matching the transcriptional response to the cell's needs. Future studies on organelle structure-function relationships will benefit from identifying the entire repertoire of building blocks that determine organelle morphology, and elucidating how they contribute to organelle and cell function.

Acknowledgments

We thank Will Prinz, Rebecca Meseroll and Alison Walters for excellent comments on the manuscript, and apologize for all those whose work could not be cited due to space limitations. RH is supported by NIH: R01 GM057839 and GM098766. OCF is supported by intramural funding from NIDDK.

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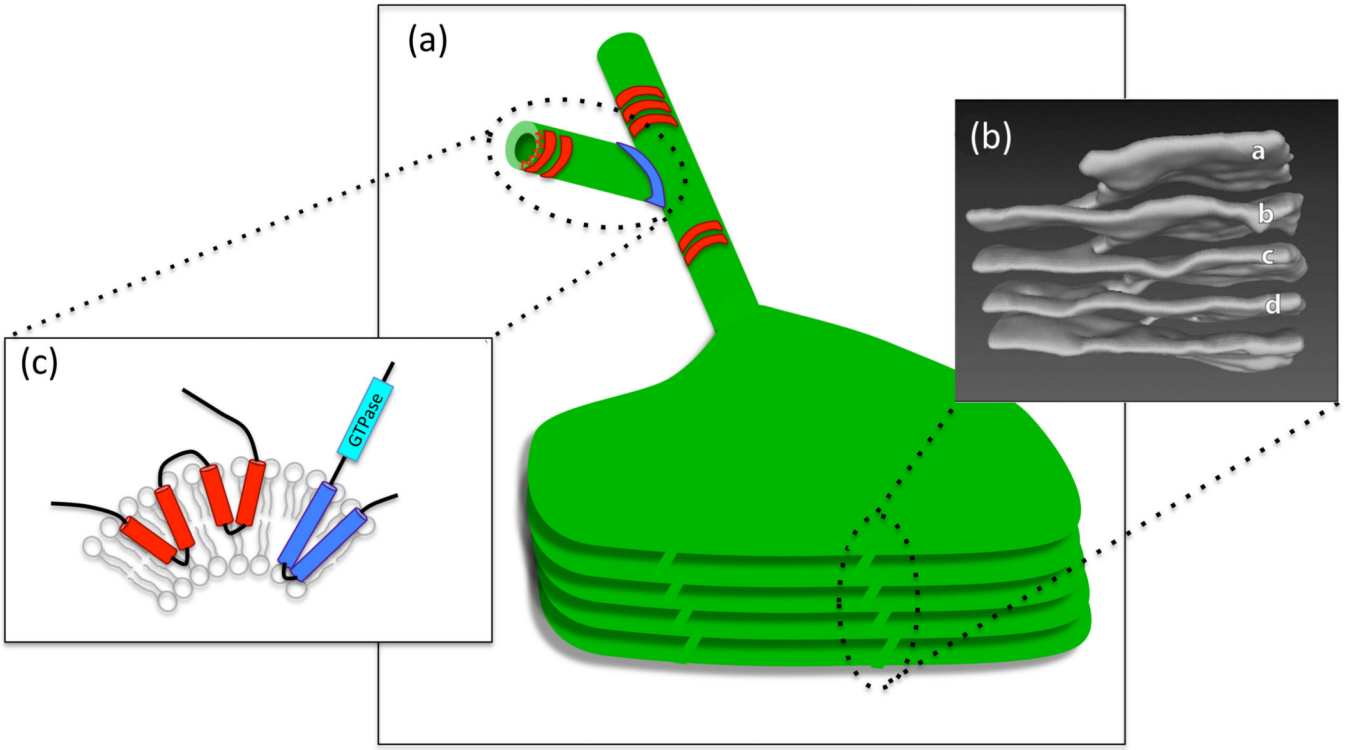

Figure 1.

Diverse membrane structures in the ER. (a) The ER is an interconnected network of composed of branched tubules and sheets, some of which can form stacks, as shown in the illustration. ER tubules are stabilized by the oligomerization of proteins such as reticulons and DP1/Yop1/REEps (in red), while 3-way junctions are mediated by proteins such as atlastins (in blue). (b) The structure of reticulons and atlastin. Membrane curvature is induced by the insertion of protein "wedges" (two in the case of reticulons and one in the case of atlastin) that traverse only one lipid bilayer, forcing the membrane to curve. Atlastin has an in addition GTPase activity that is necessary for fusing membranes and generating 3-way junctions. (c) Helicoidal membrane structure in stacked ER sheets. A 3D reconstruction of a region of stacked ER sheets from an acinar cell of a mouse salivary gland. The letters (a through d) mark the ER sheets that are connected through a helicoidal structure (to the left). From Terasaki et al. Cell 154, 285–296, 2013.

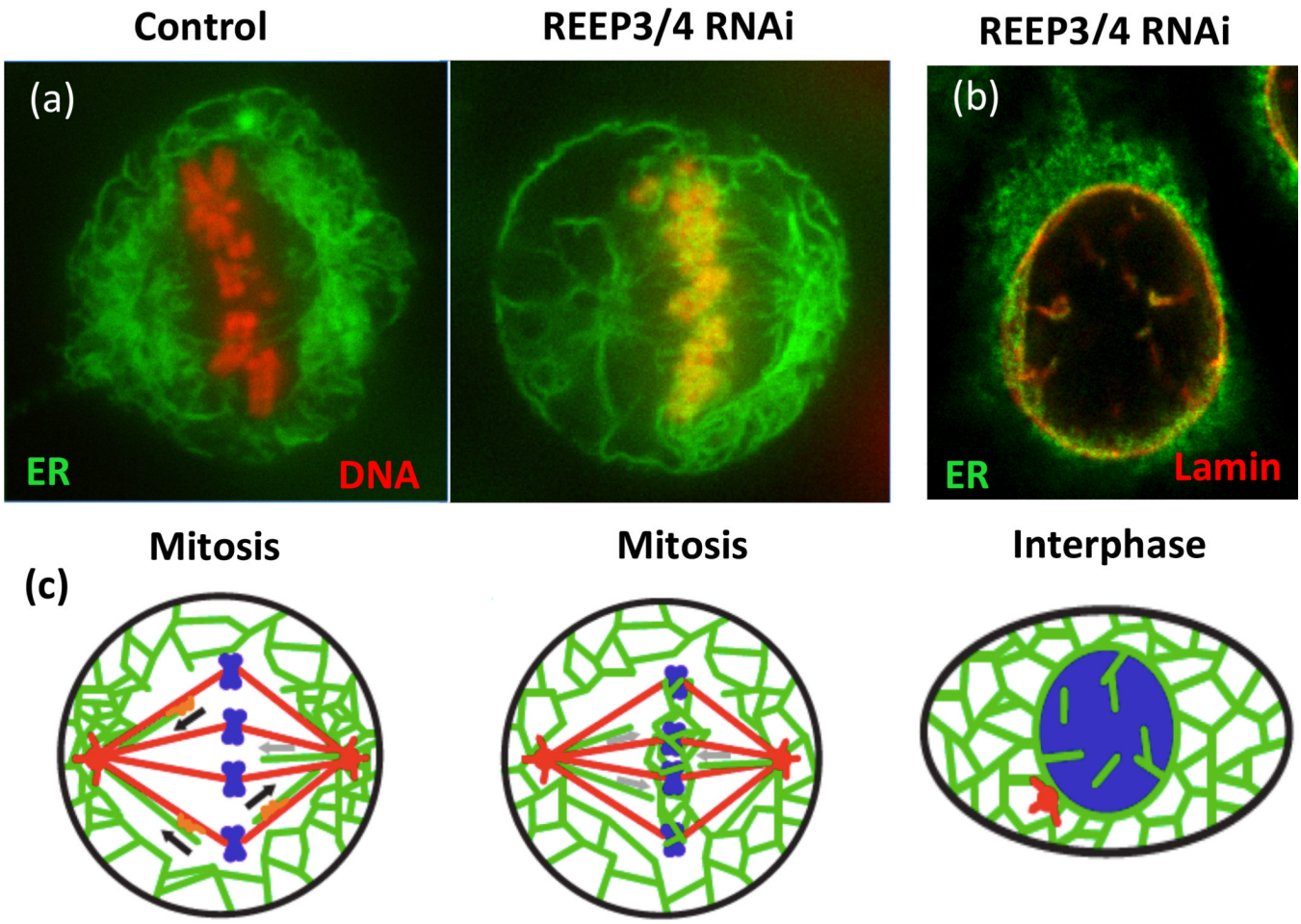

Figure 2.

Depletion of REEP3/4 causes accumulation of ER on mitotic chromosomes and leads to intranuclear membranes and lamina. A. HeLa cells expressing RFP-histone (red) to label the DNA and GFP-Sec61 (green) to mark the ER were subjected to control or REEP3/4 RNAi and imaged during mitosis. Note the colocalization of ER and mitotic chromosomes in the absence of REEP3/4. (b) An interphase REEP3/4 RNAi-treated HeLa cell expressing GFP-Sec61 (green) was fixed and stained for nuclear lamin B1 (red). Both NE markers are aberrantly localized to structures inside the nucleus. (c) Schematic of phenotypes with microtubules in red, DNA in blue and ER in green. Adapted from Schlaitz et al. Dev. Cell 26, 316–323, 2013. Images courtesy of Anne-Lore Schlaitz and Rebecca Heald.

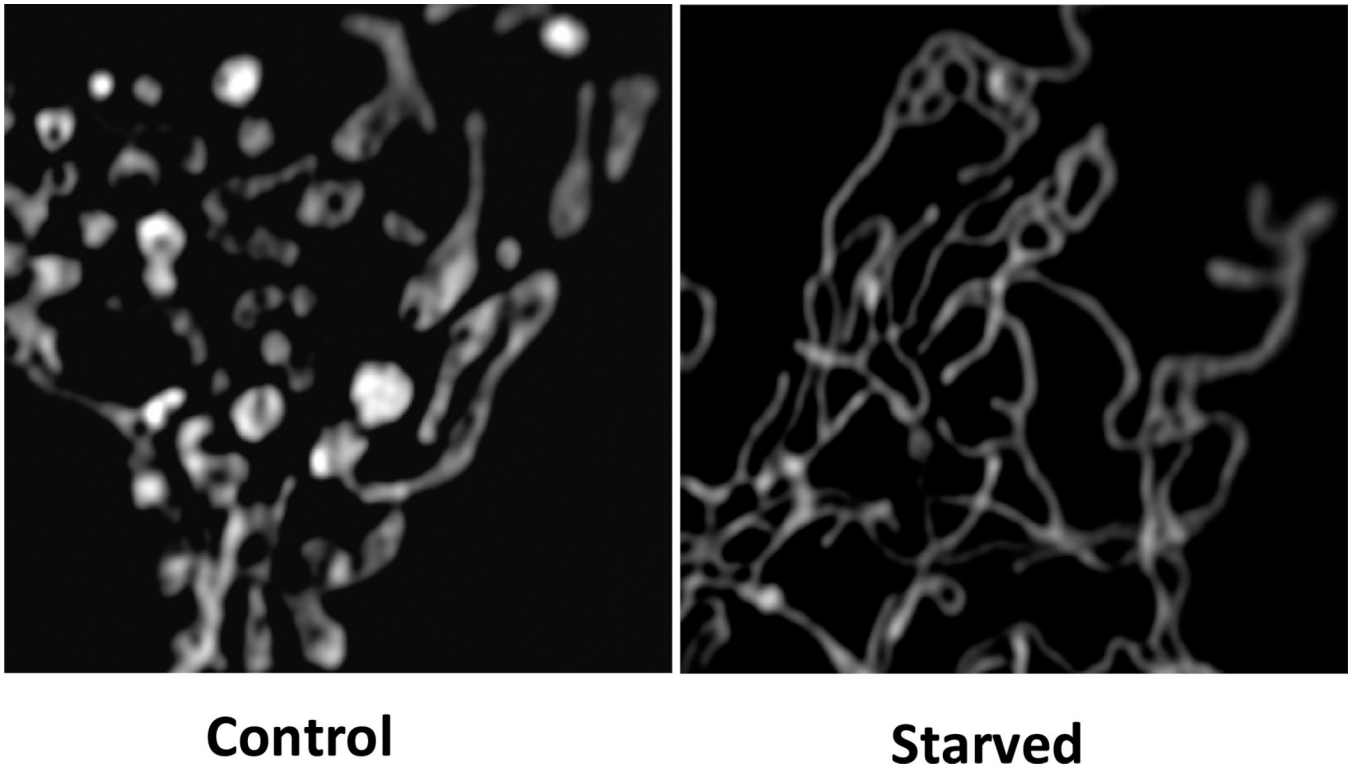

Figure 3.
Starvation leads to unopposed mitochondrial fusion. Mouse embryo fibroblasts transfected with mitoRFP were incubated in full nutrient medium (Control), or starvation medium (Starved) for 6 hours. Starved cells show a continuous network of mitochondria. Cells were fixed and images acquired by Structured Illumination Microscopy. Images courtesy of Angelika Rambold and Jennifer Lippencott-Schwartz.

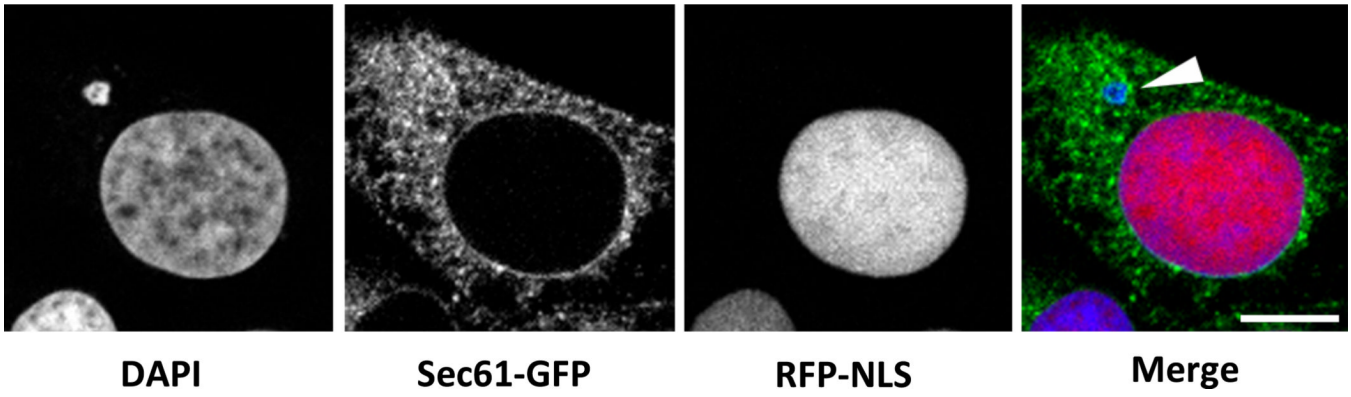

Figure 4.

Micronuclei are unstable in somatic cells. The images show a U2OS cell containing an intact nucleus and a disrupted micronucleus (arrowhead). The micronucleus fails to accumulate the fluorescent nuclear protein RFP-NLS, and has been invaded by ER as indicated by the presence of Sec61-GFP. Scale bar = 10 microns. Images courtesy of Emily Hatch and Martin Hetzer.