CELL BIOLOGY

SevERing Mitochondria

The endoplasmic reticulum is an active participant in the division of another organelle, the mitochondrion.

Angelika S. Rambold and Jennifer Lippincott-Schwartz

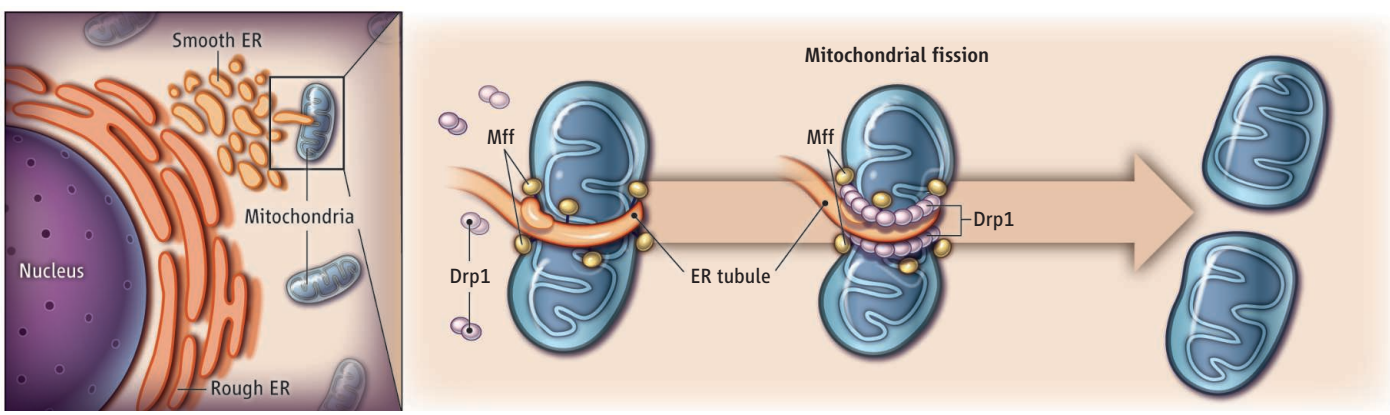
Mitochondria are the cell's metabolic headquarters, fueling oxidative phosphorylation for adenosine 5′-triphosphate production, and driving reactions to manufacture core metabolites for the biosynthesis of fats, DNA, and proteins. In addition to their metabolic roles, these organelles regulate various cellular processes, including proliferation (*1*), immune responses (*2*–*4*), and apoptotic cell death (*5*). Mitochondrial function in many of these processes is coupled to their specific morphology, which ranges from small individual mitochondrial elements to large interconnected networks (*6*). These diverse shapes result from fission into smaller forms or fusion into larger structures (*7*, *8*), events thought to occur autonomously. However, a study by Friedman *et al*. in *Science* Express (*9*) reveals that mitochondrial division is intimately coupled to another organelle, the endoplasmic reticulum (ER).

Mitochondrial division is driven by the fission protein Dnm1 in yeast, and its homolog Drp1 in higher eukaryotes. Dnm1 and Drp1 belong to a family of dynamin-related proteins that are thought to regulate membrane fission by forming contractile helices that wrap around membrane to constrict it (requiring guanosine 5′-triphosphate hydrolysis) (*7*, *10*). Most Drp1 in higher eukaryotes is dispersed throughout the cytosol; only a small fraction is recruited onto mitochondria and assembles into oligomeric structures in a process that depends on the membrane protein mitochondrial fission factor (Mff in mammals) (*11*). Whereas Dnm1/Drp1 assemblies are always found at mitochondrial fission sites, not all Dnm1/Drp1 sites define sites of division (*7*). Friedman *et al*. discover that ER-mitochondria interaction sites mark the sites of mitochondrial fission and suggest that the ER may be an active participant in mitochondrial division.

The ER and mitochondria exhibit tightly coupled dynamics and have extensive contacts (*12*). Using sophisticated imaging approaches, Friedman *et al*. found that mitochondrial fission occurs at regions of contact between mitochondria and ER that are characterized by ER tubules crossing and nearly enwrapping mitochondria. At, or close to, these ER-mitochondrial contact sites, the mitochondria first become partially constricted, and then completely divide. Notably, the ER-mitochondrial contact sites involve the activity of ER tubules; sheetlike regions of the ER did not appear to be important. Even shifting ER morphology toward sheetlike architecture (through deletion of the yeast ER-shaping proteins, Rtns/Yop1) did not prevent small tubules from extending off sheetlike ER to interact with mitochondria.

Time-lapse imaging further identified the sequential nature of ER-based mitochondrial division. The appearance of ER-mitochondria contact sites coincides with constriction of mitochondria at these sites. Drp1 is then recruited to these sites, either from the cytosol or from other mitochondrial sites, and is followed by mitochondrial fission (see the figure). Initial mitochondrial constrictions at sites of ER-mitochondrial contact were still observed in the absence of Drp1 or Mff, which suggests that constriction preceding full fission is independent of both proteins and is potentially mediated by the ER-mitochondria contact itself. This might occur if ER-mitochondrial tethering proteins interact as ER tubules wrap around mitochondria, and could actively contribute to preconstriction, and/or to the fission process itself.

The findings of Friedman *et al*. raise questions about whether the ER actively contributes to mitochondrial fission and what proteins are required. The authors hypothesize that partially constricting mitochondria could physically be important for assembling Drp1 helices around mitochondria, because Drp1 ring width is smaller than the mitochondrial diameter. ER-induced mitochondrial constriction could therefore facilitate the stabilization and/or oligomerization of Drp1 at division sites. But proteins residing on the ER or mitochondria could also contribute to mitochondrial constriction and/or fission. Potential candidates include the tethering proteins Mfn2 in higher eukaryotes or a complex in yeast called the ER-mitochondria encounter structure (*13*, *14*). Other ER-mitochondria



ER-dependent mitochondrial fission. In this model, the major mitochondrial fission protein Drp1 is recruited from cytosolic or mitochondrial spots to ER-mitochondria contacts sites (containing the Drp1-receptor Mff). At sites of interorganellar contact, Drp1 stabilizaton and/or oligomerization into helices might be facilitated by ER tubule–dependent mitochondrial constriction.

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functions such as calcium or lipid transfer (*12*, *15*) also could play a role during fission. ER-mediated release of calcium could spatially activate Drp1-dependent fission close to ER-mitochondria contacts (*7*). Furthermore, changes in mitochondrial lipid composition, as a consequence of ER-mitochondria lipid transfer, could contribute to fission.

Clearly, tight ER-mitochondrial coupling could contribute to mitochondrial fission in several ways, but it is unclear whether mitochondria-ER contacts are essential for fission. Friedman *et al*. extend the complexity of mitochondrial fission, with potential implications for diseases of ER- or mitochondrial-shaping proteins. Although the authors report that changes in ER architecture do not appreciably affect mitochondrial fission in yeast, specific mammalian cells could be sensitive to malfunctions of mitochondrial fission, such as neurons. Even a slight reduction in mitochondrial fission in these cells may contribute to so-called ER-architecture diseases, such as hereditary spastic paraplegia (*16*, *17*). Furthermore, the connection between ER and mitochondrial fission may be related to other processes, such as the segregation or replication of mitochondrial DNA, and other cellular functions, such as apoptotic cell death. There may even be bidirectional coupling between mitochondrial fission and ER activities, in which ER-facilitated mitochondrial fission produces feedback to affect ER properties.

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CHEMISTRY

Shining Light on Diabolic Points

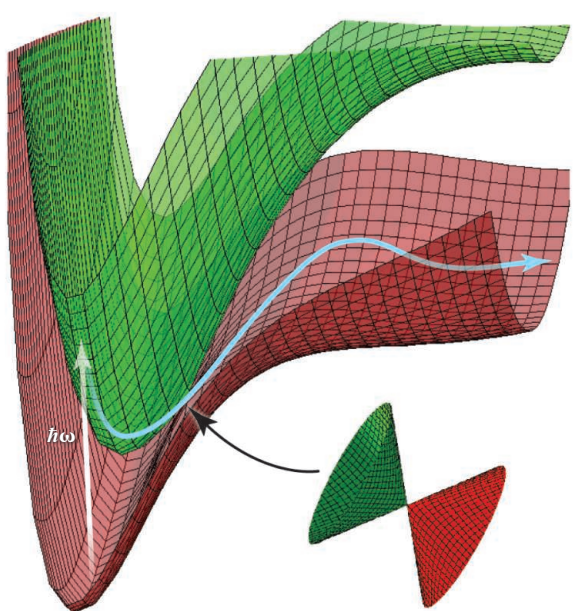
A direct probe of the electronic dynamics where excited states intersect has been achieved by using high-harmonic spectroscopy.

Benjamin J. Whitaker

Chemical reactions are described at a fundamental level in terms of how the potential energy of molecules changes as a function of distance between the constituent atoms. These potential energy surfaces, which describe the barriers that must be overcome as reactants form products, are calculated with molecular orbital theory, which approximates the real wave functions of molecules as combinations (configurations) of many one-electron wave functions. This approach is accepted by chemists because it accounts for the rates of many reactions, but can it be directly verified? On page 208 of this issue, Wörner *et al*. (*1*) test the validity of these descriptions of electronic structure.

Their experiment probed the electron dynamics of a molecule at a conical intersection, or diabolic point, where two different electronic states cross at the same energy and create strong coupling between nuclear and electronic motions. The name diabolic comes from the resemblance of the intersection to the juggler's Diabolo top on a string and to conjure the notion that the molecular dynamics close to these points is devilishly tricky to calculate. The authors used high-harmonic generation, a technique for converting optical laser pulses into higher frequency radiation, to resolve the electronic state of molecules at diabolic points.

An example of the simplest conical intersection, where two surfaces meet at a single point, is shown in the lower right in the figure. More generally, for higher dimensional potential surfaces, the singularity is described by a conical intersection seam in the space of nuclear coordinates (*2*, *3*). Conical intersections play a crucial role in the photochemistry of polyatomic molecules because they act as funnels that convert the electronic energy of excited states into nuclear kinetic energy. Normally, such transitions between electronic states lose energy by emitting photons, but at conical intersections, these processes are nonradiative and waste no energy. Conical intersections are the key to understanding



Brief but important meetings. Conical intersections, or diabolic points, are critical points on the molecular potential energy landscape where states of the same symmetry meet. They play a crucial role in photochemistry because they act as conduits to convert electronic energy into nuclear kinetic energy. A simple version of such a point is shown in the lower right. The main panel shows a photon of energy $\hbar\omega$ exciting a molecule from the ground-state electronic surface (red) to the first excited-state surface (green). The trajectory shown in blue depicts a vibrational motion induced by the transition. The molecule crosses back to the ground state at the diabolic point depicted with the arrow. Wörner *et al*. (*1*) literally shined light on these points by using ultrafast laser pulses to probe the electronic dynamics directly as the electronic character of an NO_2 molecule changes on passing through a diabolic point.

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