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REVIEW

Intracellular organelle networks: Understanding their organization and communication through systems-level modeling and analysis

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BACKGROUND: Membrane-bound intracellular organelles are biochemically distinct compartments used by eukaryotic cells for serving specialized physiological functions and organizing their internal environment. Recent studies revealed surprisingly extensive communication between these organelles and highlighted the network nature of their organization and communication. Since organization and communication of the organelles are carried out at the systems level through their networks, systems-level studies are essential for understanding the underlying mechanisms.
METHODS: We reviewed recent studies that used systems-level quantitative modeling and analysis to understand organization and communication of intracellular organelle networks.
RESULTS: We first review modeling and analysis studies on how fusion/fission and degradation/biogenesis, two essential and closely related classes of activities of individual organelles, collectively mediate the dynamic organization of their networks. We then turn to another important aspect of the dynamic organization of the organelle networks, namely how organelles are physically connected within their networks, a property referred to as the topology of the networks in mathematics, and summarize some of their distinct properties. Lastly, we briefly review modeling and analysis studies that aim to understand communication between different organelle networks, focusing on cellular calcium homeostasis as an example. We conclude with a brief discussion of future directions for research in this area.
CONCLUSIONS: Together, the reviewed studies provide critical insights into how diverse activities of individual organelles collectively mediate the organization and communication of their networks. They demonstrate the essential role of systems-level modeling and analysis in understanding complex behavior of such networks.

Keywords intracellular organelle, organelle network, organelle communication, network analysis, systems modeling

Introduction

Formation of membrane-bound intracellular organelles is a basic strategy used by eukaryotic cells for organizing their internal environment. With different organelles serving as biochemically distinct compartments for specialized physiological functions, this strategy of compartmentalization and specialization provides important structural and functional benefits. In the meantime, however, it makes communication between the organelles crucial because their specialized functions must constantly be coordinated and integrated for cell physiology. To date, organelle communication mechanisms such as vesicle trafficking (Bonifacino and Glick, 2004; Lee et al., 2004) and membrane fusion (Martens and McMahon, 2008; McNew et al., 2013) have been extensively studied. Vesicle trafficking, for example, has been shown to mediate communication between heterotypic organelles, such as the endoplasmic reticulum with the Golgi apparatus, whereas membrane fusion has been shown to mediate communication between homotypic organelles, e.g., endosome with endosome, as well as heterotypic organelles, e.g., endosome with lysosome. Despite these connections, until recently, organelles were often thought to be autonomous, i.e., structurally and functionally independent of each other, and different types of organelles were thought to act as

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isolated islands, with little communication between them except for the few cases known. However, new evidence from recent studies has started to fundamentally change this notion and suggests a very different view in which organelles communicate and interact with each other much more closely and extensively than previously thought.

An important line of evidence comes from studies of mitochondrial fusion and fission (Chan, 2012; Youle and van der Bliek, 2012) as well as transport and anchoring mediated spatial distribution (Frederick and Shaw, 2007; Sheng and Cai, 2012; Sheng, 2014). The initial notion of mitochondria as autonomous and separate compartments was motivated in part by observations of discrete mitochondria in neurons and various other cell types (Frazier et al., 2006; Kuznetsov et al., 2009) as well as findings of substantial heterogeneity in mitochondrial structural organization and function (Kuznetsov and Margreiter, 2009; Wikstrom et al., 2009). However, this notion could not be easily reconciled with observations of highly interconnected tubular networks of mitochondria in budding yeast and many higher eukaryotic cells (Okamoto and Shaw, 2005; Frazier et al., 2006; Kuznetsov et al., 2009) as well as findings of connectivity and continuity in mitochondrial structural organization and function (Rutter and Rizzuto, 2000; Jakobs et al., 2003; Karbowski et al., 2004). Recent findings on the molecular machineries and mechanisms of fusion and fission (Chan, 2012; Hoppins et al., 2007; Labbé et al., 2014; Sheng, 2014) as well as transport and anchoring (Frederick and Shaw, 2007; Sheng and Cai, 2012) of mitochondria firmly established a new understanding of their intracellular organization, namely, individual mitochondria are far from being autonomous. Instead, they work together through fusion and fission as well as transport and anchoring as a network to respond to internal or external stimuli. The heterogeneity observed in mitochondrial organization and function within a single cell as well as among different cells (Frazier et al., 2006; Kuznetsov et al., 2009; Kuznetsov and Margreiter, 2009; Wikstrom et al., 2009) likely results from differential structural and functional responses of mitochondrial networks to diverse intracellular and/or extracellular stimuli. In addition to mitochondria, organelles such as endosomes (Brandhorst et al., 2006; Gautreau et al., 2014) and lysosomes (Luzio et al., 2007) have also been shown to form networks through fusion and fission. Increasingly, related studies suggest that network formation through fusion and fission may serve as a general mechanism for organizing homotypic organelles.

Another important line of evidence comes from recent findings on membrane contact sites (MCSs) between different types of organelles (Helle et al., 2013; Prinz, 2014; Schrader et al., 2015). To date, MCSs have been identified between nearly all types of intracellular organelles, and direct contact between them through MCSs has been shown to mediate many important physiological functions (Helle et al., 2013; Prinz, 2014; Schrader et al., 2015; Levine and Patel, 2016). Thus, communication between different types of organelles is far more common than previously thought. Together, the different lines of evidence highlight the network nature of intracellular organelle organization and communication: organelles of the same kind work closely together by forming a network through mechanisms such as fusion/fission and transport/anchoring, whereas different organelle networks communicate extensively through mechanisms such as vesicle trafficking, membrane fusion, or membrane contact.

Since organization and communication of intracellular organelles are carried out at the systems-level through their networks, systems approaches are required for understanding related mechanisms and for linking such mechanisms with their molecular machineries. To date, significant advances have been made in dissecting the molecular machineries of organelle network organization and communication, and there are comprehensive reviews of related studies (Prinz, 2014; Schrader et al., 2015; Levine and Patel, 2016; Phillips and Voeltz, 2016). However, detailed knowledge of the molecular machineries must be integrated at the systems level for a holistic understanding of organelle network organization and communication. In this paper, we review recent studies that use systems-level quantitative modeling and analysis for achieving such an understanding.

This review consists mainly of three parts. In the first part, we survey studies that use systems-level modeling and analysis to understand how fusion and fission as well as degradation and biogenesis of individual organelles, two essential and closely related classes of activities, collectively mediate dynamic organization of their networks. In the second part, we focus on another key aspect of the dynamic organization of the organelle networks, namely their topology, which defines how organelles are physically connected within their networks. Using concepts from network analysis (Newman, 2003; Zhu et al., 2007; Barrat et al., 2008; Newman, 2010), we identify several distinct properties of the organelle networks that distinguish them from other biological networks such as gene regulatory networks or protein interaction networks. In the third part, we briefly survey systems-level modeling and analysis studies that aim to understand communication between different organelle networks, focusing on cellular calcium homeostasis as a specific example. We conclude with a brief discussion of future directions for research in this field. Together, the systems-level studies reviewed provide critical insights into some of the fundamental principles governing organization and communication of the organelle networks. They demonstrate the crucial role of systems-level modeling and analysis in understanding their complex behavior.

Understanding dynamic organization of organelle networks through systems-level modeling and analysis of fusion/fission and degradation/biogenesis

Intracellular organelle networks must be dynamically

organized to respond to changing internal and external stimuli. This dynamic organization ultimately is achieved through activities of individual organelles. An important class of such activities is the fusion and fission of organelles, which enable them to exchange their soluble and membranous contents. Mitochondria, endosomes, and lysosomes all undergo homotypic fusion and fission within their networks (Brandhorst et al., 2006; Luzio et al., 2007; Chan, 2012; Youle and van der Bliek, 2012; Gautreau et al., 2014). Since fusion requires spatial proximity of organelles whereas fission requires spatial separation of organelles, they must be closely coordinated with organelle transport and anchoring, which mediate spatial distribution of the organelle networks (Frederick and Shaw, 2007; Sheng, 2014). While organelles are serving their specialized physiological functions, their health is constantly monitored for quality control, and dysfunctional or damaged organelles are targeted for degradation through autophagy (Mizushima, 2007; Nakatogawa et al., 2009). Removal of dysfunctional or damaged organelles must be balanced by addition of new organelles through biogenesis to maintain homeostasis (Nunnari and Walter, 1996; Palikaras and Tavernarakis, 2014). Together, degradation and biogenesis constitute another important class of organelle activities. Here, we focus on mitochondrial and endosomal networks as examples and review recent studies that use systems-level modeling and analysis to understand how fusion/fission and degradation/biogenesis of individual organelles collectively mediate dynamic organization of their networks.

Modeling and analysis of fusion/fission and degradation/biogenesis in dynamic organization of mitochondrial networks

Mitochondria undergo repeated cycles of fusion and fission, which enable mixing of their soluble and membranous contents. This process is thought to serve as a quality control mechanism by maintaining a healthy and homogeneous network (Chan, 2012), whereas degradation of damaged mitochondria through autophagy (mitophagy) provides another quality control mechanism (Youle and Narendra, 2011). Extensive experimental evidence has shown that these two processes are closely related (Chen and Chan, 2009; Ni et al., 2015). To understand how they collectively mediate dynamic organization of mitochondrial networks, Shirihai and colleagues developed systems-level kinetic models of mitochondrial fusion, fission, damage, degradation, and biogenesis (Mouli et al., 2009). Using simple event probabilities as kinetic parameters, their fusion/fission model characterized frequency and duration of fusion as well as asymmetry of fission. Their damage model characterized frequency and extent of mitochondrial damage, and their degradation/biogenesis model characterized frequency of degradation of damaged mitochondria as well as frequency of addition of new mitochondria through replication. Their modeling and simulation study was motivated by their experimental study of the mitochondrial network in insulin-producing β-cells, which indicated that fusion and fission work synergistically with autophagy to facilitate removal of damaged mitochondria (Twig et al., 2008a). Two key assumptions based on experimental studies were made. First, fusion followed by fission mediates asymmetric content distribution between two daughter mitochondria (Barsoum et al., 2006; Twig et al., 2008a). Second, fusion is selective in that only healthy and polarized mitochondria can undergo fusion. Depolarized mitochondria are excluded from fusion and are targeted for degradation by autophagy (Elmore et al., 2001; Priault et al., 2005; Twig et al., 2010). Based on their systems-level models, the authors conducted Monte-Carlo simulations to understand the relations between fusion/fission and degradation/biogenesis in network quality control, a critically important aspect of the dynamic organization of mitochondrial networks.

The study found that by mediating asymmetric exchange of mitochondrial contents, fusion and fission accelerate removal of damaged mitochondria (Mouli et al., 2009). The study also found that the selectivity of fusion, which excludes depolarized mitochondria from fusion and leaves them for targeted degradation by autophagy, is crucial because it makes fusion/fission and autophagy complementary rather than competing processes. Based on these findings, the authors proposed that fusion, fission, and autophagy work synergistically as a bioenergetic quality control system (Twig et al., 2008b). Overall, the study demonstrates the power of systems-level modeling and simulation in understanding complex and non-intuitive relations between fusion/fission and degradation/biogenesis and how these diverse activities of individual mitochondria collectively mediate dynamic organization of their networks.

One of the limitations of the study is that its fusion/fission model does not take into account spatial distribution of the mitochondrial network (Mouli et al., 2009). Consequently, the kinetic rates of mitochondrial quality control estimated from the theoretical models could not be directly compared with actual measured rates from experiments. This limitation was resolved in a follow-up study (Patel et al., 2013), in which mitochondrial fusion and fission were modeled spatially within a simple square cell geometry. Attaching and detaching between mitochondria and microtubules were characterized by first-order kinetic rates (Patel et al., 2013), with parameters taken from experimental studies (Liu et al., 2009). Mitochondrial degradation was modeled largely as in (Mouli et al., 2009), but mitochondrial biogenesis was modeled explicitly as a separate replication process. An integrative systems-level model was developed, which took into account all activities of individual mitochondria, including fusion, fission, transport, damage, degradation, replication, and microtubule attaching and detaching, in a spatially dependent manner. Based on the model and Monte-Carlo simulations, the study made several findings. First,

spatial density and motility of mitochondria affect their quality control by modulating frequency of fusion. Second, optimized quality control is achieved when selectivity of fusion and autophagy, defined by thresholds of inner membrane potential Ψ_m, is matched. Third, discrete content exchange in fusion is critical for mitochondrial quality control. The study further demonstrates the power of systems-level modeling and simulation in understanding how complex and diverse activities of individual mitochondria collectively mediate organization of their network.

The two studies reviewed thus far predict that increasing mitochondrial fusion/fission rates would accelerate removal of damaged mitochondria and therefore improve mitochondrial quality control. This prediction, however, was contradicted by experimental observations in several aging models. For example, rates of fusion and fission were found to be significantly reduced in aged cells compared to young cells in a human endothelial cell aging model (Jendrach et al., 2005). Reduction of mitochondrial fission was also found to increase life span and fitness of two fungal aging models (Scheckhuber et al., 2007). To understand the mechanisms underlying these observations, Meyer-Hermann and colleagues developed systems-level models similar to those in the two previously reviewed studies (Figge et al., 2012). However, different from the two studies, they proposed that repeated cycles of fusion and fission facilitate removal of damaged mitochondria but also induce additional damages on daughter mitochondria, which they referred to as "infectious damage" (Figge et al., 2012). Their study could explain how decreasing fusion/fission rates may improve mitochondrial quality control by reducing "infectious damage." Overall, the study provides an example of applying systems-level modeling and analysis to understand how small differences in activities of individual mitochondria can lead to large differences in behavior of their networks.

The studies we have reviewed so far focus on quality control of mitochondrial networks without examining the many specific processes involved in detail. One of such processes is the maintenance of mitochondrial DNA. Systems-level modeling and analysis were used to study this specific process (Tam et al., 2013). It should be emphasized that dynamic organization of mitochondrial networks goes much beyond network quality control. Other important aspects of the organization of mitochondrial networks include maintaining their overall morphological and spatial distribution, which are mediated by fusion/fission and transport/anchoring of mitochondria. Systems-level modeling and analysis have been used to understand these aspects of mitochondrial network organization (Sukhorukov and Meyer-Hermann, 2015).

Modeling and analysis of fusion/fission in dynamic organization of endosomal networks

Fusion and fission also play important roles in mediating dynamic organization of the early endosomal network by enabling content exchange of cargoes to facilitate their distribution and trafficking through the network (Gautreau et al., 2014). Unlike removal of damaged mitochondria from their network by autophagy, early endosomes leave their network primarily through conversion to late endosomes (Bucci et al., 1992; Rink et al., 2005). In addition to fusion and fission, early endosomes can also take up additional cargoes by fusing with endocytic vesicles, or unload cargoes by budding off endocytic vesicles (Gautreau et al., 2014). To understand how these diverse activities of individual early endosomes collectively mediate the organization of their network, Julicher and colleagues developed a systems-level deterministic model of relations between the overall distribution of cargo contents and the activities of individual endosomes over time (Foret et al., 2012). By a high-throughput imaging assay, they experimentally measured the level of low-density lipoprotein (LDL) as a representative of cargo contents in individual endosomes over time. By fitting the overall distributions of LDL based on measurements from thousands of individual endosomes with their theoretical model, they were able to estimate kinetic parameters of cargo trafficking from the experimental data. Their systems-level model could fully account for experimentally measured LDL distributions over time. Overall, the study found that homotypic fusion between endosomes plays a key role in cargo trafficking through the endosome network and that Rab GTPase conversion (Bucci et al., 1992; Rink et al., 2005), rather than vesicle budding, is the main mechanism of cargo transport from early endosomes to late endosomes. Overall, this study demonstrates the power of systems-level modeling and analysis in understanding dynamic organization of a different type of organelle networks.

Discussion

Without systems-level modeling and analysis, it would be very difficult, if not impossible, to fully and quantitatively understand relations between complex and diverse activities of individual organelles and dynamic organization of their networks. However, systems-level modeling and analysis studies such as those reviewed here have their limitations. In particular, systems-level models must make substantially simplified assumptions regarding the complex biochemical processes underlying the activities of individual organelles. Such assumptions, such as those on mitochondrial biogenesis (Mouli et al., 2009; Patel et al., 2013) and on mitochondrial damage (Figge et al., 2012), remain to be experimentally validated. Furthermore, the systems-level models, such as the integrative model in (Patel et al., 2013), also remain to be experimentally validated to ensure they accurately recapitulate key dynamic behavior of the organelle networks. Despite such limitations, the reviewed studies demonstrate that systems-level modeling and analysis are essential in understanding how complex and diverse activities of

individual organelles collectively mediate systems-level organization of their networks.

Understanding dynamic organization of organelle networks through network analysis of their physical connections

Network analysis of physical connections of organelle networks

The systems-level modeling and analysis studies we reviewed so far addressed several important aspects of the dynamic organization of organelle networks, including quality control of mitochondrial networks and cargo distribution in endosomal networks. However, a key aspect of the dynamic organization of organelle networks not addressed by the studies is the way in which their components are physically connected, referred to as the topology of the networks in mathematics. The topology of organelle networks is crucial to their function. For example, a high level of connections protects the mitochondrial network from degradation by autophagy during nutrient starvation and allows it to maintain ATP production to ensure cell survival (Gomes et al., 2011; Rambold et al., 2011; Youle and van der Bliek, 2012). As another example, dynamic connections of the ER network are essential to its close interaction with the cytoskeleton and its communication with other organelles through membrane contacts (Westrate et al., 2015). Thorough and rigorous understanding of connections of organelle networks requires concepts and techniques of network analysis, a technical field developed over the past few decades for studying basic and common properties of networks, especially their topology (Newman, 2003; Barrat et al., 2008; Newman, 2010). Examples of networks are abundant in nature and society, such as ecological networks, social networks, and transportation networks, and inside cells, such as metabolic networks, gene regulatory networks, and cell signaling networks (Barabasi and Oltvai, 2004; Zhu et al., 2007). Despite the diverse sources of these networks, their connections can be understood using the same concepts and techniques of network analysis. Network analysis, for example, has been applied to identify which connections within a network are critical to its structural and functional integrity (Newman, 2003; Barrat et al., 2008; Newman, 2010).

A network is usually represented mathematically by a graph (Fig. 1A), which is a set of components referred to as nodes or vertices, with their connections. Nodes of graphs can represent very different objects, e.g., organelles, genes, or proteins, while their connections, also referred to as edges, represent interaction or association between these objects. Each edge can be assigned a number, referred to as its weight, which represents the level of interaction or association between the objects it connects. Dynamic networks are those whose nodes and edges change over time (Fig. 1B and 1C). Network analysis concepts and techniques have become standard tools in understanding many biological networks (Barabasi and Oltvai, 2004; Zhu et al., 2007). Although network analysis studies of organelle networks such as (Sukhorukov et al., 2012) currently remain very limited, extensive experimental studies on organelle networks already revealed some fundamental properties of their connections. Here, using concepts of network analysis, we review and summarize several distinct topological properties of organelle networks that differentiate them from other biological

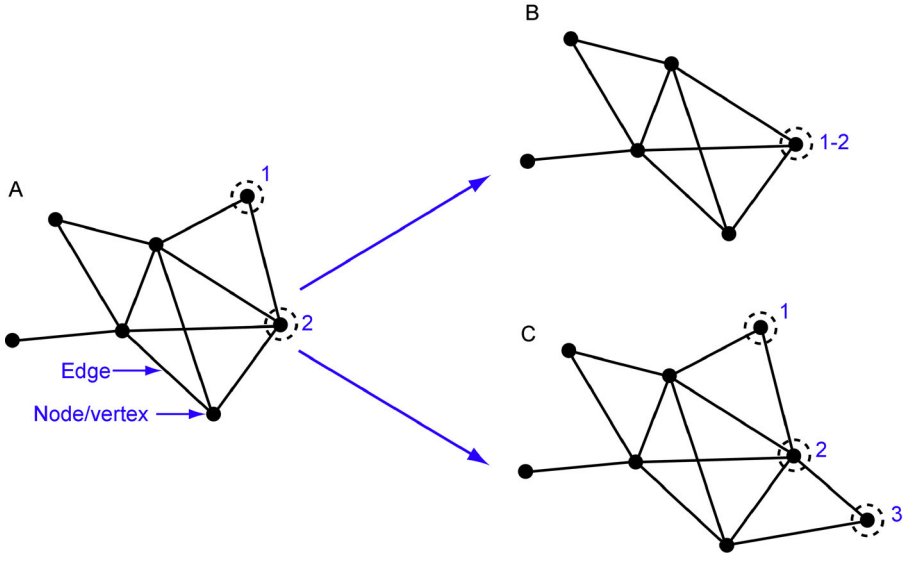

Figure 1 Graph representation of a dynamic network. (A) Graph representation of a network with 7 nodes and 11 edges. (B) The network in (A) after merging of node 1 with node 2. (C) The network in (A) after splitting of node 3 from node 2.

networks such as gene regulatory networks. Given the diversity and complexity of intracellular organelle networks, an exhaustive summary of such properties is not our goal in this paper.

Property I: Organelle networks are dynamic spatial networks

A basic property of the organelle networks is that their topology changes constantly because of organelle activities such as fusion and fission. Figure 2A and 2B show mitochondrial networks in the axon of a Drosophila motor neuron and within a Muntjac skin fibroblast cell, respectively. Individual mitochondria in such networks can be represented by nodes of a graph, and the connection weight between two nodes may be used to represent for example likelihood of fusion between the two mitochondria they represent. Fusion between two mitochondria can be represented by the merger of two nodes into one (Fig. 1B), whereas fission of a single mitochondrion can be represented by the split of one node into two (Fig. 1C). For the highly interconnected tubular network of ER (Fig. 2C), the branching points and the end/terminal points can be naturally represented by nodes of a graph, whereas their physical connections can be represented by edges. In this case, branching of new tubules can be represented by splitting of existing nodes and addition of new connections, while merging of existing tubules can be represented by merging of existing nodes and removal of their connections. Since their topology changes constantly, mitochondrial networks and ER networks are dynamic networks by definition (Barabasi and Oltvai, 2004; Boccaletti et al., 2006). They are different from, for example, gene regulatory networks whose nodes, i.e., genes, do not merge or split.

Another basic property of the organelle networks is that their spatial distribution changes constantly because of organelle activities such as transport and anchoring. Organelle networks generally maintain characteristic spatial distributions, which enable them to serve their functions within the heterogeneous intracellular environment. In particular, proper spatial distributions of organelles are essential for their communication through membrane fusion or membrane contact because such interactions require physical proximity between organelles. In response to internal or external stimuli, organelle networks can drastically change their spatial distributions. For example, under nutrient starvation and autophagy induction, lysosomal networks can change from their typically uniform distribution in the cytoplasm to aggregation in the perinuclear region for fusion with autophagosomes (Korolchuk et al., 2011; Li et al., 2016). Since their function depends critically on their spatial distribution, intracellular organelle networks are spatial networks by definition (Boccaletti et al., 2006).

Although the identification of organelle networks as dynamic spatial networks is conceptually very simple, it establishes connections to a wide range of analysis techniques developed for studying dynamic and spatial networks (Boccaletti et al., 2006; Barrat et al., 2008). For example, robustness analysis techniques developed for studying dynamic networks (Boccaletti et al., 2006) may be used to determine whether partial damage of an organelle network will cause cascading failure of the entire network, and population analysis techniques developed for studying spatial behavior of ecological networks (Campbell et al., 2007) may be used to understand the spatial behavior of organelle networks.

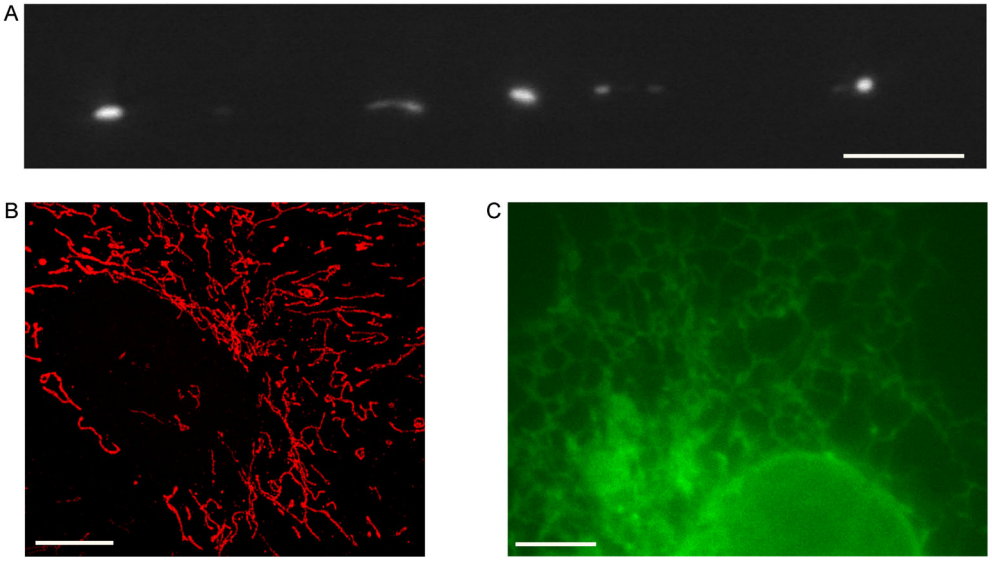

Figure 2 Examples of different topology exhibited by different organelle networks. (A) Discrete mitochondrial compartments in the axon of a Drosophila motor neuron. Scale bar: 10 μm. (B) Partially connected mitochondrial tubules in a Muntjac skin fibroblast cell. Scale bar: 2 μm. (C) Extensively connected ER network in a COS-7 cell. Scale bar: 2 μm.

Property II: Organelle networks maintain size homeostasis in interphase but undergo size scaling and division in cell division

Despite that organelle networks undergo constant turnover in their components and connections, they maintain an overall dynamic equilibrium in their structure and function, a concept referred to as organelle homeostasis, an essential part of cell homeostasis. A basic requirement of organelle homeostasis is that individual organelles and their networks maintain stable physical sizes. Several hypotheses regarding how cells sense and regulate sizes of their organelles have been proposed (Chan and Marshall, 2012; Marshall, 2015), and advances have been made in dissecting molecular machineries and mechanisms for size control of some organelles, such as the Golgi apparatus (Sengupta and Linstedt, 2011) and certain secretory granules (Ferraro et al., 2014). Overall, however, our knowledge of related molecular machineries and mechanisms remains limited. Remarkably, organelle homeostasis is temporarily broken during cell division when intracellular organelle networks undergo doubling in size and are then divided equally between the two daughter cells, a process referred to as organelle inheritance (Warren and Wickner, 1996). The ability of organelles networks to maintain their sizes during interphase and to undergo controlled size doubling during cell division is one of their unique properties.

The dramatic changes of the organelle networks during cell division provide unique opportunities to further understand their dynamic organization. Organelle inheritance has been studied extensively in yeast cells (Knoblach and Rachubinski, 2015). In a recent study, size scaling of the mitochondrial network in budding yeast during its asymmetric cell division was quantitatively analyzed (Rafelski et al., 2012). The study found that yeast cells actively sense sizes of their mitochondrial networks and maintain a stable ratio between mitochondrial network size and cell size despite asymmetry in cell division. An earlier study of HeLa cells found similar mitochondrial network size scaling during cell division (Posakony et al., 1977). Overall, the studies suggest the existence of a mechanism for global organelle network size control. After their size scaling, organelle networks can be divided equally through cytokinesis without active regulation (Warren and Wickner, 1996). However, recent studies have indicated that division of at least some organelle networks may be actively regulated (Rohn et al., 2014; Shneyer et al., 2016).

Property III: Organelle networks are structurally and functionally heterogeneous

The intracellular environment is dynamically organized and highly heterogeneous. In response to this environment, many organelle networks exhibit substantial heterogeneity in their structure and function. For example, individual mitochondria within their network were found to be remarkably heterogeneous in their morphology, spatial distribution, and function in a wide variety of cell lines (Collins et al., 2002), and potential mechanisms underlying such heterogeneity have been discussed (Kuznetsov and Margreiter, 2009; Wikstrom et al., 2009). Heterogeneity of the mitochondrial network is also apparent in neurons, which are structurally and functionally polarized. Within mature neurons, only around 30%–40% mitochondria were found to be motile (Kang et al., 2008; Yu et al., 2016), and stationary and moving mitochondria were found to differ substantially in their morphology, spatial distribution, and function (Yu et al., 2016). As another example, the network of endosomes is also heterogeneous because it consists of three structurally and functionally different subgroups: early endosomes, late endosomes, and recycling endosomes (Grant and Donaldson, 2009; Huotari and Helenius, 2011). Networks of single-copy organelles such as ER and Golgi are also structurally and functionally heterogeneous as they are organized into different domains or modules (Klumperman, 2011; Nakamura et al., 2012; Westrate et al., 2015). Overall, structural and functional heterogeneity of organelle networks is often closely associated with their spatial distributions. Different subgroups or domains of the networks are often spatially separated or exhibit different spatial patterns. Although other biological networks such as gene regulatory networks and cell signaling networks are also organized into separate modules (Barabasi and Oltvai, 2004; Zhu et al., 2007), these modules are defined by structural and functional interactions between genes or signaling molecules, whereas modules or domains of organelle networks are defined by their actual physical structures. Network analysis techniques developed for heterogeneous networks (Newman, 2003; Boccaletti et al., 2006; Newman, 2010) may be used for studying organelle networks.

Discussion

Owing to the distinct properties of organelle networks, which differentiate them from other biologic networks such as gene regulatory networks and cell signaling networks, new network analysis methods are required to fully understand such properties.

Understanding communication between different organelle networks through systems-level modeling and analysis

So far, our focus has been on systems-level modeling and analysis studies of dynamic organization of single organelle networks. Since specialized functions of different organelle networks must be coordinated and integrated for cell physiology, communication between them is crucial. Vesicle trafficking (Bonifacino and Glick, 2004; Lee et al., 2004)

(Fig. 3A) and membrane fusion (Martens and McMahon, 2008; McNew et al., 2013) (Fig. 3B) have been extensively studied as two key mechanisms for communication between different organelle networks. Recent findings on membrane contact sites (MCSs) (Fig. 3C) have established membrane contact as another key communication mechanism (Helle et al., 2013; Prinz, 2014; Schrader et al., 2015). Here, we briefly review several systems-level modeling and analysis studies for understanding communication between different organelle networks.

Coupling between different organelle networks through their communication

Vesicle trafficking and membrane fusion enable communication between a selected group of organelle networks, including communication between the ER network and the Golgi network and between the endosomal network and the lysosomal network. In comparison, the range of organelle network communication enabled by membrane contact is much broader. To date, MCSs have been identified between nearly all intracellular organelles (Helle et al., 2013; Prinz, 2014; Schrader et al., 2015) (Fig. 3D). While early studies on MCSs have identified their roles in mediating ion and lipid exchange between organelles, recent studies have also revealed their roles in mediating cellular functions such as intracellular cell signaling, organelle fission, distribution, and inheritance (Elbaz and Schuldiner, 2011; Helle et al., 2013; Klecker et al., 2014; Prinz, 2014; Schrader et al., 2015; Levine and Patel, 2016; Murley and Nunnari, 2016). For example, in addition to mediating lipid transfer and biosynthesis (Murley and Nunnari, 2016; Phillips and Voeltz, 2016) as well as Ca^{2+} exchange and homeostasis (Csordás et al., 2010; Murley and Nunnari, 2016), membrane contacts between ER and mitochondria also mark sites of mitochondrial fission (Friedman et al., 2011). Owing to their extensive communication, different organelle networks are structurally and functionally coupled. As specialized functions of different organelle networks must be coordinated and integrated at the systems-level, systems-level modeling and analysis are required for understanding related mechanisms.

Modeling and analysis of communication between different organelle networks in cellular calcium homeostasis

Ca^{2+} is an important cellular signal that regulates a broad range of cellular processes. Ca^{2+} signaling is mediated by an extensive molecular toolkit (Berridge et al., 2003). Major organelle networks involved in Ca^{2+} signaling include networks of the ER, Golgi, mitochondria, endosome, and lysosome (Dupont et al., 2016). Their primary function is to sequester and release Ca^{2+}. To maintain a dynamic equilibrium of Ca^{2+} signaling within the cellular environment, referred to as calcium homeostasis (Carafoli, 1987; Brini et al., 2013), specialized functions of the organelle networks involved must be coordinated and integrated through communication between them. Systems-level modeling and analysis have been used extensively in related studies to understand detailed mechanisms.

A system-level model was developed to study Ca^{2+} homeostasis globally in yeast cells (Cui and Kaandorp, 2006), in which vacuoles (yeast lysosomes) and ER/Golgi were modeled as Ca^{2+} stores and uptake of Ca^{2+} was modeled using a Michaelis-Menten equation. The study could explain how a low cytosolic Ca^{2+} level is maintained under a high extracellular Ca^{2+} level through feedback control and why this feedback control is robust against fluctuations in the extracellular Ca^{2+} level. Exchange of Ca^{2+} through membrane contact was not modeled explicitly (Cui and Kaandorp, 2006) but was studied in great detail by Patel and colleagues (Penny et al., 2014), in which systems-level modeling and

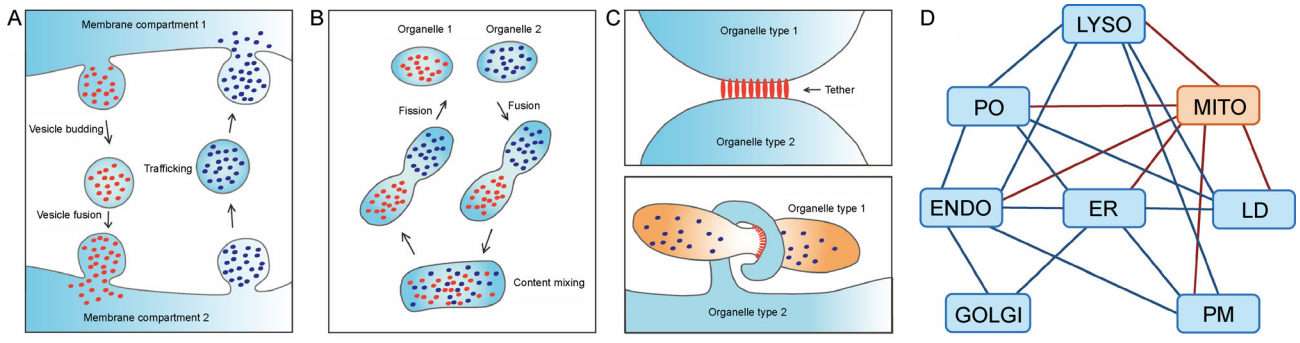

Figure 3 Currently known mechanisms for communication between different types of organelle networks. (A) Communication through vesicle trafficking. (B) Communication through membrane fusion and fission. (C) Communication through membrane contact. Upper panel: membrane contact is mediated by tether proteins, shown in red. Lower panel: membrane contact mediates a wide range of cellular functions, such as organelle fission. (D) A diagram that summarizes some currently known communication pathways between organelle networks. All organelles except mitochondria belong to the endomembrane system, hence the different colors. ENDO, endosome; ER, endoplasmic reticulum; GOLGI, Golgi apparatus; LD, lipid droplets; LYSO, lysosome; MITO, mitochondria; PM, plasma membrane; PO, peroxisome.

analysis were used to understand the behavior of Ca^{2+} microdomains (Csordás et al., 2010) at lysosome-ER contact sites. The proposed systems-level model consisted of four compartments including the lysosome, ER, microdomain, and cytosol. The study found that the distribution and density of lysosomal enzyme leakage largely determined the function of microdomains (Penny et al., 2014). Neither of these two studies took into account how different geometric shapes of organelles may affect their function. This question was addressed by a numerical simulation study of the propagation of Ca^{2+} in realistic ER geometry (Means et al., 2006). Overall, systems-level modeling and analysis studies have been conducted extensively to understand how functions of different organelle networks are coordinated and integrated in mediating Ca^{2+} homeostasis, including how MCSs contribute to the coordination and integration (Dupont et al., 2016). An important strategy utilized by these studies is to characterize MCSs at the functional rather than structural level. In this way, detailed knowledge of diverse MCS molecular machineries in different organelles can be effectively integrated for understanding their roles in Ca^{2+} homeostasis.

Conclusions and outlook

Significant advances have been made recently in our understanding of the molecular machineries and mechanisms that mediate communication between intracellular organelles, especially in our understanding of MCSs. These advances highlighted the fact that the organelles are structurally and functionally organized as networks. In this paper, we focused on reviewing systems-level studies for a holistic understanding of the organization and communication of the organelle networks. The studies reviewed demonstrate the essential role of systems-level modeling and analysis in understanding how complex and diverse activities of individual organelles collectively mediate dynamic behavior of their networks. Overall, understanding the organization and communication of the organelle networks will provide critical insights into how the internal environment of eukaryotic cells is organized and will enable us to engineer the organelle networks effectively for applications such as targeted intracellular delivery for disease intervention (Torchilin, 2006; Ma et al., 2016).

However, fundamental questions regarding the organization of individual organelle networks remain to be answered. For example, our understanding of the topological properties of the organelle networks remains limited. We still cannot explain how the networks of organelles such as mitochondria not only maintain homeostasis against perturbations but also rapidly break from such homeostasis to respond to the changing needs of cells. Given our knowledge of the substantial heterogeneity in the organelle networks, are some parts of the networks structurally and functionally more important than others? Are there common principles that govern the topology of all organelle networks? Or, do different organelle networks follow different principles? Established network analysis techniques, which have found broad applications in studying, for example, gene regulatory networks and cell signaling networks, will help answer these questions, but new network analysis techniques will also need to be developed to fully understand the distinct properties of organelle networks.

Fundamental questions regarding the communication between different organelle networks also remain to be answered. For example, a key requirement of communication through membrane fusion or membrane contact is spatial proximity of the organelles involved. Currently, however, our understanding of how the organelle networks are spatially distributed remains limited. Do contacts between organelles change spatial distribution of their networks, or vice versa? How are membrane contacts established in the highly polarized neurons? Another important question is how specialized functions of different organelle networks are coordinated and integrated through their communication at the whole-cell level to rapidly respond to different stimuli. Answering these questions also requires new tools for characterizing and modeling communication and coordination between different organelle networks. Techniques such as agent-based modeling (Sukhorukov et al., 2012; Namtame and Chen, 2016) may become essential for this purpose. Despite the technical challenges ahead, there is no doubt that the extraordinary intricacy and functionality of intracellular organelle networks will provide many exciting opportunities for discoveries.

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Compliance with ethics guidelines

Qinle Ba and Ge Yang declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

Barabasi A L, Oltvai Z N (2004). Network biology: understanding the cell's functional organization. Nat Rev Genet, 5(2): 101–113

Barrat A, Barthelemy M, Vespignani A (2008). Dynamic Processes on Complex Networks. Cambridge University Press.

Barsoum M J, Yuan H, Gerencser A A, Liot G, Kushnareva Y, Gräber S, Kovacs I, Lee W D, Waggoner J, Cui J, White A D, Bossy B, Martinou J C, Youle R J, Lipton S A, Ellisman M H, Perkins G A,

Bossy‐Wetzel E (2006). Nitric oxide‐induced mitochondrial fission is regulated by dynamin‐related GTPases in neurons. EMBO J, 25(16): 3900–3911

Berridge M J, Bootman M D, Roderick H L (2003). Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol, 4 (7): 517–529

Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang D U (2006). Complex networks: Structure and dynamics. Phys Rep, 424(4-5): 175–308

Bonifacino J S, Glick B S (2004). The mechanisms of vesicle budding and fusion. Cell, 116(2): 153–166

Brandhorst D, Zwilling D, Rizzoli S O, Lippert U, Lang T, Jahn R (2006). Homotypic fusion of early endosomes: SNAREs do not determine fusion specificity. Proc Natl Acad Sci USA, 103(8): 2701–2706

Brini M, Calì T, Ottolini D, Carafoli E (2013). Intracellular Calcium Homeostasis and Signaling. In: Banci L, editor. Metallomics and the Cell. Springer Netherlands, Dordrecht. 119–168

Bucci C, Parton R G, Mather I H, Stunnenberg H, Simons K, Hoflack B, Zerial M (1992). The small GTPase rab5 functions as a regulatory factor in the early endocytic pathway. Cell, 70(5): 715–728

Campbell G E H, Lowe W H, Fagan W F (2007). Living in the branches: population dynamics and ecological processes in dendritic networks. Ecol Lett, 10(2): 165–175

Carafoli E (1987). Intracellular calcium homeostasis. Annu Rev Biochem, 56(1): 395–433

Chan D C (2012). Fusion and fission: interlinked processes critical for mitochondrial health. Annu Rev Genet, 46(1): 265–287

Chan Y H M, Marshall W F (2012). How cells know the size of their organelles. Science, 337(6099): 1186–1189

Chen H, Chan D C (2009). Mitochondrial dynamics–fusion, fission, movement, and mitophagy–in neurodegenerative diseases. Hum Mol Genet, 18(R2): R169–R176

Collins T J, Berridge M J, Lipp P, Bootman M D (2002). Mitochondria are morphologically and functionally heterogeneous within cells. EMBO J, 21(7): 1616–1627

Csordás G, Várnai P, Golenár T, Roy S, Purkins G, Schneider T G, Balla T, Hajnóczky G (2010). Imaging interorganelle contacts and local calcium dynamics at the ER-mitochondrial interface. Mol Cell, 39(1): 121–132

Cui J, Kaandorp J A (2006). Mathematical modeling of calcium homeostasis in yeast cells. Cell Calcium, 39(4): 337–348

Dupont G, Falcke M, Kirk V, Sneyd J (2016). Models of Calcium Signaling. Springer International Publishing

Elbaz Y, Schuldiner M (2011). Staying in touch: the molecular era of organelle contact sites. Trends Biochem Sci, 36(11): 616–623

Elmore S P, Qian T, Grissom S F, Lemasters J J (2001). The mitochondrial permeability transition initiates autophagy in rat hepatocytes. FASEB J, 15(12): 2286–2287

Ferraro F, Kriston-Vizi J, Daniel J (2014). A two-tier Golgi-based control of organelle size underpins the functional plasticity of endothelial cells. Dev Cell, 29(3): 292–304

Figge M T, Reichert A S, Meyer-Hermann M, Osiewacz H D (2012). Deceleration of fusion-fission cycles improves mitochondrial quality control during aging. PLOS Comput Biol, 8(6): e1002576

Foret L, Jonathan E D, Villasenor R, Collinet C, Deutsch A, Brusch L, Zerial M, Kalaididis Y, Julicher E. (2012). A general theoretical framework to infer endosomal network dynamics from quantitative image analysis. Curr Biol, 22(15): 1381–1390

Frazier A E, Kiu C, Stojanovski D, Hoogenraad Nicholas J, Ryan Michael T (2006). Mitochondrial morphology and distribution in mammalian cells. Biol Chem, 387(12): 1551–1558

Frederick R L, Shaw J M (2007). Moving mitochondria: establishing distribution of an essential organelle. Traffic, 8(12): 1668–1675

Friedman J R, Lackner L L, West M, DiBenedetto J R, Nunnari J, Voeltz G K (2011). ER tubules mark sites of mitochondrial division. Science, 334(6054): 358–362

Gautreau A, Oguievetskaia K, Ungermann C (2014). Function and regulation of the endosomal fusion and fission machineries. Cold Spring Harb Perspect Biol, 6(3): a016832

Gomes L C, Benedetto G D, Scorrano L (2011). During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. Nat Cell Biol, 13(5): 589–598

Grant B D, Donaldson J G (2009). Pathways and mechanisms of endocytic recycling. Nat Rev Mol Cell Biol, 10(9): 597–608

Helle S C J, Kanfer G, Kolar K, Lang A, Michel A H, Kornmann B (2013). Organization and function of membrane contact sites. *Biochimica et Biophysica Acta (BBA)* - Mol Cell Res, 1833(11): 2526–2541

Hoppins S, Lackner L, Nunnari J (2007). The machines that divide and fuse mitochondria. Annu Rev Biochem, 76(1): 751–780

Huotari J, Helenius A (2011). Endosome maturation. EMBO J, 30(17): 3481–3500

Jakobs S, Schauss A C, Hell S W (2003). Photoconversion of matrix targeted GFP enables analysis of continuity and intermixing of the mitochondrial lumen. FEBS Lett, 554(1-2): 194–200

Jendrach M, Pohl S, Vöth M, Kowald A, Hammerstein P, Bereiter-Hahn J (2005). Morpho-dynamic changes of mitochondria during ageing of human endothelial cells. Mech Ageing Dev, 126(6-7): 813–821

Kang J S, Tian J H, Pan P Y, Zald P, Li C, Deng C, Sheng Z H (2008). Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation. Cell, 132(1): 137–148

Karbowski M, Arnoult D, Chen H, Chan D C, Smith C L, Youle R J (2004). Quantitation of mitochondrial dynamics by photolabeling of individual organelles shows that mitochondrial fusion is blocked during the Bax activation phase of apoptosis. J Cell Biol, 164(4): 493–499

Klecker T, Böckler S, Westermann B (2014). Making connections: interorganelle contacts orchestrate mitochondrial behavior. Trends Cell Biol, 24(9): 537–545

Klumperman J (2011). Architecture of the mammalian Golgi. Cold Spring Harb Perspect Biol, 3(7): a005181

Knoblach B, Rachubinski R A (2015). Sharing the cell's bounty – organelle inheritance in yeast. J Cell Sci, 128(4): 621–630

Korolchuk V I, Saiki S, Lichtenberg M, Siddiqi F H, Roberts E A, Imarisio S, Jahreiss L, Sarkar S, Futter M, Menzies F M, O'Kane C J, Deretic V, Rubinsztein D C (2011). Lysosomal positioning coordinates cellular nutrient responses. Nat Cell Biol, 13(4): 453–460

Kuznetsov A V, Hermann M, Saks V, Hengster P, Margreiter R (2009). The cell-type specificity of mitochondrial dynamics. Int J Biochem Cell Biol, 41(10): 1928–1939

Kuznetsov A V, Margreiter R (2009). Heterogeneity of mitochondria and mitochondrial function within cells as another level of mitochondrial complexity. Int J Mol Sci, 10(4): 1911–1929

Labbé K, Murley A, Nunnari J (2014). Determinants and functions of mitochondrial behavior. Annu Rev Cell Dev Biol, 30(1): 357–391

Lee M C S, Miller E A, Goldberg J, Orci L, Schekman R (2004). Bi-directional protein transport between the ER and Golgi. Annu Rev Cell Dev Biol, 20(1): 87–123

Levine T P, Patel S (2016). Signalling at membrane contact sites: two membranes come together to handle second messengers. Curr Opin Cell Biol, 39: 77–83

Li X, Rydzewski N, Hider A, Zhang X, Yang J, Wang W, Gao Q, Cheng X, Xu H (2016). A molecular mechanism to regulate lysosome motility for lysosome positioning and tubulation. Nat Cell Biol, 18 (4): 404–417

Liu X, Weaver D, Shirihai O, Hajnóczky G (2009). Mitochondrial 'kiss‐and‐run': interplay between mitochondrial motility and fusion–fission dynamics. EMBO J, 28(20): 3074–3089

Luzio J P, Pryor P R, Bright N A (2007). Lysosomes: fusion and function. Nat Rev Mol Cell Biol, 8(8): 622–632

Ma X, Gong N, Zhong L, Sun J, Liang X J (2016). Future of nanotherapeutics: targeting the cellular sub-organelles. Biomat, 97: 10–21

Marshall W F (2015). How cells measure length on subcellular scales. Trends Cell Biol, 25(12): 760–768

Martens S, McMahon H T (2008). Mechanisms of membrane fusion: disparate players and common principles. Nat Rev Mol Cell Biol, 9 (7): 543–556

McNew J A, Sondermann H, Lee T, Stern M, Brandizzi F (2013). GTP-dependent membrane fusion. Annu Rev Cell Dev Biol, 29(1): 529–550

Means S, Smith A J, Shepherd J, Shadid J, Fowler J, Wojcikiewicz R J H, Mazel T, Smith G D, Wilson B S (2006). Reaction diffusion modeling of calcium dynamics with realistic ER geometry. Biophys J, 91(2): 537–557

Mizushima N (2007). Autophagy: process and function. Genes Dev, 21 (22): 2861–2873

Mouli P K, Twig G, Shirihai O S (2009). Frequency and selectivity of mitochondrial fusion are key to its quality maintenance function. Biophys J, 96(9): 3509–3518

Murley A, Nunnari J (2016). The emerging network of mitochondria-organelle contacts. Mol Cell, 61(5): 648–653

Nakamura N, Wei J H, Seemann J (2012). Modular organization of the mammalian Golgi apparatus. Curr Opin Cell Biol, 24(4): 467–474

Nakatogawa H, Suzuki K, Kamada Y, Ohsumi Y (2009). Dynamics and diversity in autophagy mechanisms: lessons from yeast. Nat Rev Mol Cell Biol, 10(7): 458–467

Namtame A, Chen S H (2016). Agent-based Modeling and Network Analysis. Oxford University Press

Newman M E J (2003). The structure and function of complex networks. SIAM Rev, 45(2): 167–256

Newman M E J 2010. Networks. Oxford University Press.

Ni H M, Williams J A, Ding W X (2015). Mitochondrial dynamics and mitochondrial quality control. Redox Biol, 4: 6–13

Nunnari J, Walter P (1996). Regulation of organelle biogenesis. Cell, 84 (3): 389–394

Okamoto K, Shaw J M (2005). Mitochondrial morphology and dynamics in yeast and multicellular eukaryotes. Annu Rev Genet, 39(1): 503–536

Palikaras K, Tavernarakis N (2014). Mitochondrial homeostasis: The interplay between mitophagy and mitochondrial biogenesis. Exp Gerontol, 56: 182–188

Patel P K, Shirihai O, Huang K C (2013). Optimal dynamics for quality control in spatially distributed mitochondrial networks. PLOS Comput Biol, 9(7): e1003108

Penny C J, Kilpatrick B S, Han J M, Sneyd J, Patel S (2014). A computational model of lysosome–ER Ca^{2+} microdomains. J Cell Sci, 127(13): 2934–2943

Phillips M J, Voeltz G K (2016). Structure and function of ER membrane contact sites with other organelles. Nat Rev Mol Cell Biol, 17(2): 69–82

Posakony J W, England J M, Attardi G (1977). Mitochondrial growth and division during the cell cycle in HeLa cells. J Cell Biol, 74(2): 468–491

Priault M, Salin B, Schaeffer J, Vallette F M, di Rago J P, Martinou J C (2005). Impairing the bioenergetic status and the biogenesis of mitochondria triggers mitophagy in yeast. Cell Death Differ, 12(12): 1613–1621

Prinz W A (2014). Bridging the gap: membrane contact sites in signaling, metabolism, and organelle dynamics. J Cell Biol, 205(6): 759–769

Rafelski S M, Viana M P, Zhang Y, Chan Y H M, Thorn K S, Yam P, Fung J C, Li H, Costa L D F, Marshall W F (2012). Mitochondrial network size scaling in budding yeast. Science, 338(6108): 822–824

Rambold A S, Kostelecky B, Elia N, Lippincott-Schwartz J (2011). Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc Natl Acad Sci USA, 108(25): 10190–10195

Rink J, Ghigo E, Kalaidzidis Y, Zerial M (2005). Rab conversion as a mechanism of progression from early to late endosomes. Cell, 122 (5): 735–749

Rohn J L, Patel J V, Neumann B, Bulkescher J, Mchedlishvili N, McMullan R C, Quintero O A, Ellenberg J, Baum B (2014). Myo19 ensures symmetric partitioning of mitochondria and coupling of mitochondrial segregation to cell division. Curr Biol, 24(21): 2598–2605

Rutter G A, Rizzuto R (2000). Regulation of mitochondrial metabolism by ER Ca^{2+} release: an intimate connection. Trends Biochem Sci, 25 (5): 215–221

Scheckhuber C Q, Erjavec N, Tinazli A, Hamann A, Nystrom T, Osiewacz H D (2007). Reducing mitochondrial fission results in increased life span and fitness of two fungal ageing models. Nat Cell Biol, 9(1): 99–105

Schrader M, Godinho L F, Costello J, Islinger M (2015). The different facets of organelle interplay-an overview of organelle interactions. Front Cell Dev Biol, 3: 56

Sengupta D, Linstedt A D (2011). Control of organelle size: The Golgi complex. Annu Rev Cell Dev Biol, 27(1): 57–77

Sheng Z H (2014). Mitochondrial trafficking and anchoring in neurons: new insight and implications. J Cell Biol, 204(7): 1087–1098

Sheng Z H, Cai Q (2012). Mitochondrial transport in neurons: impact on synaptic homeostasis and neurodegeneration. Nat Rev Neurosci, 13 (2): 77–93

Shneyer B I, Ušaj M, Henn A (2016). Myo19 is an outer mitochondrial membrane motor and effector of starvation-induced filopodia. J Cell Sci, 129(3): 543–556

Sukhorukov V M, Dikov D, Reichert A S, Meyer-Hermann M (2012).

Emergence of the mitochondrial reticulum from fission and fusion dynamics. PLOS Comput Biol, 8(10): e1002745

Sukhorukov V M, Meyer-Hermann M (2015). Structural heterogeneity of mitochondria induced by the microtubule cytoskeleton. Sci Rep, 5: 13924

Tam Z Y, Gruber J, Halliwell B, Gunawan R (2013). Mathematical modeling of the role of mitochondrial fusion and fission in mitochondrial DNA maintenance. PLoS One, 8(10): e76230

Torchilin V P (2006). Recent approaches to intracellular delivery of drugs and DNA and organelle targeting. Annu Rev Biomed Eng, 8 (1): 343–375

Twig G, Elorza A, Molina A J A, Mohamed H, Wikstrom J D, Walzer G, Stiles L, Haigh S E, Katz S, Las G, Alroy J, Wu M, Py B F, Yuan J, Deeney J T, Corkey B E, Shirihai O S (2008a). Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J, 27(2): 433–446

Twig G, Hyde B, Shirihai O S (2008b). Mitochondrial fusion, fission and autophagy as a quality control axis: The bioenergetic view. *Biochimica et Biophysica Acta (BBA)* - Bioenergetics, 1777(9): 1092–1097

Twig G, Liu X, Liesa M, Wikstrom J D, Molina A J A, Las G, Yaniv G, Hajnóczky G, Shirihai O S (2010). Biophysical properties of mitochondrial fusion events in pancreatic β-cells and cardiac cells unravel potential control mechanisms of its selectivity. Am J Physiol Cell Physiol, 299(2): C477–C487

Warren G, Wickner W (1996). Organelle inheritance. Cell, 84(3): 395–400

Westrate L M, Lee J E, Prinz W A, Voeltz G K (2015). Form follows function: The importance of endoplasmic reticulum shape. Annu Rev Biochem, 84(1): 791–811

Wikstrom J D, Twig G, Shirihai O S (2009). What can mitochondrial heterogeneity tell us about mitochondrial dynamics and autophagy? Int J Biochem Cell Biol, 41(10): 1914–1927

Youle R J, Narendra D P (2011). Mechanisms of mitophagy. Nat Rev Mol Cell Biol, 12(1): 9–14

Youle R J, van der Bliek A M (2012). Mitochondrial fission, fusion, and stress. Science, 337(6098): 1062–1065

Yu Y, Lee H C, Chen K C, Suhan J, Qiu M, Ba Q, Yang G (2016). Inner membrane fusion mediates spatial distribution of axonal mitochondria. Sci Rep, 6: 18981

Zhu X, Gerstein M, Snyder M (2007). Getting connected: analysis and principles of biological networks. Genes Dev, 21: 1010–1024