JB Commentary

Paradigm shift from ‘Compartment’ to ‘Zone’ in the understanding of organelles

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Organelles are intracellular compartments that are delineated by lipid bilayers and play specific roles in regulating various cellular events. Organelle dysfunction contributes to the pathological mechanisms of various diseases. The development and prevalence of super-resolved fluorescence microscopy have enabled the characterization of various functional regions and organelar dynamics by a number of cell biologists. These local functional organelle regions are named ‘zones’, and three review articles in this issue summarize three different organelle zones, namely, the ‘Response zone’, ‘Communication zone’ and ‘Sorting zone’. This newest organelar concept may shed light on a novel biological aspect and the elucidation of mechanisms of unresolved diseases.

Keywords: communication zone; organelle zone; organelar communication; response zone; sorting zone.


Abbreviations: ER, endoplasmic reticulum; ERES, ER exit sites; PALM, photo-activated localization microscopy.

A eukaryotic cell is subdivided into multiple membrane-enclosed compartments termed organelles. Each organelle comprises its own characteristic set of phospholipids, membrane proteins, luminal proteins, ions and other molecules, and exerts its own specialized function. Complex and elaborate systems for the precise placement of organelle-localized molecules enable the maintenance of organelar homeostasis, resulting in the strictly regulated function of eukaryotic cells. To date, a number of researchers have revealed detailed mechanisms of protein translocation into organelles [e.g. the endoplasmic reticulum (ER), Golgi apparatus, mitochondrion, chloroplast, peroxisome or nucleus] and intracellular vesicular traffic from the ER to other organelles or the plasma membrane. Moreover, organelles have been shown to maintain their quality via highly conserved systems from yeast to mammals. For example, the ER restores its stress condition via an ER stress sensor-mediated signaling pathway called the unfolded protein response (1, 2). The removal of damaged mitochondria by selective autophagy, a process called mitophagy, and fusion/fission is critical for maintaining proper cellular functions (3, 4). However, cell biologists are also aware that there are a number of questions that need to be resolved in the organelar research field. During protein sorting, are a variety of cargo proteins transported among organelles by the same vesicle and do these proteins diffuse in budding organelles or targeted organelles? Is the structure of one organelle uniform? The ER is a single organelle that is spread throughout the cell and consists of two structurally different types, namely, sheets and tubules; however, whether there is a functional difference between the two is unclear. Although the organelle exerts its own physiological function through the membrane, do the functional sites broadly distribute anywhere on one organelle membrane? When we focus on organelar communication, electron microscopic analysis of intracellular structure reveals a number of membrane contacts between one organelle and another (e.g. the ER-mitochondria). For what purpose do these organelles touch each other? The recent rapid development of imaging techniques has clarified the details of organelle dynamics, demonstrating that (i) various functional regions are dynamically formed within organelles and that (ii) organelar functions are made possible by the comprehensive actions of these functional regions. These functional regions have been named ‘organelle zones’ (Fig. 1).

Cell biological analysis of organelar molecules has been based on confocal laser scanning microscopy, which is limited by its resolution of cellular structures or molecules that are at least 200–350 nm apart. The new super-resolution technologies dramatically improve fluorescence microscopy and enable resolution in the range of ~30–100 nm (5). These super-resolved fluorescence microscopic approaches [structured illumination microscopy, stimulated emission depletion microscopy, photoactivated localization microscopy (PALM) and stochastic optical reconstruction microscopy] are now commercially available for researchers and will clarify the details of organelle zones. Moreover, several of the newest experimental techniques, including fluorescent molecular probes, multiwell cell imaging microscopy, genome-wide gene deletion systems involving siRNA or clustered regularly interspaced short palindromic repeat (CRISPR) Cas and highly sensitive mass spectrometry, will provide a paradigm shift from the intracellular compartment to the organelle zone in our understanding of organelles.

Response zone in the organelle

Mitochondria are multifunctional organelles that produce ATP and heat, initiate cell death and activate...
innate immunity against RNA viruses. The ER possesses multiple functions, including the generation of transmembrane and secretory proteins, phospholipids and cholesterol; the storage of calcium ions; and protection against virus infection. In addition to mitochondria and the ER, other organelles (e.g. the Golgi apparatus and lysosome) are also multifunctional organelles, and their organelar stress responses must be mediated without any confusion (6). For each organelle to exert its multiple functions, a ‘Response zone’, which is a specific functional region that appears in organelles in response to various stressors, is strategically beneficial for each organelle. As an example, analysis of Bak localization during apoptosis using PALM has revealed that Bak proteins are broadly dispersed on the mitochondrial outer membrane, whereas death stimuli induce cluster formation in limited areas of the outer membrane. These results suggest that the emergence of the apoptosis response zone depends on the mitochondrial alteration. Shimizu summarizes various mitochondrial response zones in this issue (7).

Communication zone in the organelle

One organelle forms contact sites with multiple other organelles simultaneously (8). These ‘Communication zones’ enable the exchange of various molecules between different organelles and permit the functional integrity of organelles in eukaryotic cells. However, the entity of tethering factors among organelles is mostly unexplored except for the ER–mitochondria encounter structure complex, which directly connects the ER membrane to the mitochondrial outer membrane in yeast (9). Although several tethering factors of ER–mitochondria contact sites in mammals have been reported (10), the mitochondria-associated ER membrane is still controversial. The ER-mitochondria contact site contributes to a number of biological functions, such as lipid synthesis and transport, calcium transport, apoptosis, mitochondrial DNA synthesis, mitochondrial division and autophagosome formation. There might be different tethering factors in the organelar communication zone that are responsible for each biological function. An elucidation of the essential molecules involved in the formation of these organelle contact sites is desirable, and the visualization of inter-organelle contact sites using fluorescent probes might be useful.

Sorting zone in the organelle

The ‘Sorting zone’ is a region within the ER and Golgi apparatus, in which macromolecules are specifically modified and sorted to their appropriate destinations. The function of the Golgi apparatus has been considered to be to modify macromolecules within a series of compartments (cis, medial and trans) and to determine its destination at the trans-Golgi network. However, the ER and Golgi apparatus are thought to consist of several different sorting zones, in which macromolecules are modified and sorted towards their final destinations. In Drosophila cells, different localizations among distinct Golgi units of molecules involved in glycosylation underlie the diversity of glycan modification (11). The export of proteins from the ER to the cis-Golgi is facilitated via coat protein II (COPII)-coated vesicles, which form in specialized
sorting zones within the ER, called ER exit sites (ERES). Super high-resolution 4D live fluorescence imaging has revealed that the mobile cis-Golgi complex approaches and contacts ERES and captures cargo directly from the ER (12). Based on these observations, there should be specialized sorting zones to traffic cargo proteins accurately and safely and execute the effective posttranslational modifications. Live imaging using spatiotemporal super-resolved fluorescence microscopy enables the analysis of these sorting zones, leading to the next generation of organelle studies (13).

Conclusion
Conducting organelle next-generation studies with the novel concept of ‘organelle zone’ will enable the elucidation of the molecular machinery of organelle responses and organelle communication in various cellular situations and the molecules and mechanisms of the sorting machinery in the ER, Golgi apparatus and trafficking vesicles. The discovery of the nature of the abovementioned zones should promote a paradigm shift from organelle (intracellular compartment) biology to organelle zone biology and hence lead to the development of a new style of cell biology.

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Conflict of Interest
None declared.

References

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