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Stepping outside the comfort zone of membrane contact site research

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Abstract

The past decade has seen striking progress in our understanding of communication between organelles via close appositions of their membranes, known as contact sites. Recent systematic studies highlight that the cellular contact site landscape is much more intricate than previously anticipated and that most, if not all, organelles are capable of establishing such contacts with one another. Hence, the big challenge for this research field is to now step outside the comfort zone of the few highly studied examples of contact sites and a handful of molecules that are transferred at these sites, and to investigate the diversity of organelle contacts and the plethora of their cellular roles.

Into the great wide open

Membrane contact sites are cellular structures wherein the surfaces of distinct organelles are physically linked via proteinaceous and lipid-based tether machineries, placing them in very close proximity to each other. These organelle contacts are emerging as key mediators of interorganellar communication. First described were contacts established by the endoplasmic reticulum (ER), including those with the plasma membrane, mitochondria and the endolysosomal compartments. However, numerous new contact sites have been discovered in the past few years, many of which do not involve the ER. Importantly, two recent systematic approaches, one based on systems-level spectral imaging1 and the other involving the systematic application of an organelle proximity detection method2, provided evidence for the presence of contacts between all cellular membranes that were tested. Some of these contact sites have never been studied before, and the underlying machineries, the identity of the molecules transferred through them, and the biological functions of most of them are currently unknown.

These findings are challenging the contact site research field, which has long been primarily focused on studying a few specific contact sites. Although veering into uncharted territory is not an easy task, as fewer tools are available and common practices are yet to be built, we strongly believe that a true understanding of contact site biology will only arise once the diversity of all contact sites is holistically evaluated. For instance, the physiology of contact

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sites between small, dispersed organelles probably has fundamental inherent differences to contact sites between large organelles, such as the contacts between the ER and mitochondria or the plasma membrane.

Just keep digging

The intense interest in ER contacts with other organelles has brought about ground-breaking findings in the past few years3. These include identification and detailed characterization of tether machineries, discovery of intricate regulatory mechanisms that govern dynamic contact site adaptation to environmental cues, impressive structural work on contact site effector proteins in complex with their cargoes, and identification of links between contact site functions and human diseases.

Many of these seminal studies have uncovered universal features of contact sites. A recent discovery that is opening new research avenues was the identification of functionally distinct ER–plasma membrane contacts, which are mediated by different types of tether machineries4. Although it has long been appreciated that all studied contact sites rely on multiple tethering proteins, these were generally believed to operate within the same organelle interface. Thus, contact sites have been colloquially named, to date, by the two organelles that participate in them (ER–mitochondria, ER–plasma membrane, etc.). However, the observation that a single organelle pair can establish structurally and functionally distinct types of contact sites has shed new light on the versatility of contact sites.

Spatial separation of contact site machineries with different biological roles might allow for independent regulation of distinct aspects of organelle communication throughout the cell and also broaden the range of collaborative functions that a given organelle pair can fulfil. In the future, we might therefore have to consider distinct subtypes of contacts between two organelles (ER–plasma membrane type I, ER–plasma membrane type II, etc.). The question of spatial differentiation in interorganellar communication promises exciting findings for the future.

The great beyond

Years of work on contact sites between the ER and the plasma membrane as well as between the ER and mitochondria have led to the development of tools for the tracking of molecule transfer between these organelles. Similar tools to study membrane contact sites between other organelles are not available yet, which has limited our understanding of how communication through contact sites occurs.

For a very long time, the field has mainly studied the exchange of only two types of contact site cargoes: phospholipids and Ca^{2+}. The strong focus on these molecules stems from the historically rooted ER-centric view on contact sites. The ER has a special role in Ca^{2+} regulation, and the contribution of Ca^{2+} signalling at ER–plasma membrane interfaces to muscle contraction is an important contact site function that was unravelled very early on. Furthermore, the ER is a central hub in phospholipid biosynthesis, and it communicates via contact sites with other organelles that require and sometimes further metabolize

phospholipids. However, considering the abundance of detectable contact sites, and the multitude of tethers and additional protein components so far identified in the more extensively studied contacts, it is very likely that contact sites support the transfer of numerous other types of molecules.

Phospholipids are known to be transferred from one bilayer to the other by contact site resident lipid transfer proteins that accommodate the phospholipid in a hydrophobic cavity and thus shield it from the aqueous cytosol. Only recently has it become apparent that, in addition to phospholipids, sterols, ceramides and fatty acids are transported across contact sites. It is plausible that any type of hydrophobic compound, for example, ubiquinone, fat soluble vitamins or polyprenols, could utilize similar mechanisms of transport. Furthermore, contact site-mediated transfer might be equally important for water soluble compounds. Similar to the case of Ca^{2+}, localized transport of any other solute might enable local concentration peaks required for its downstream effects. More broadly, direct transfer at places of close membrane apposition might make solute transfer much more specific and/or efficient, by reducing the loss of molecules to other organelles and their dilution in the cytosol, and might support the compartmentalization of biological processes. Recently, it has been suggested that acetyl-CoA derivatives (such as citrate) are transported across peroxisome–mitochondria contact sites, a mechanism that likely facilitates β-oxidation2, and many other contact site cargoes surely await discovery.

Taking it up a notch

Research on contact sites has come a long way in the past decade, and recent ground-breaking works are highlighting the emerging roles of contact sites in regulating cell function. For example, a key player in insulin secretion from pancreatic β-cells, phospholipid transfer protein C2CD2L (also known as TMEM24), was recently recognized as an ER–plasma membrane contact site component. C2CD2L mediates pulsatile insulin secretion through dynamic coordination of Ca^{2+} and phosphoinositide signalling at the plasma membrane–ER interface, placing a contact site-based mechanism in the context of insulin secretion dysfunction and type 2 diabetes5. Such studies are offering us a glimpse of where the field is heading. They also give us a tantalizing foretaste of potential implications, including therapeutic applications, of moving outside our comfort zone and taking on the challenge of understanding the landscape of all cellular contact sites, to uncover the spectrum of signals transmitted and to explore the diversity of contact site biology in distinct cell types and in different contexts. Eventually, this effort will allow a holistic view on how contact sites impact cellular function and behaviour under various physiological and pathological conditions.

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