Journal Club

ORGANELLES

MAPPING ORGANELLE SUPPLY CHAINS

An unexpected consequence of the COVID-19 pandemic has been the realization of how the modern supply-and-demand economy influences our everyday life. Supply chain issues and shortages of common household items like toilet paper are being felt on a global scale like never in recent memory. Like in the macroscopic world, individual cells must also manage supply chains among their organelles and adjust them to their current needs, a topic of major research focus in many labs. A study from Jean Vance initiated the mechanistic dissection of how one such inter-organelle supply chain — phospholipid exchange between the endoplasmic reticulum (ER) and mitochondria — is orchestrated.

> Today, many studies reveal inter-organelle contacts as conduits for lipid and metabolite exchange

The paper is noteworthy because it demonstrated that following biochemical fractionation, a fraction of mitochondria co-purified with the ER network. Importantly, this so-called mitochondria-associated membrane (MAM) sample exhibited remarkable enzymatic properties: it could efficiently convert phosphatidylserine (PS), which is generated in the ER, to phosphatidylethanolamine (PE), made within mitochondria. Isolated mitochondria were not capable of this step-wise synthesis. This indicated that the MAM fraction (referred to as fraction X) contained reconstituted junctions between the two organelles that enabled lipid exchange and the synthesis of PE from PS, thereby demonstrating the important role of inter-organelle communication in glycerophospholipid metabolism.

Published in 1990 as a single-author article, the study represents a milestone in understanding inter-organelle crosstalk. Pioneering work from George Palade and others had visualized ER–mitochondria contact sites with electron microscopy, but the cellular roles for these junctions remained generally underexplored. Vance's biochemical work beautifully complements the microscopy-based approaches of Palade. Together, these studies are a prime example of the emergence of modern cell biology as a discipline blending microscopy and biochemical approaches to dissect inter-organelle communication.

Today, many studies reveal inter-organelle contacts as conduits for lipid and metabolite exchange, indicating that these membrane contact sites serve as versatile metabolic synthesis platforms. As we try to deal with the supply chain issues in our modern human world, we need to look no further than within our cells to understand that life is constantly challenged with the issue of delivering supplies efficiently across space and time.

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Competing interests
The author declares no competing interests.

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Journal Club

STRUCTURAL BIOLOGY

FIRST PREDICTION OF SEQUENCE-SPECIFIC RECOGNITION OF DOUBLE-HELIX NUCLEIC ACIDS BY PROTEINS

"Imagination is more important than knowledge." This Albert Einstein quote certainly applies to a study by Seeman, Rosenberg and Rich published in the *Proc. Natl Acad. Sci. USA* in 1976. With knowledge of the crystal structures of DNA and RNA dinucleotide mini-duplexes and of transfer RNA ($tRNA^{Phe}$) and with information from nucleic acids fibre diffraction studies in hand, but five years before the introduction of the first crystal structure of a DNA–protein complex, they pondered the question: how can proteins recognize specific sequences in double-helix nucleic acids? Specifically, they considered the unique identification of the four possible base pairs A•U(T), U(T)•A, G•C and C•G by protein side chains.

Seeman and colleagues correctly assumed that the duplex backbones will serve as a frame of reference from which to probe the information in the major and minor grooves. Hydrogen bonds would serve as the key mediator of DNA–protein interactions, unlike hydrophobic contacts or stacking. By comparing the stereochemistry of base pair steps, they identified six potential recognition sites along base pair edges in the major groove and another three sites in the minor groove. Careful analysis of the ways to discriminate between base pairs using these sites led to the conclusion that a single hydrogen bond would not allow distinction between sequences with sufficient precision.

However, pairs of hydrogen bonds could afford a mechanism to do just that. Inspired by hydrogen bonding patterns between nucleobases in crystal structures, base triplets in tRNA and fibre diffraction studies, the authors devised interactions between amino-acid side chains and bases in both grooves. These interactions were restricted to a single base pair plane and included asparagine–A (or glutamine–A) and arginine–G in the major groove and asparagine–G (or glutamine–G) in the minor groove. Interactions spanning adjacent base pairs or out-of-plane modes of recognition were not considered.

> Remarkably, the predicted arginine–G pair has been found in virtually every protein–DNA complex structure determined to date

Remarkably, the predicted arginine–G pair has been found in virtually every protein–DNA complex structure determined to date. It also inspired the design and synthesis of a cytosine analogue that forms five hydrogen bonds (both Watson–Crick and Hoogsteen types) with guanosine.

We dedicate this article to the memory of Ned Seeman (1945–2021), pioneer of protein–DNA recognition and founder of the field of DNA nanotechnology.

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