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This Week's Citation Classic

Green D E & Fleischer S. The role of lipids in mitochondrial electron transfer and oxidative phosphorylation. *Biochim. Biophys. Acta.* **70**:554-82, 1963.
[Institute for Enzyme Research, University of Wisconsin, Madison, WI]

The interactions of phospholipids with membrane complexes or membrane proteins are of two types–electrostatic and hydrophobic. The electron transfer function of lipiddepleted complexes can be reconstituted by adding back phospholipid (hydrophobic interaction). Cytochrome c forms complexes with phospholipid that are soluble in organic solvents (electrostatic interaction). Intrinsic membrane proteins such as structural protein combine hydrophobically with phospholipids to form stable complexes with unique properties. The structure and function of membranes are largely determined by lipid-protein interactions. [The *SCI*® indicates that this paper has been cited over 285 times since 1963.]

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"Historically, this article marked a turning point in the membrane field – traditionally the preserve of anatomists and electron microscopists. The emphasis exclusively on the lipid bilayer dominated thinking about the structure of membranes until the 1960s. The protein was relegated to a minor role, if any, in the determination of membrane structure. After a long period of exploration, the technology was finally developed in our laboratory for resolving the mitochondrial energy coupling system into its component elements –the electron transfer complexes (Y. Hatefi, D. Ziegler), the headpiece-stalk sector (T. Oda, P. Blair, H. Fernandez-Moran) and the membrane proteins (R. Criddle).

"At this stage we became aware that the function as well as the structure of membrane systems (complexes as well as proteins) depended in an absolute way on interactions between protein and phospholipid. S. Fleischer, G. Brierley, R. Lester, and F. Crane were the principal investigators in these pioneer studies. It then became necessary to specify the nature of lipidprotein interactions and to determine why these interactions were crucial for the exercise of membrane function.

"The *BBA* article was the first introduction to this realm of lipid-protein interactions –opening the door to the study of membrane structure via function. Strange to realize that in the 1960s ours was the only laboratory in the world to study both membrane structure and function at the same time and in the same place. The *BBA* article was widely read, as the *Science Citation Index*® indicates, but did it modify the prevailing thinking? In part, yes; in part, no. The concept of intrinsic membrane proteins, as well as the reality of lipidprotein interactions, was universally accepted. But there was no relaxation of the insistence on the paramount position of the lipid bilayer in the determination of membrane structure. Proeins became the raisins in the pudding instead of the icing on the cake. That was the extent of progress induced by this article.

"It is interesting that developments in the study of mitochondrial function have traditionally compelled new assessments in the membrane field. The recent evidence that the transducing function of the mitochondrial inner membrane is localized in a ribbon continuum, and that the protein domain of this membrane is a continuous structure, may provide the extra leverage that the original article lacked. It may finally set the proper course for the membrane field."[1]

REFERENCE

1. **Haworth R A, Komai H, Green D E & Vail W J.** The ribbon structure of the mitochondrial inner membrane. *J. Bioenerg. Biomembrane* **9**: 151-70, 1977.