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CAVEOLAE AND LIPID RAFTS: ROLES IN SIGNAL TRANSDUCTION AND THE PATHOGENESIS OF HUMAN DISEASE

VOLUME EDITORS
Michael P. Lisanti and Philippe G. Frank

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Series Editor

E. Edward Bittar
University of Wisconsin – Madison
Madison, Wisconsin

Volume Editors

Philippe G. Frank
Departments of Molecular Pharmacology and Urology
Albert Einstein College of Medicine
Bronx, New York

Michael P. Lisanti
Department of Molecular Pharmacology
Albert Einstein College of Medicine
Bronx, New York

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Section IV. Caveolae and Pathologies

Contributors

Soman N. Abraham *Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710*

Barbara P. Atshaves *Department of Physiology and Pharmacology, Texas A & M University, College Station, Texas 77843-4466*

Judith M. Ball *Department of Pathobiology, Texas A & M University, College Station, Texas 77843-4467*

Ken L. Chambliss *Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390*

Matthew J. Duncan *Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, North Carolina 27710*

William V. Everson *University of Kentucky, Sanders Brown Center on Aging, Lexington, Kentucky 40536-0230*

Olivier Feron *University of Louvain Medical School, Unit of Pharmacology and Therapeutics, B-1200 Brussels, Belgium*

Philippe G. Frank *Departments of Molecular Pharmacology and Urology, Albert Einstein College of Medicine, Bronx, New York 10461*

Adalberto M. Gallegos *Department of Pathobiology, Texas A & M University, College Station, Texas 77843-4467*

Ghada S. Hassan *Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York 10461*

Huan Huang *Department of Physiology and Pharmacology, Texas A & M University, College Station, Texas 77843-4466*

Junsuke Igarashi *Department of Cardiovascular Physiology, Kagawa University Faculty of Medicine, 761-0793 Kagawa, Japan*

Jean-François Jasmin *Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York 10461*

Ann B. Kier *Department of Pathobiology, Texas A & M University, College Station, Texas 77843-4467*

Michael P. Lisanti *Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York 10461*

J. C. Steve Liu *Computer Science Department, Texas A & M University, College Station, Texas 77843-3312*

Avery L. McIntosh *Department of Physiology and Pharmacology, Texas A & M University, College Station, Texas 77843-4466*

M. A. McNiven *Department of Biochemistry and Molecular Biology, and Center for Basic Research in Digestive Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota 55905*

L. S. Orlichenko *Department of Biochemistry and Molecular Biology, and Center for Basic Research in Digestive Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota 55905*

Friedhelm Schroeder *Department of Physiology and Pharmacology, Texas A & M University, College Station, Texas 77843-4466*

Philip W. Shaul *Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390*

Eric J. Smart *University of Kentucky, Sanders Brown Center on Aging, Lexington, Kentucky 40536-0230*

Peter Strålfors *Department of Cell Biology and Diabetes Research Centre, Linköping University, SE58185 Linköping, Sweden*

Matthias Vorgerd *Department of Neurology, Neuromuscular Center Ruhrgebiet, Ruhr-University Bochum, D-44789 Bochum, Germany*

Preface

Caveolae are 50–100 nm plasma membrane invaginations found at the surfaces of most terminally differentiated cell types. Palade (1953) and Yamada (1955) first morphologically identified caveolae (a.k.a., plasmalemmal vesicles) about fifty years ago–in both endothelial and epithelial cells. Their organization and cellular localization indicated that these organelles might play an important role in the transport of molecules between different peripheral compartments. However, at that time, their molecular composition remained completely unknown.

In 1992, almost 40 years later, Glenney & Soppet (1992) and Rothberg *et al.* (1992) were the first to identify the most important structural protein of caveolae, namely caveolin. This protein was re-named caveolin–1 after the discovery of two other caveolin genes, caveolin–2 and caveolin–3. Subsequent studies clearly demonstrated the essential role of caveolin–1 in the formation of caveolae, as well as in the regulation of cell signaling.

The existence of caveolae was initially considered controversial (Severs, 1988); they were thought to represent an EM fixation artifact. However, several groups have now biochemically purified caveolae, using caveolin–1 as a marker protein for the organelle (Lisanti *et al.*, 1994a; Schnitzer *et al.*, 1995; Smart *et al.*, 1995; Anderson, 1998). In addition, the absence of caveolae in caveolin–1 deficient mice dramatically demonstrates their existence in a normal in vivo environment (Drab *et al.*, 2001; Razani *et al.*, 2001; Zhao *et al.*, 2002; Cao *et al.*, 2003).

Simons and collaborators were among the first to propose the concept and the existence of lipid raft domains (Simons and Ikonen, 1997); it is now well accepted that caveolae represent a subset of these lipid rafts. The specific lipid composition of caveolae (sphingolipid and cholesterol-rich) led to the idea that these microdomains may play an important role in the regulation of cellular cholesterol homeostasis (Brown and London, 1998; Liscum and Munn, 1999; Fielding and Fielding, 2001) (see Section 1 of the book).

Besides the important role of caveolae in the regulation of endocytosis (see Section 2 of the book), the enrichment of signaling molecules in caveolae suggested that these domains play a key role in the regulation and organization of various cell-signaling cascades—forming "pre-assembled signaling complexes" (Lisanti *et al.*, 1994b) (see Section 3 of the book).

Finally, more recent studies using caveolin-deficient mice have confirmed many of the "controversial hypotheses" put forth in earlier publications (Drab *et al.*, 2001; Razani *et al.*, 2001; Zhao *et al.*, 2002; Cao *et al.*, 2003). However, even if caveolin proteins are not essential for life, they still play a critical role in the pathogenesis of a number of human diseases, as highlighted in studies using caveolin-deficient mouse animal models.

These studies have shown that caveolin proteins play an important role in regulating muscular, cardiovascular, and pulmonary patho-physiology (see Section 4 of the book). Furthermore, the negative regulatory role of caveolin–1 in various signaling pathways has suggested that caveolin–1 may indeed function as a tumor suppressor gene. Clear genetic links between the caveolin proteins and human disease have now been established in patients suffering from muscular dystrophy, cardiomyopathy, and breast cancer.

Overall, this book summarizes the essential features and functions of caveolae in cells, mouse animal models, and in human disease. We thank all the excellent contributors who extensively participated in making this book possible.

Philippe G. Frank and Michael P. Lisanti

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