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Preface

To commemorate the twenty-first anniversary of the publication of J. D. Watson and F. H. C. Crick's famous article on the structure of DNA, the April 26, 1974, issue of *Nature* featured a special section entitled "Molecular biology comes of age." While the origin of the field of membrane fusion research cannot be traced to a single article, two comprehensive reviews on virus-induced cell fusion and on membrane fusion appeared in 1972 and 1973, respectively (G. Poste, *Int. Rev. Cytol.* **33**, 157–252; G. Poste and A. C. Allison, *Biochim. Biophys. Acta* **300**, 421–465). In the two decades since, there has been a rapid growth in the number of studies on the molecular mechanisms of membrane fusion, culminating in several books on the subject (A. E. Sowers, ed., "Cell Fusion," Plenum Press, 1987; S. Ohki, D. Doyle, T. D. Flanagan, S. W. Hui, and E. Mayhew, eds., "Molecular Mechanisms of Membrane Fusion," Plenum Press, 1988; N. Düzgüneş, ed., "Membrane Fusion in Fertilization, Cellular Transport, and Viral Infection," Academic Press, 1988; J. Wilschut and D. Hoekstra, eds., "Membrane Fusion," Marcel Dekker, 1991). With the publication of Volumes 220 and 221 of *Methods in Enzymology* dedicated to this subject, it is not entirely inappropriate to declare the field of membrane fusion as having come of age.

The chapters in this and the accompanying Volume 220 present not only the details of methods used in membrane fusion research, but also a critical analysis of the methods, their advantages and shortcomings, and possible artifacts. While several sections focus on the elucidation of the mechanisms of fusion in various experimental systems (Fusion of Liposomes and Other Artificial Membranes; Fusion of Viruses with Target Membranes; Cell–Cell Fusion Mediated by Viruses and Viral Proteins; Conformational Changes of Proteins during Membrane Fusion; Membrane Fusion during Exocytosis; Intracellular Membrane Fusion; Membrane Fusion in Fertilization), several others describe applications of membrane fusion technology (Induction of Cell–Cell Fusion; Introduction of Macromolecules into Cells by Membrane Fusion; Protoplast Fusion). The methodology presented should be of value not only to newcomers to membrane fusion research who wish to employ some of the techniques described in these books, but also to researchers in the field who need to adopt an alternative technique.

I would like to thank the contributors to this volume, without whose willing and able collaboration this work would not even have begun. I would also like to express my appreciation for their patience with me and with their fellow authors, not all of whom were able to submit their

manuscripts at the same time. I thank Shirley Light of Academic Press for her patience, understanding, encouragement, and persistence in producing this volume, and Cynthia Vincent for her invaluable editorial assistance. I also thank my wife Diana Flasher for her constant support and enthusiasm for this project, despite countless weekends I spent editing manuscripts. Finally, I wish to dedicate this volume to my aunt Sevim Uygurer, my brother Arda Düzgüneş, and my wife Diana Flasher, in grateful appreciation of their love, support, and understanding.

NEJAT DÜZGÜNEŞ

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By JEFFREY D. LIFSON

Introduction

Processes involving membrane fusion events are an essential part of the life cycle of many pathogenic enveloped viruses.[1] Fusion between the virion envelope and either the plasmalemma of target cells or the membrane of a cellular endocytic vacuole may be required for establishment of productive infection.[1-3] In addition, virally induced cell fusion gives rise to the multinucleated giant cells, or *syncytia,* typically observed in many *in vitro* assay systems used to study replication of these viruses, and in histological sections of tissues infected *in vivo*.[4]

Perhaps the best characterized of these viruses, with regard to mechanistic aspects of virally induced membrane fusion phenomena, is the orthomyxovirus influenzavirus.[3,5-9] In the influenzavirus system, the envelope protein (hemagglutinin, HA) precursor HA_0 is synthesized in infected cells and cleaved to yield two subunits (designated HA_1 and HA_2), which are present on the plasma membrane of infected cells as well as on the lipid bilayer of budded viral particles.[5,10,11] The endoproteolytic cleavage that generates HA_1 and HA_2 also exposes a highly conserved hydrophobic stretch (approximately 30 residues) within HA_0, which becomes the amino-terminal domain of HA_2. It has been postulated that binding of the trimeric form of HA produces a conformational change that positions this hydrophobic domain in proximity to host cell membranes.[9] Entry of this hydrophobic domain of HA_2 into the lipid bilayer of a host cell membrane is believed to initiate membrane fusion, which results in fusion of the

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