Membrane molecular biology of neoplastic cells

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with contributions by

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Foreword

Like the bark of a tree or the skin of an animal, the plasma membrane is a highly specialized organ combining barrier functions that widely surpass the performance of the most closely guarded borders, with highly regulated bilateral exchange functions. Dr. Wallach's view that membranes are laterally segregated into domains of different composition and behavior provides a rational basis for this duality, characteristic for *all* cells. In higher organisms, cell differentiation adds a further, formidable superstructure of composition and function. The membrane becomes an array of specialized organelles essential to a wide variety of receptor transduction and signalling functions, involving both contactual, short-range and humorally mediated, long-range interactions. Differentiated membrane structures are beginning to be recognized as morphological, functional or antigenic units. The mapping of these entities is still in its earliest beginnings, although some cells, e.g. lymphocytes, already provide a certain amount of information, useful to the membranologist, the student of normal lymphocyte function and the lymphopathologist. A rapid increase of information can be expected with regard to other cell types.

The last few years have provided proof for the originally surprising concept that many proteins penetrate into or through the apolar cores of biomembranes in dynamic association with membrane lipids. Wallach's definition of the interacting units of a membrane lattice, which he calls protomers, as the intramembranous segments of membrane proteins associated with their boundary layer lipid is a further step towards a more concrete definition of this dynamic system. Studies on capping, redistribution, protein 'shedding' and ligand-induced 'shedding' have now become the favorite playtoys of membranologists, immunologists

and experimental oncologists. Relatively simple experimental designs, including direct microscopial observation, have provided hitherto unparalleled insights into the interdependence or independence of different membrane-associated antigenic or receptor units, their mobilities or anchorages, their 'shedding', modulation, degradation and regeneration. Unexpected and as yet unexplained differences have been found in the behavior of different receptors on the same cell and of the same receptor on different cells. Suggestive differences between normal and neoplastic cells are beginning to emerge and are particularly interesting.

The thought that neoplasia is essentially a 'membrane disease' has been raised by Wallach at an early stage and with force. It is an exciting thought, because the cell membrane is an almost compulsory transfer point for the action of growth controlling signals. Changes in critically important membrane sites, or, as Wallach puts in, the alteration of concerted membrane behavior by oncogenic agents, may bring about the free-wheeling of the cell cycle recognized as neoplastic growth. Insertion of new, virally determined subunits or functional modification of existing units by the action of viral or non-viral agents may be responsible. The reality of such phenomena is strongly suggested by the documented existence of membrane changes in tumors, expressed as altered contact inhibition, anchorage independence, appearance of new and change or disappearance of old membrane antigens and changes in membrane permeability and transport. In addition to the notorious difficulty of distinguishing between causal and consequential phenomena, differences between normal and neoplastic cells must be interpreted with great caution, however, it is particularly important to scrutinize the representativeness of the normal cell since uniclonal tumor lines often express clonal markers present on a minority but not the majority of the control cell population. It is therefore of considerable significance that reproducible changes in membrane biochemistry are found to accompany the reversible transitions between transformed and non-transformed cellular phenotypes induced by shifts between permissive and non-permissive temperatures, in cells transformed by temperature-sensitive, oncogenic virus mutants.

Equally significant is the extensive evidence that membrane anomalies in neoplastic cells are not restricted to the plasma membrane and therewith the emergence of clues as to the metabolic mechanisms underlying both membrane-associated and other peculiarities of tumor cells.

All this strongly suggests that the biochemical and functional study of biomembranes has come to stay as one of the most important areas in tumor biology. The book of Wallach is an admirable review of the present status of the field, written by an outstanding 'membranologist', with a profound interest in tumor cell membranes from the outset and one who never loses sight, while analyzing the impressive wealth of factual information presented in this book, either of the biological problems or of the desperate need of this field to keep

apart hard from soft facts, or well-founded hypotheses from premature generalizations. The triple capacity of the author as biochemist, physician and Scientific Director of a department devoted not only to tumor biology but also to tumor therapy accounts for the special interest and flavor of this book.

Stockholm, Sweden GEORGE KLEIN
September, 1975

Preface

O glücklich wer noch hoffen kann,
Aus diesem Meer des Irrtums aufzutauchen!
Was man nicht weiss, dass eben brauchte man,
Und was man weiss, kann man nicht brauchen.

GOETHE, (*Faust*, I, 1065)

The membrane biology of tumor cells has become a most active field of biomedicine. The area has excited the interest of scholars from numerous and diverse disciplines for many reasons, some relating to cancer as a disease and others to neoplasia as a fundamental biological process. Prominent among these reasons is the suspicion that the normal social interactions between tissue cells depend directly upon their surface membranes and that the invariable disruption of tissue homeostasis in cancer derives from cell surface deviations. Equally important is the realization that numerous metabolic functions commonly abnormal in tumor cells involve diverse intracellular membranes. Other sources of interest are the recognition that surface membranes can act as restriction sites in cancer-chemotherapy, as well as targets in immunotherapy, and the anticipation that the elucidation of tumor cell membrane anomalies will provide new therapeutic strategies. Finally, the remarkable maturation of general membrane technology and the great increase in understanding of fundamental membrane processes, now allows experimental and conceptual approaches to tumor membrane biology that were not accessible until recently.

In my efforts to achieve some understanding of the membrane anomalies of neoplastic cells and the relevance of these anomalies to malignancy, I have encountered some formidable obstacles that assuredly also trouble others in the field. Of these the polymorphism of tumor cells and the intricacies of membrane biology are features inherent in the biological problem. However, additional difficulties come from the fragmented character of the explosively growing literature, the oftentimes deficient cohesion between diverse research strategies and the inadequate integration of tumor membrane biology with basic membrane studies and experimentation on normal cells. Such factors, while understandable

in view of the complexity of the field and of the social pressure to 'cure cancer', generate intellectual hindrances that appear as troublesome as the biological obstacles.

My purpose in writing this book is to integrate existing biochemical, biophysical and molecular biological information relevant to the field of tumor membrane biology, to relieve some of the communication problems in the area and to create some new perspectives. I have therefore attempted to present an objective, topical and rather comprehensive survey of membrane molecular biology *as it now applies to comparisons of normal and neoplastic* cells, integrating data and hypotheses from multiple sources and disciplines in a manner accessible to specialists in both tumor biology and membrane biology, as well as to a wide circle of graduate students and other scholars in diverse fields of biomedicine. It is my hope that the book will prove as helpful for the reader as it has been challenging to the writer.

This book could not have been completed without a great deal of support. I would therefore like to express my particular appreciation to R. Schmidt-Ullrich for his assistance in Chapters 2 and 6. In addition, I extend my sincere thanks to the following colleagues for their inspiration, constructive criticism and frequent permission to read important manuscripts prior to publication: J. Borysenko, H. Chen, L. Furcht, J.M. Graham, S.I. Hakomori, M. Hatanaka, A.A. Kandutsch, L. Kwock, P.S. Lin, A.L. Lehninger, C. McKhann, Jr., R. Mikkelsen, V. Najjar, F. Oosawa, C.A. Pasternak, J. Sheridan, S. Tevethia and R. Weinstein. I am particularly indebted to Kate Scheller and Tina Monroy for their invaluable help in preparing the manuscript and to the officers of ASP Biological and Medical Press, Jack Franklin in particular, for their continued interest and patient support.

Finally, I want to express my deep gratitude to my wife, both for her encouragement and for her patience in enduring the many evenings and weekends spent in the conception and writing of this book.

Boston, Mass.
May, 1975

DONALD F. HOELZL WALLACH

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