

This is a free sample of content from **The Mammary Gland as an Experimental Model**.
Click here for more information or to buy the book.

The Mammary Gland as an Experimental Model

A subject collection from *Cold Spring Harbor Perspectives in Biology*

**OTHER SUBJECT COLLECTIONS FROM COLD SPRING HARBOR
PERSPECTIVES IN BIOLOGY**

The Biology of Lipids: Trafficking, Regulation, and Function

Auxin Signaling: From Synthesis to Systems Biology

The Nucleus

Neuronal Guidance: The Biology of Brain Wiring

Cell Biology of Bacteria

RNA Worlds: From Life's Origins to Diversity in Gene Regulation

Cell–Cell Junctions

Generation and Interpretation of Morphogen Gradients

Immunoreceptor Signaling

NF- κ B: A Network Hub Controlling Immunity, Inflammation, and Cancer

Symmetry Breaking in Biology

The Origins of Life

The p53 Family

This is a free sample of content from *The Mammary Gland as an Experimental Model*.
Click here for more information or to buy the book.

The Mammary Gland as an Experimental Model

A subject collection from *Cold Spring Harbor Perspectives in Biology*

EDITED BY

Mina J. Bissell

Lawrence Berkeley National Laboratory

Kornelia Polyak

Harvard Medical School

Jeffrey M. Rosen

Baylor College of Medicine



COLD SPRING HARBOR LABORATORY PRESS
Cold Spring Harbor, New York • www.cshlpress.com

© 2011 by Cold Spring Harbor Laboratory Press

The Mammary Gland as an Experimental Model

A Subject Collection from *Cold Spring Harbor Perspectives in Biology*
Articles online at www.cshperspectives.org

All rights reserved

© 2011 by Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York

Printed in the United States of America

Executive Editor	Richard Sever
Managing Editor	Maria Smit
Project Manager	Barbara Acosta
Permissions Administrator	Carol Brown
Production Editor	Antonella Caiazza-Moeller
Production Manager	Denise Weiss

Publisher John Inglis

Front cover artwork: Ten week virgin FVB inguinal mammary gland in diestrus. (Image courtesy of Alvin T. Lo and Mina J. Bissell.)

Library of Congress Cataloging-in-Publication Data

The mammary gland as an experimental model : a subject collection from Cold Spring Harbor perspectives in biology / edited by Mina J. Bissell, Kornelia Polyak, Jeffrey M. Rosen.
p. cm.

Includes bibliographical references and index.

ISBN 978-0-879699-06-2

1. Mammary glands--Molecular aspects. 2. Breast--Cancer--Genetic aspects. I. Bissell, Mina. II. Polyak, Kornelia. III. Rosen, Jeffrey M.

QP188.M3M358 2011

612.6'64--dc23

2011018361

10 9 8 7 6 5 4 3 2 1

All World Wide Web addresses are accurate to the best of our knowledge at the time of printing.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Cold Spring Harbor Laboratory Press, provided that the appropriate fee is paid directly to the Copyright Clearance Center (CCC). Write or call CCC at 222 Rosewood Drive, Danvers, MA 01923 (978-750-8400) for information about fees and regulations. Prior to photocopying items for educational classroom use, contact CCC at the above address. Additional information on CCC can be obtained at CCC Online at <http://www.copyright.com/>.

All Cold Spring Harbor Laboratory Press publications may be ordered directly from Cold Spring Harbor Laboratory Press, 500 Sunnyside Blvd., Woodbury, New York 11797-2924. Phone: 1-800-843-4388 in Continental U.S. and Canada. All other locations: (516) 422-4100. FAX: (516) 422-4097. E-mail: cshpress@cshl.edu. For a complete catalog of Cold Spring Harbor Laboratory Press publications, visit our website at <http://www.cshlpress.com/>.

Contents

Preface, vii

SECTION I: HISTORICAL BACKGROUND

Of Mice and Women: A Short History of Mouse Mammary Cancer Research with an Emphasis on the Paradigms Inspired by the Transplantation Method, 1

Daniel Medina

A Compendium of the Mouse Mammary Tumor Biologist: From the Initial Observations in the House Mouse to the Development of Genetically Engineered Mice, 13

Robert D. Cardiff and Nicholas Kenney

Choosing a Mouse Model: Experimental Biology in Context—The Utility and Limitations of Mouse Models of Breast Cancer, 25

Alexander D. Borowsky

SECTION II: STEM CELLS

Murine Mammary Epithelial Stem Cells: Discovery, Function, and Current Status, 41

Jane E. Visvader and Gilbert H. Smith

Stem Cells in the Human Breast, 55

Ole William Petersen and Kornelia Polyak

SECTION III: SIGNALING

Hormone Action in the Mammary Gland, 71

Cathrin Brisken and Bert O'Malley

Mammary Gland Growth Factors: Roles in Normal Development and in Cancer, 87

Nancy E. Hynes and Christine J. Watson

Cell–Matrix Interactions in Mammary Gland Development and Breast Cancer, 105

John Muschler and Charles H. Streuli

Mammary Gland ECM Remodeling, Stiffness, and Mechanosignaling in Normal Development and Tumor Progression, 123

Pepper Schedin and Patricia J. Keely

Oncogenes and Tumor Suppressor Genes, 145

Eva Y.H.P. Lee and William J. Muller

Contents

SECTION IV: MAMMARY GLAND DEVELOPMENTAL BIOLOGY AND CANCER

The Role of the Microenvironment in Mammary Gland Development and Cancer, 163

Kornelia Polyak and Raghu Kalluri

Molecular Mechanisms Guiding Embryonic Mammary Gland Development, 177

Pamela Cowin and John Wysolmerski

TGF- β Biology in Mammary Development and Breast Cancer, 191

Harold Moses and Mary Helen Barcellos-Hoff

Mammary Gland Reprogramming: Metalloproteinases Couple Form with Function, 205

Rama Khokha and Zena Werb

Leukocytes in Mammary Development and Cancer, 225

Lisa M. Coussens and Jeffrey W. Pollard

Systems Biology and Genomics of Breast Cancer, 247

Charles M. Perou and Anne-Lise Borresen-Dale

Using Functional Genetics to Understand Breast Cancer Biology, 265

Alan Ashworth and Rene Bernards

Chromatin Remodeling in Mammary Gland Differentiation and Breast Tumorigenesis, 277

Tim H.-M. Huang and Manel Esteller

In Vivo Imaging in Cancer, 293

John Condeelis and Ralph Weissleder

Afterword, 315

Index, 319

Preface

ALMOST A QUARTER OF A CENTURY AGO, two pioneers of mammary gland biology, Margaret C. Neville and Charles W. Daniel, edited a book entitled *The Mammary Gland: Development, Regulation, and Function* (1987). As stated in the introduction to that book, “this was one of the first attempts to bring the current studies on the developmental, cellular and molecular biology of the mammary gland together in one volume.” A lot has happened in the two and half decades since. Accordingly, we felt it was again time to bring together experts working on different aspects of mammary gland biology and ask them not only to discuss the remarkable progress in the field but also to provide an historical perspective (see chapters by Medina, Cardiff and Kenney, and Borowsky) for the many young investigators who have been attracted to this area, so they can learn both where the field is today and more about its “roots.”

In 1998, following a meeting at the National Cancer Institute on Charting the Course: Priorities for Breast Cancer Research, Hal Moses and Nancy Davidson wrote in a summary statement that “[o]ur understanding of the biology and developmental genetics of the normal mammary gland is a barrier to progress. . . a more complete understanding of the normal mammary gland at each stage of development. . . will be a critical underpinning of continued advances in detecting, preventing and treating breast cancer.” This basic philosophy—elucidating the mechanisms involved in normal development in order to understand the alterations that occur in breast cancer—has had a major impact on the field. Indeed, this volume contains at least as many chapters on normal mammary gland biology as on breast cancer.

We decided to cover topics slightly differently than a traditional collection of reviews would. In each case, we asked two independent scientists, each with their own ideas and research focus, to collaborate to write a chapter. We then took another unconventional approach, asking a third expert to pen a short commentary on either what had been written in a given chapter or other related ideas that had not been addressed in those chapters. These commentaries are available online at www.cshperspectives.org and allow a dynamic dialogue to develop on each area covered. We welcome comments on either the regular chapters or the commentaries themselves. We hope this experiment results in a constructive and informative exchange of ideas between both the authors and other members of the mammary gland biology community that also allows for newcomers.

Studies of the mammary gland have been at the forefront of many advances in our understanding of hormone action (see Brisken and O’Malley, and Hynes and Watson), genetics (see Perou and Børresen-Dale, and Ashworth and Bernards), cell biology (see Muschler and Streuli, Polyak and Kalluri, Schedin and Keely, and Khokha and Werb), stem cell biology (see Petersen and Polyak, and Visvader and Smith), and cancer biology (see Lee and Muller, Ashworth and Bernards, Coussens and Pollard, and others). This is not solely a result of substantial increases in funding for these studies over the past three decades but also of the attractiveness of the mammary gland as an experimental system. Charles Daniel referred to the end bud of the mammary gland as an “experimental organism.” Others have called it the “*Drosophila eye*” of mammalian functional genomics. Indeed we would argue that the mammary gland itself can be thought of as an experimental organism.

What features of the mammary gland lead us to draw such analogies? The mammary gland is unique in that most of its development occurs postnatally, and that at least in rodents there are

Preface

multiple glands readily accessible for study. The advent of transgenic and gene knockout mice facilitated both gain- and loss-of-function studies in the mammary gland, which allowed us to elucidate the functions of novel genes and signaling pathways (see chapter by Cowin and Wysolmerski) in an *in vivo* context. The subsequent development of methods for tissue-specific overexpression and deletion of genes meant their roles in the organ could be studied independently of the rest of the animal, reinforcing the notion that the mammary gland is analogous to an experimental organism (see chapter by Lee and Muller). Similarly, an important mammary-specific virus, MMTV, became a versatile tool used by virologists and cancer biologists, and *WNT*, a gene first identified in the mammary gland, provided a model for “hit and run” oncogenesis. One of the first genetically engineered mouse tumor models was the MMTV-*c-myc* “oncomouse,” in which a specific oncogene (*MYC*) was essentially targeted to the mammary gland. Another important breakthrough came later when investigators developed methods for specific deletion of tumor suppressor genes, such as p53, in the mammary gland. Transplantation of both tissue and mammary epithelial cells into cleared fat pads provided the biological foundation for many of these studies, allowing a direct comparison in the same animal of a control mammary outgrowth with one in which the epithelium had been genetically manipulated (see chapter by Medina). This technology also provided a functional assay for mammary stem and progenitor cells in the normal mammary gland and breast cancer (see Visvader and Smith). Thus, it is not surprising that after the pioneering studies in leukemia, the first studies of “cancer stem cells” in solid tumors were performed by fluorescence-activated cell sorting (FACS) of pleural effusions from breast cancers followed by transplantation into the mammary fat pad.

Breast cancer is not a single disease, however, and one of the first applications of gene profiling to cancer led to the identification of several different breast cancer subtypes with different clinical outcomes (see Perou and Børresen-Dale). Thus, it became important to identify the different cell lineages in the mammary gland (see Visvader and Smith, and Petersen and Polyak) so that we could better understand the cells of origin of these different cancer subtypes. Because of the many genetically engineered mouse models of breast cancer available, it was possible to also do comparative oncogenomics studies and generate preclinical models for the different breast cancer subtypes.

Mammary development is influenced by systemic hormones as well as by local cell–cell, cell–extracellular matrix (ECM), and cell–stromal interactions (see Muschler and Streuli, Cowin and Wysolmerski, Moses and Barcellos-Hoff, and Polyak and Kalluri). This distinguishes the postnatal mammary gland from organ systems in which morphogenesis is regulated during embryonic development solely by local interactions. Both steroid and peptide hormones regulate postnatal mammary gland development, and not surprisingly, the majority of breast cancers are hormone dependent. In fact, the selective estrogen receptor modulator tamoxifen was the first targeted therapy for cancer (see Briskin and O’Malley). The mammary gland is, therefore, an attractive model for studies aimed at identifying the mechanisms of actions of steroid and peptide hormones, as well as crosstalk between the signaling pathways regulated by these hormones. Non–cell autonomous interactions are critical in mammary development, illustrating the importance of local paracrine factors in development.

Finally, the recognition of the importance of cell context and the local microenvironment led to the development of novel three-dimensional culture models in an attempt to better mimic the *in vivo* environment. Again investigators studying the mammary gland took the lead developing these models, resulting in major conceptual advances in our understanding of the role of the microenvironment both in normal development and in cancer initiation and progression. Such models have made invaluable contributions to our understanding of the factors regulating glandular tissue polarity and architecture in the normal mammary gland and how these are altered in breast cancer. The availability of these culture models as well as the accessibility of the mammary gland

in vivo have made the mammary gland an excellent model system for the application of live cell imaging (see the chapter by Condeelis and Weissleder).

It is our hope that the conceptual and technical advances in mammary gland biology discussed in this collection will provide the foundation for future discoveries as well as a continuing resource for future investigators in this vibrant field.

We wish to thank Richard Sever for bringing this project to life, Negest Williams for being the conduit between ourselves and Cold Spring Harbor Laboratory Press, and Barbara Acosta for managing the manuscripts in this book and facilitating completion of the project.

MINA J. BISSELL
KORNELIA POLYAK
JEFFREY M. ROSEN