# *MYC* and the Pathway to Cancer

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

## OTHER SUBJECT COLLECTIONS FROM *COLD SPRING HARBOR PERSPECTIVES IN MEDICINE*

*Bacterial Pathogenesis*
*Transplantation*
*Cystic Fibrosis: A Trilogy of Biochemistry, Physiology, and Therapy*
*Hemoglobin and its Diseases*
*Addiction*
*Parkinson's Disease*
*Type 1 Diabetes*
*Angiogenesis: Biology and Pathology*
*HIV: From Biology to Prevention and Treatment*
*The Biology of Alzheimer Disease*

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

*The Origin and Evolution of Eukaryotes*
*Endocytosis*
*Mitochondria*
*Signaling by Receptor Tyrosine Kinases*
*DNA Repair, Mutagenesis, and Other Responses to DNA Damage*
*Cell Survival and Cell Death*
*Immune Tolerance*
*DNA Replication*
*Endoplasmic Reticulum*
*Wnt Signaling*
*Protein Synthesis and Translational Control*
*The Synapse*
*Extracellular Matrix Biology*
*Protein Homeostasis*
*Calcium Signaling*
*The Golgi*
*Germ Cells*
*The Mammary Gland as an Experimental Model*
*The Biology of Lipids: Trafficking, Regulation, and Function*
*Auxin Signaling: From Synthesis to Systems Biology*
*The Nucleus*
*Neuronal Guidance: The Biology of Brain Wiring*

# *MYC* and the Pathway to Cancer

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

EDITED BY

Chi V. Dang

*Abramson Cancer Center at the University of Pennsylvania*

Robert N. Eisenman

*Fred Hutchinson Cancer Research Center*

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

*MYC* and the Pathway to Cancer
**A Subject Collection from *Cold Spring Harbor Perspectives in Medicine***
**Articles online at www.perspectivesinmedicine.org**



| | |
|---|---|
| **Executive Editor** | Richard Sever |
| **Managing Editor** | Maria Smit |
| **Senior Project Manager** | Barbara Acosta |
| **Permissions Administrator** | Carol Brown |
| **Production Editor** | Diane Schubach |
| **Cover Design** | Denise Weiss |
| **Publisher** | John Inglis |

*Front cover artwork:* Biological assembly image of 1nkp from the Myc:Max Protein databank file. Image created with the PyMOL Molecular Graphics System by Lisa McFerrin (Fred Hutchinson Cancer Research Center). S.K. Nair and S.K. Burley produced the structural data in 2003. Image is free of all copyright restrictions and made fully and freely available for both noncommercial and commercial use.

*Library of Congress Cataloging-in-Publication Data*

MYC and the pathway to cancer : a subject collection from Cold Spring Harbor perspectives in medicine / edited by Chi V. Dang, University of Pennsylvania, and Robert N. Eisenman, Fred Hutchinson Cancer Research Center.
page cm
Includes index.
ISBN 978-1-62182-008-6 (hardcover : alk. paper)
1. Myc oncogenes. 2. Cancer genes. 3. Cancer--Genetic aspects. 4. Cancer--Prevention. I. Dang, Chi V., 1954- editor of compilation. II. Eisenman, R. N. (Robert N.), editor of compilation. III. Cold Spring Harbor perspectives in medicine.

RC268.44.M93M93 2013
616.99'4042--dc23
2013028844

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.



For a complete catalog of all Cold Spring Harbor Laboratory Press publications, visit our website at www.cshlpress.org.

# Contents

Contents

# Preface

THE DISCOVERY OF THE *MYC* ONCOGENE WAS a major milestone along the road leading to our current understanding of genetic alterations in cancer and how transcription contributes to tumorigenesis. The study of *MYC* began more than three decades ago and has now accumulated more than 26,000 publications listed in PubMed. With ramifications in almost every area of biological and medical sciences, the *MYC* field is poised for a book that captures not only key historical findings but also the latest advances and controversies. The immediate impetus for this volume came as the result of a Banbury Conference on *MYC* and cancer held in November 2011. Several things became apparent at this meeting. First, an immense amount of diverse information has been gathered on nearly every aspect of the regulation and activities of *MYC*. Second, exciting new experiments are continually forcing us to revise our picture of *MYC* and its functions. Third, there is still a great deal, much of it fundamental, to learn about the function of *MYC* in both normal and neoplastic cells.

*MYC* encodes a master transcription factor that dimerizes with MAX to control diverse biological processes that influence normal cell growth and proliferation. However, when deregulated, *MYC* becomes an oncogene that transforms cells in concert with other genetic alterations, including loss of tumor-suppressor checkpoints. Research on *MYC* over the past several decades has provided us with an understanding of how multiple cellular processes can be affected by a single transcriptional regulator and how the collective alterations of these processes result in cancer. The chapters in this volume have been arranged so that the topics move from a mechanistic focus on the MYC protein (regulation of expression, protein–protein interactions, genomic recognition, and transcriptional functions) through MYC's biological activities in normal cellular processes (roles in pluripotency, vertebrate and invertebrate development, DNA replication, apoptosis, and metabolism) to the activities of MYC that render it a major driver of oncogenicity (regulatory mutations, induction of genomic instability, cell competition, and metabolic reprogramming). Other chapters examine specific examples of MYC's diverse roles in human cancers (Burkitt lymphoma, medulloblastoma, and neuroblastoma) and consider approaches to attenuate MYC in tumors (synthetic lethal screens and targeted chemotherapy).

One fundamental area of research that receives considerable attention in this volume concerns the precise function of MYC as a regulator of gene expression. The generally accepted model that MYC acts as a transcriptional on/off switch has been challenged by the hypothesis that MYC functions solely to alleviate the widespread transcriptional pausing by RNA polymerases and thus amplifies the expression of genes that are already expressed in a given cellular context. The data supporting this "universal amplifier" model are described here in two chapters while these findings and their consequences are further considered and debated in several other chapters. We expect that the debate concerning MYC's transcriptional functions will provide an impetus for further research focused on a deeper understanding of the mechanism(s) underlying the transforming potential of *MYC* oncogenes.

The editors thank Barbara Acosta, Richard Sever, and their colleagues at Cold Spring Harbor Laboratory Press for their help and excellent editorial efforts in assembling this book. We are indebted to all the authors, who have generously dedicated their time to contribute superb chapters that capture the essence and highlight important findings in their chosen topics. We dedicate this

book to Michael Potter, whose research and workshops on *MYC* and B-cell neoplasia over the years inspired many of us to pursue this enigmatic oncogene.

Chi V. Dang
Robert N. Eisenman