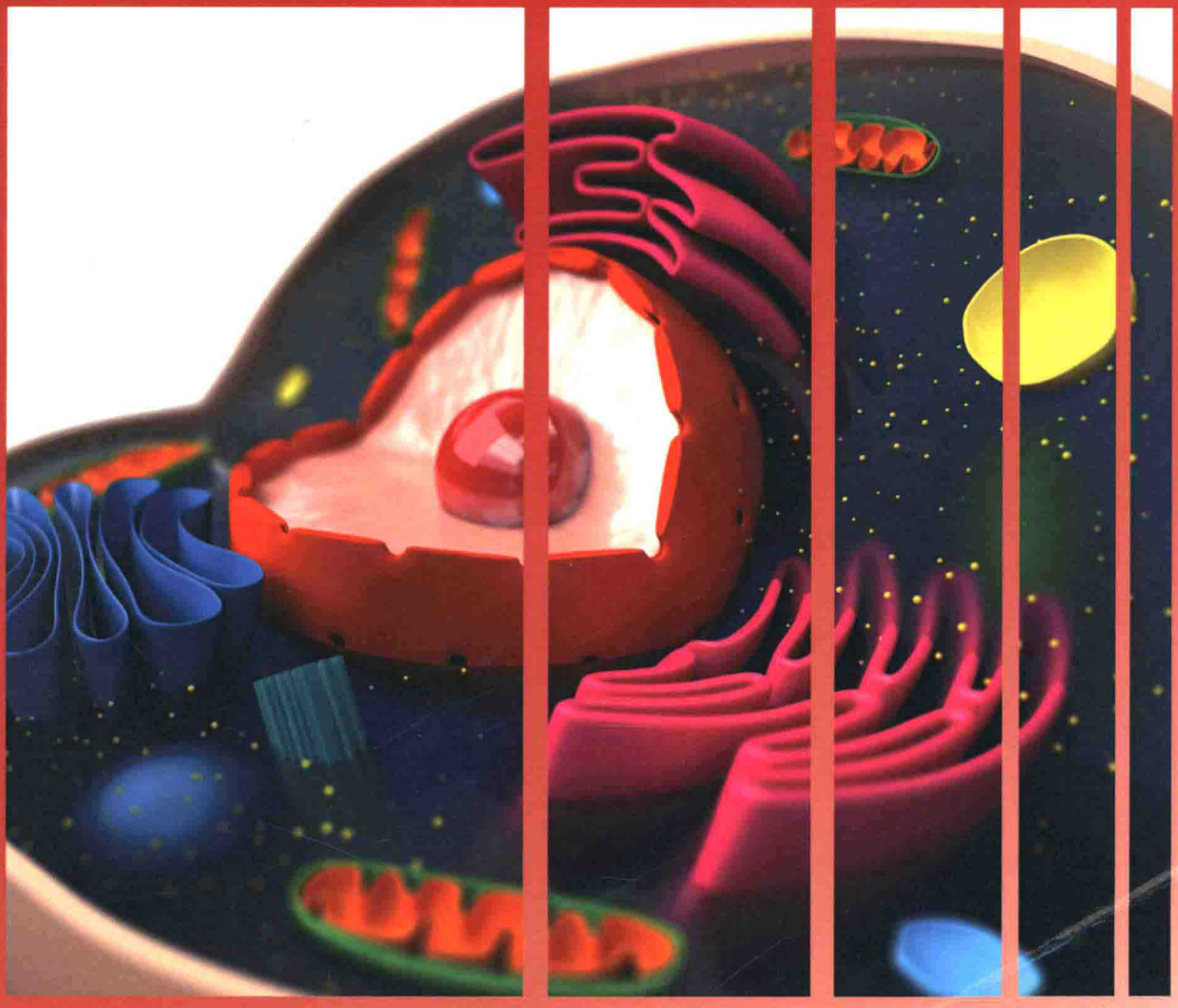
CellPress

REVIEWS

Core Concepts in Cell Biology



APCell PRESS

Cell Press Reviews

Core Concepts in Cell Biology

Curated by

Rebecca Alvania; Scientific Editor, Cell Press

Original Articles Edited by the Following Cell Press Scientific Editors

Rebecca Alvania
Marie Bao
Karen Carniol
Kara Cerveny
Michaeleen Doucleff
Anne Knowlton
Robert Kruger
Florian Madersbacher
Cyrus Martin
Sri Devi Narasimhan
Deborah Taylor

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

AP Cell is an imprint of Elsevier

APCell PRESS

CellPress

Emilie Marcus, CEO, Editor-in-Chief
Joanne Tracy, Vice President of Business Development
Keith Wollman, Vice President of Operations
Peter Lee, Publishing Director
Deborah Sweet, Publishing Director
Katja Brose, Editorial Director, Reviews Strategy
Elena Porro, Editorial Director, Content Development
Meredith Adinolfi, Director of Production
Jonathan Atkinson, Director of Marketing

Science and Technology Books

Suzanne BeDell, Managing Director
Laura Colantoni, Vice President & Publisher
Amorette Pedersen, Vice President, Channel Management & Marketing Operations
Tommy Doyle, Senior Vice President, Strategy, Business Development & Continuity Publishing
Dave Cella, Publishing Director, Life Sciences
Janice Audet, Publisher
Elizabeth Gibson, Editorial Project Manager
Julia Haynes, Production Manager
Ofelia Chernock, Portfolio Marketing Manager
Melissa Fulkerson, Senior Channel Manager
Cory Polonetsky, Director, Channel Strategy & Pricing

AP Cell is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

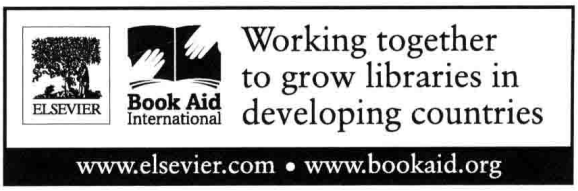
Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-420193-4

Typeset by TNQ Books and Journals Pvt. Ltd.

Printed and bound in Singapore by Markono Print Media Pte Ltd

Transferred to digital print 2012



Cell Press Reviews: Core Concepts in Cell Biology

About Cell Press

Cell Press is a leading publisher in the biological sciences and is committed to improving scientific communication through the publication of exciting research and reviews. Cell Press publishes 30 journals, including the Trends reviews series, spanning the breadth of the biological sciences. Research titles published by Cell Press include *Cell*, *Cancer Cell*, *Cell Stem Cell*, *Cell Host & Microbe*, *Cell Metabolism*, *Chemistry & Biology*, *Current Biology*, *Developmental Cell*, *Immunity*, *Molecular Cell*, *Neuron*, *Structure*, and the open-access journal *Cell Reports*. In addition to publishing high-impact findings, Cell Press research journals publish a wide variety of peer-reviewed review and opinion articles, essays from leaders in the field, graphical SnapShots, science news articles, and much more. Cell Press is also the publisher of three society journals: *Biophysical Journal*, *American Journal of Human Genetics*, as well as the open-access journal *Stem Cell Reports*.

The *Trends* reviews journals are also part of the Cell Press family and consist of 14 monthly review titles that publish in a range of areas across the biological sciences. Peer-reviewed and thoroughly edited review and opinion articles cover the most recent developments in relevant fields in an authoritative, succinct and broadly accessible manner. Together with a range of additional shorter formats, *Trends* journals collectively provide a forum for hypothesis and debate.

As part of its mission to be a leader in scientific communication, Cell Press also organizes scientific meetings across a wide range of topics, hosts online webinars to bring leading scientists to the broadest international audience, and is committed to promoting innovation in science publishing.

Contributors

Corresponding authors and affiliations

Bruno Antonny
Institut de Pharmacologie Moléculaire et Cellulaire, Université de Nice Sophia Antipolis et CNRS, 06560 Valbonne, France

Vytas A. Bankaitis
Department of Cell and Developmental Biology, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7090, USA; Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7090, USA

Clemens Cabernard
Biozentrum, University of Basel, CH-4056 Basel, Switzerland

David G. Drubin
Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720-3202, USA

Zvulun Elazar
Department of Biological Chemistry, The Weizmann Institute of Science, Rehovot, 76100, Israel

Scott D. Emr
Weill Institute for Cell and Molecular Biology, Cornell University, Weill Hall, Ithaca, NY 14853, USA; Department of Molecular Biology and Genetics, Cornell University, Weill Hall, Ithaca, NY 14853, USA

Daniel A. Fletcher
Bioengineering Department and Biophysics Program, University of California, Berkeley, CA 94720, USA; Physical Biosciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

Nathan W. Goehring
Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG), Pfotenhauerstraße 108, 01307 Dresden, Germany; Max Planck Institute for the Physics of Complex Systems (MPI-PKS), Nöthnitzer Straße 38, 01187 Dresden, Germany; Cancer Research UK London Research Institute, Lincoln's Inn Fields Laboratories, 44 Lincoln's Inn Fields, London WC2A 3LY, UK

Stephan W. Grill
Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG), Pfotenhauerstraße 108, 01307 Dresden, Germany; Max Planck Institute for the Physics of Complex Systems (MPI-PKS), Nöthnitzer Straße 38, 01187 Dresden, Germany

Gregg G. Gundersen
Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA

Barry Honig
Department of Biochemistry and Molecular Biophysics, Columbia University, 1150 Saint Nicholas Avenue, New York, NY 10032, USA; Howard Hughes Medical Institute, Columbia University, 1130 Saint Nicholas Avenue, New York, NY 10032, USA; Center for Computational Biology and Bioinformatics, Columbia University, 1130 Saint Nicholas Avenue, New York, NY 10032, USA

Junjie Hu
Department of Genetics and Cell Biology, College of Life Sciences, and Tianjin Key Laboratory of Protein Sciences, Nankai University, Tianjin 300071, China

Geert J.P.L. Kops
Department of Medical Oncology, Department of Molecular Cancer Research and Cancer Genomics Centre, University Medical Center Utrecht, 3584 CG Utrecht, The Netherlands

Galit Lahav
Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA

Jean-Claude Martinou
Department of Cell Biology, University of Geneva, Faculty of Sciences, 30 quai Ernest-Ansermet, 1211 Geneva 4, Switzerland; Surgical Neurology Branch, NINDS, National Institute of Health, Bethesda, MD 20892, USA

Tom Misteli
National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Ewa Paluch
Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, 01307, Germany; International Institute of Molecular and Cell Biology, Warsaw, 02-109, Poland

Tom A. Rapoport
Howard Hughes Medical Institute, Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA

Anne J. Ridley
Randall Division of Cell and Molecular Biophysics, King's College London, New Hunt's House, Guy's Campus, London SE1 1UL, United Kingdom

David C. Rubinsztein
Department of Medical Genetics, Cambridge Institute for Medical Research, Wellcome/MRC Building, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0XY, UK

Guillaume Salbreux
Max Planck Institute for the Physics of Complex Systems, Dresden, 01187, Germany

Lawrence Shapiro
Department of Biochemistry and Molecular Biophysics, Columbia University, 1150 Saint Nicholas Avenue, New York, NY 10032, USA

Berend Snel
Theoretical Biology and Bioinformatics, Department of Biology, Science Faculty, Utrecht University, 3584 CH Utrecht, The Netherlands

Manuel Théry
Laboratoire de Physiologie Cellulaire et Végétale, Institut de Recherche en Technologies et Sciences pour le Vivant, CNRS/UJF/INRA/CEA, 17 Rue des Martyrs, 38054, Grenoble, France

Frank Uhlmann
Chromosome Segregation Laboratory, Cancer Research UK London Research Institute, 44 Lincoln's Inn Fields, London WC2A 3LY, UK

Orion D. Weiner
Cardiovascular Research Institute and Department of Biochemistry, University of California San Francisco, San Francisco, CA 94143, USA

Howard J. Worman
Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA; Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA

Richard J. Youle
Surgical Neurology Branch, NINDS, National Institute of Health, Bethesda, MD 20892, USA

Preface

We are very pleased to present *Cell Press Reviews: Core Concepts in Cell Biology*, which brings together review articles from Cell Press journals in order to offer readers a comprehensive and accessible entry point into some of the most important topics in cell biology today. Articles were selected by the editorial staff at Cell Press with an eye toward providing readers an introduction to timely and cutting-edge research written by leaders in the field. While *Cell Press Reviews: Core Concepts in Cell Biology* is not an exhaustive overview of current cell biological advances, our aim is to give readers insight into some of the most exciting recent developments and the challenges that remain. A wide range of topics are covered within this publication, including the cell biology of genomes, mechanochemical patterning in cell polarity, mechanisms of membrane curvature, and insights into processes such as organelle growth, cell motility, and morphogenesis.

We are pleased to be able to include contributions from Tom Misteli, National Cancer Institute; Galit Lahav, Harvard Medical School; Scott D. Emr, Cornell University; David G. Drubin, University of California, Berkeley; Tom Rapoport, Harvard Medical School; Anthony A. Hyman, Max Planck Institute of Molecular and Cell Biology, Dresden; and many other prominent researchers in the field. Their insights will offer readers, both experts and those new to the field, a fascinating perspective into this critically important and evolving area of research.

Cell Press Reviews: Core Concepts in Cell Biology is one in a series of books being published as part of an exciting new collaboration between Cell Press and Elsevier Science and Technology Books. Each book in this series is focused on a highly timely topic in the biological sciences. Editors at Cell Press carefully select recently published review articles in order to provide a comprehensive overview of the topic. With the wide range of journals within the Cell Press family, including research journals such as *Cell, Current Biology*, and *Developmental Cell* as well as review journals like *Trends in Cell Biology*, these compilations provide a diverse and accessible assortment of articles appropriate for a wide variety of readers. You can find additional titles in this

series at http://www.store.elsevier.com/CellPressReviews. We are happy to be able to offer this series to such a wide audience via the collaboration with Elsevier Science and Technology Books, and we welcome all feedback from readers on how we might continue to improve the series.

Contents

Cell

The Cell Biology of Genomes: Bringing the Double Helix to Life

Tom Misteli[1,*]

[1]National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

*Correspondence: mistelit@mail.nih.gov

Cell, Vol. 152, No. 6, March 14, 2013 © 2013 Elsevier Inc.

http://dx.doi.org/10.1016/j.cell.2013.02.048

SUMMARY

The recent ability to routinely probe genome function at a global scale has revolutionized our view of genomes. One of the most important realizations from these approaches is that the functional output of genomes is affected by the nuclear environment in which they exist. Integration of sequence information with molecular and cellular features of the genome promises a fuller understanding of genome function.

INTRODUCTION

It was a moment of scientific amazement in 1953 when Watson and Crick revealed the structure of DNA. The magnificence of the double helix and its elegant simplicity were awe inspiring. But more than just being beautiful, the double helix immediately paved the way forward; its structure implied fundamental biological processes such as semiconservative replication and the notion that chemical changes in its composition may alter heritable traits. The linear structure of DNA laid the foundation for the concept that a string of chemical entities could encode the information that determines the very essence of every living organism. The beauty of the double helix was the promise that, if the sequence of bases in the genome could be mapped and decoded, the genetic information that underlies all living organisms would be revealed and the secret of biological systems would be unlocked.

The idea of linearly encoded genetic information has been spectacularly successful, culminating in the recent development of powerful high-throughput sequencing methods that now allow the routine reading of entire genomes. The conceptual elegance of the genome is that the information contained

in the DNA sequence is absolute. The order of bases can be determined by sequencing, and the result is always unequivocal. The ability to decipher and accurately predict the behavior of genome sequences was appealing to the early molecular biologists, has given rise to the discipline of molecular genetics, and has catalyzed the reductionist thinking that has driven and dominated the field of molecular biology since its inception.

But the apparent simplicity and deterministic nature of genomes can be deceptive. One of the most important lessons learned from our ability to exhaustively sequence DNA and to probe genome behavior at a global scale by mapping chromatin properties and expression profiling is that the sequence is only the first step in genome function. In intact living cells and organisms, the functional output of genomes is modulated, and the hard-wired information contained in the sequence is often amplified or suppressed. While mutations are an extreme case of genome modulation, most commonly occurring changes in genome function are more subtle and consist of fluctuations in gene expression, temporary silencing, or temporary activation of genes. Although not caused by mutations, these genome activity changes are functionally important.

Several mechanisms modulate genome function (Figure 1). At the transcription level, the limited availability of components of the transcription machinery at specific sites in the genome influences the short-term behavior of genes and may make their expression stochastic. Epigenetic modifications are capable of overriding genetically encoded information via chemical modification of chromatin. Similarly, changes in higher-order chromatin organization and gene positioning within the nucleus alter functional properties of genome regions.

The existence of mechanisms that modulate the output of genomes makes it clear that a true understanding of genome function requires integration of what we have learned about genome sequence with what we are still discovering about how genomes are modified and how they are organized in vivo in the cell nucleus.

THE STOCHASTIC GENOME

The genome is what defines an organism and an individual cell. It is therefore tempting to assume that identical genomes behave identically in a population of cells. We now know that this is not the case. Individual, genetically identical cells can behave very differently even in the same physiological environment. It is rare to find a truly homogeneous population of cells even under controlled laboratory conditions, as anyone who has tried to make a cell line stably expressing a transgene knows. Much of the variability in

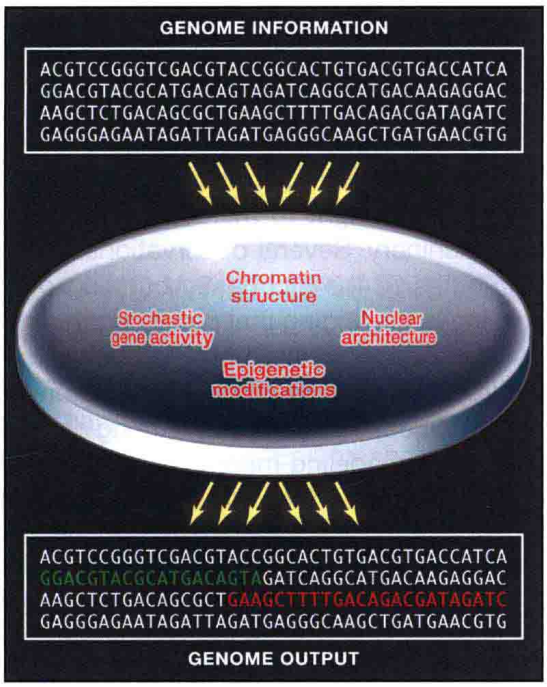


FIGURE 1 From Primary Sequence to Genome Output

The hard-wired primary information contained in the genome sequence is modulated at short or long timescales by several molecular and cellular events. Modulation may lead to activation (green) or silencing (red) of genome regions.

biological behavior between individual cells comes from stochastic activity of genes (Raj and van Oudenaarden, 2008).

Genes are by definition low-copy-number entities, as each typically only exists in two copies in the cell. Similarly, many transcription factors are present in relatively low numbers in the cell nucleus. The low copy number of genes and transcription factors makes gene expression inherently prone to stochastic effects (Raj and van Oudenaarden, 2008). Numerous observations make it clear that gene expression is stochastic in vivo. For example, dose-dependent increases in gene expression after treatment of cell populations with stimulating ligands, such as hormones, are often brought about by high expression of target genes in a relatively small number of cells in the population rather than by a uniform increase in the activity in all cells. Stochastic gene behavior is most evident in single-cell imaging approaches, and mapping by fluorescence in situ hybridization of multiple genes, which according to population-based PCR analysis are active in a given cell population, shows that only a few cells transcribe all "constitutively active" genes at any given time. Most cells only express a subset of genes, and the combinations vary considerably between individual cells. These observations