THE PHYSICS OF CANCER

Recent years have witnessed an increasing number of theoretical and experimental contributions to cancer research from different fields of physics, from biomechanics and soft-condensed matter physics to the statistical mechanics of complex systems.

Reviewing these contributions and providing a sophisticated overview of the topic, this is the first book devoted to the emerging interdisciplinary field of cancer physics. Systematically integrating approaches from physics and biology, it includes topics such as cancer initiation and progression, metastasis, angiogenesis, cancer stem cells, tumor immunology, cancer cell mechanics and migration.

Biological hallmarks of cancer are presented in an intuitive and yet comprehensive way, providing graduate-level students and researchers in physics with a thorough introduction to this important subject. The impact of the physical mechanisms of cancer are explained through analytical and computational models, making this an essential reference for cancer biologists interested in cutting-edge quantitative tools and approaches coming from physics.

CATERINA A. M. LA PORTA is Associate Professor of General Pathology at the University of Milan and group leader of the Molecular Oncology Laboratory there. In 2015 she founded the university's Center for Complexity and Biosystems. She has organized several interdisciplinary workshops on the physics of cancer funded by CECAM and ESF.

STEFANO ZAPPERI is Professor of Theoretical Physics at the University of Milan, where he coordinates the Center for Complexity and Biosystems, and Research Leader at the ISI Foundation in Torino. He is an expert in the statistical mechanics of non-equilibrium complex systems and has worked in fracture, plasticity, friction, magnetism and biophysics. He is the recipient of numerous awards and is currently the chairman of the steering committee of the Conference on Complex Systems.

THE PHYSICS OF CANCER

CATERINA A. M. LA PORTA
Università degli Studi di Milano

STEFANO ZAPPERI
Università degli Studi di Milano

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE
UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

4843/24, 2nd Floor, Ansari Road, Daryaganj, Delhi – 110002, India

79 Anson Road, #06–04/06, Singapore 079906

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning and research at the highest international levels of excellence.

www.cambridge.org
Information on this title: www.cambridge.org/9781107109599
DOI: 10.1017/9781316271759

First published 2017

Printed in the United Kingdom by TJ International Ltd. Padstow Cornwall

A catalogue record for this publication is available from the British Library.

Library of Congress Cataloging-in-Publication Data
Names: La Porta, Caterina, 1966– | Zapperi, Stefano.
Title: The physics of cancer / Caterina La Porta, Università degli Studi di
Milano, Stefano Zapperi, IENI-CNR, Milan.
Description: Cambridge : Cambridge University Press, 2017. |
Includes bibliographical references and index.
Identifiers: LCCN 2016057382 | ISBN 9781107109599
Subjects: LCSH: Eukaryotic cells. | DNA replication. | Cancer. | Cancer cells.
Classification: LCC QH447 .L37 2017 | DDC 571.6–dc23
LC record available at https://lccn.loc.gov/2016057382

ISBN 978-1-107-10959-9 Hardback

To Adriana and Ginevra with love.

Contents

Cambridge University Press
978-1-107-10959-9 — The Physics of Cancer
Caterina La Porta , Stefano Zapperi
Frontmatter
More Information

Preface

Understanding how cancer initiates, grows and migrates has been a fundamental topic of biomedical research in the past decades and is still the object of intense scientific activity. Cancer is a complex disease where many factors cooperate. According to the 2000 seminal paper by Hanahan and Weinberg, six biological capabilities (the *hallmarks of cancer*) encapsulate the key features describing the remarkable variability displayed by cancer: sustaining proliferative signaling, evading growth suppression, activating invasion and metastasis, inducing angiogenesis, resisting cell death, activating invasion and metastasis, enabling replicative immortality (Hanahan and Weinberg, 2000). In a more recent review, the same authors take into account the observations that emerged in the previous ten years and add four new hallmarks: avoiding immune destruction, promoting inflammation, genome instability and mutation, deregulating cellular energetics (Hanahan and Weinberg, 2011). Hence, after ten years the hallmarks of cancer are still to be understood and have even increased in number! This is a signal in our opinion that traditional approaches need new strings in their bows. Tumors are extremely heterogeneous and their growth depends on dynamical interactions among cancer cells and between cells and the constantly changing microenvironment. All these interactive processes act together to control cell proliferation, apoptosis and migration. There is an increasing consensus that these dynamical interactions cannot be investigated purely through single biological experiments because experimental complexity usually restricts the accessible spatial and temporal scales of observations. Therefore it is necessary to study cancer as a complex system.

Advances in systems biology are already beginning to have an impact on medicine through the use of computer simulations for drug discovery. The integration of new experimental physics techniques in cancer research may help improve, for example, the capability to design more efficient cancer therapies. Understanding the biology of cancer cells and the impact of physical mechanisms, such as cell and tissue mechanics, on their biological functions could help validate biomarkers and develop more accurate diagnostic tools and individualized cancer therapies. In the past years, clinical studies have relied heavily on conventional population-based randomized clinical trials that try to identify favorable outcomes as an average over the population. Cancers are, however, extremely heterogeneous even within the same tumor class, so that an average positive outcome does not necessarily translate to a positive outcome in individual cases. A novel interdisciplinary quantitative approach to cancer where physics and biology work in an integrated manner could help in explaining the main steps involved in cancer progression and guide individualized therapeutic strategies (Deisboeck et al., 2011).

In past years, contributions to cancer research arose sporadically from different fields of physics, including, among others, biophysics, biomechanics, soft-condensed matter physics and the statistical mechanics of complex systems. Cell biophysics is becoming a mature field, both experimentally and theoretically, but contacts with forefront cancer research have been only intermittent. It is becoming clear that mechanical forces play a pivotal role in many fundamental biological functions such as cell division and cancer processes, like metastasis. Biophysical measurements that compare the mechanical properties of normal and cancer cells have consistently shown that cancer cells are softer than normal cells and that this compliance correlates with an increased metastatic potential. This is related to the fact that a softer cytoplasm corresponds to a less organized cytoplasm. Soft-condensed matter studies materials such as colloids and polymers that have a direct relevance for biology, and the distance between the two fields is rapidly shrinking. Finally, methods derived from the statistical mechanics of complex non-equilibrium systems have been applied to a wide variety of biological problems, ranging from protein folding and the analysis of genetic data, to the spreading of epidemics, but applications to cancer are still rare. These extremely promising and innovative research activities are currently shaping a new scientific field based on the physics of cancer.

Despite the fact that interesting novel contributions to cancer research grounded in physical sciences are emerging, they are so far mostly ignored by mainstream cancer research, which relies on the traditional tools of biologists, such as biochemistry and genetics. Over the years, biologists have turned to engineers or computational scientists to solve specific problems, but their role has always been somewhat ancillary. The complexity of this issue would require instead a truly interdisciplinary approach where physical scientists and engineers will become partners with biologists and clinicians in defining and addressing challenges in medicine. A similar approach could lead to fundamental advances in a wide variety of fields, such as medicine and health care, but it will only flourish when solid interdisciplinary education is finally available to students in science and medicine

(Sharp and Langer, 2011). The present book on the physics of cancer tries to contribute in filling this gap by providing a general introduction to an emerging and challenging interdisciplinary field.

The book is conceived as an introductory study concerning the physics of cancer. Its targeted readership is composed of graduate students in physics, biology and biomedical research, especially those focusing on quantitative and/or computational biology. The book should also appeal to established researchers in physical, biological and biomedical sciences who wish to enter this new field. We have thus engaged in the admittedly complex task of making the book accessible to both biologists and physicists. To this end, we strived to provide didactic explanations of basic concepts and ideas both in physics and cancer biology, avoiding excessive jargon and recourse to heavy mathematical formalism.

The book is structured into eleven chapters addressing key aspects of cancer research from an interdisciplinary perspective. Chapter 1 provides a general introduction to the biology of the cell that should be especially useful for physicists and engineers. We also discuss biophysical aspects of the cell that could be useful for biologists who may already be familiar with these topics but from a different perspective. Chapter 2 describes and discusses the biological mechanisms underlying cancer from its origin to its progression, focusing on the main processes involved such as angiogenesis and metastasis. Chapter 3 provides a discussion of modeling strategies employed to study cancer. The chapter first starts with a simple introduction to the theory of branching process and its application to cell proliferation and then continues with more involved mathematical and statistical physics models for cancer evolution and progression. We also discuss numerical simulations of metabolic pathways. While some background in mathematics and probability is needed to fully appreciate this chapter, we have worked to make the topic understandable to biologists. Chapter 4 examines in more depth angiogenesis, describing the concept of vasculogenic mimicry and its consequences for cancer development. Physics-based computational models of angiogenesis are critically discussed. A new frontier in cancer research is focusing on the presence of a more aggressive cell subpopulation, known as cancer stem cells; Chapter 5 discusses our current understanding of cancer stem cells, including stochastic models that describe their kinetics and evolution. We also point out methodological problems involved in their detection. Chapter 6 is devoted to the role of mechanical forces in tumor growth, both for individual cells and for a tumor mass inside tissues. We discuss experimental measurements of mechanical properties of cancer cells. Chapter 7 is devoted to cell migration and its role for metastasis. Chapter 8 discusses chromosomal instability and nuclear mechanics. Most tumors are immunogenic, and a possible strategy to fight the cancer is to use immunity against cancer. In Chapter 9, we provide a biological overview both of the role of immunity in cancer and a discussion of computational models to study this kind of interaction. In Chapter 10, we discuss new challenges coming up in recent years on therapeutic strategies employed to fight cancer. We discuss classical methods based on radio- and/or chemo-therapy and more recent advances grounded in the physical sciences and nanotechnologies. The final chapter is devoted to a general outlook of the problem, focusing on how to integrate biological and physical sciences to build a new interdisciplinary field of research and train a new generation of scientists.

Acknowledgments

We would like to thank all the colleagues and collaborators who have contributed to shape our understanding of the physics of cancer. In particular, we wish to acknowledge interesting discussions with Mikko Alava, Martine Ben Amar, Eytan Domany, Ben Fabry, Lasse Laurson, Heiko Rieger, Jim Sethna, Alessandro Taloni, Guido Tiana and Lev Truskinovsky. Aalto University and the Weizmann Institute of Science are gratefully acknowledged for their hospitality, providing a quiet but stimulating environment where parts of this book were written.