Carlo C. Maley
Mel Greaves *Editors*

Frontiers in Cancer Research

Evolutionary Foundations, Revolutionary Directions

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This book is dedicated by Carlo C. Maley to Athena Aktipis, whose vision, foresight, and wisdom improved this book (and his life) immeasurably

Preface

This book provides authoritative reviews of the current state of knowledge at the boundaries of cancer research with a focus on the evolutionary biology and ecology of cancer. These are the theoretical foundations of cancer biology. One of the unique features of this book is its emphasis on the open questions. Traditional textbooks focus on what is known, but science is focused on the unknown and the process of discovery. In other words, science is focused on the open questions. This has recently been recognized by the US National Cancer Institute, which initiated a research funding program around "provocative questions" in cancer research. In fact, a number of the questions addressed in this book have been chosen by the provocative question initiative for funding.

The target audience for this book is scientists and people who want to understand the current limits of our knowledge about cancer. As such, we have asked the authors of the chapters to think hard about what are the most important open questions and provide their expert advice about how to answer them. We have organized the chapters so that they progress from the theoretical basis of cancer biology to the application of that theory to cell-level evolution in cancer and finally to the application of that theory to the evolution of humans and other multicellular organisms.

Theory of Cancer

After my introduction with my personal list of important open questions, Dr. Pepper opens the book with a consideration of the role of theory in cancer research. Biology, in contrast to physics, has been notoriously heavy on experiment and light on theory, and cancer biology is no exception. Pepper contrasts the "magic bullet" theory of cancer, focused on finding the next drug target, with the somatic evolutionary theory of cancer. He discusses open questions and barriers to progress in developing that theory, as well as its application to antiangiogenic drugs, the development of biomarkers, and the role of inflammation in cancer.

In the following chapter, Sottoriva and Tavaré focus on the open questions in population genetics of neoplasms. This involves the integration of mathematical modeling with both molecular and epidemiological cancer data. There is enormous potential in the development of quantitative tools to analyze the massive amounts of cancer data that we can now produce. That is, evolutionary theory offers tools to help turn cancer data into knowledge.

Cell-Level Evolution in Cancer

In Chap. 4, Merlo reviews the literature and open problems in the diversity, or intratumor heterogeneity, within neoplasms. Genetic diversity has only been measured in a few types of neoplasms to date, though there are a variety of feasible methods for doing so. Measures of diversity should predict progression in premalignant neoplasms as well as recurrence and survival in malignant neoplasms. Diversity is thus a candidate for a universal biomarker that should be applicable across cancers.

Natural selection is driven by the generation of heritable (i.e., genetic or epigenetic) diversity and the increase in frequency of variants with a relative fitness advantage over the other variants in the population. In other words, natural selection emerges from the interaction of genetic diversity with clonal expansion. In Chap. 5, Brash reviews what is known about clonal expansions in neoplasms. Whether or not a clone expands depends on its microenvironment and in particular what happens with its competitors. This is not simply a matter of proliferation but also apoptosis and tissue architecture, making space for clones to expand. The details of these spatial dynamics and differentiation of cells within the tissue have dramatic impacts on the rate of carcinogenesis.

The dynamics of differentiation in neoplasms is also at the heart of the cancer stem cell controversy that is taken up by Graham and Leedham in Chap. 6. The cancer stem cell hypothesis, that there is only a minority of cells in a neoplasm that are capable of self-renewal, is sometimes misleadingly contrasted against the somatic evolutionary theory of cancer. They are, in fact, compatible. From an evolutionary perspective, the cancer stem cell hypothesis is simply a hypothesis that the relevant somatic evolution is occurring in a minority population within the neoplasm. This has implications for the dynamics of somatic evolution but does not contradict it.

In Chap. 7, Shibata digs into the metapopulation dynamics of neoplasms that are subdivided into glands. Much of carcinogenesis probably plays out in such subdivided populations in epithelia. The dynamics of evolution in small numbers of stem cells in a gland are likely dominated by genetic drift and so are qualitatively different from the dynamics of large populations that are dominated by selection. The dynamics of stem cell populations in subdivided epithelia also dramatically impact the process of aging. He addresses these dynamics of carcinogenesis and aging through mathematical modeling and describe the kinds of experiments that can test the models and reveal those dynamics.

Most of the initial chapters are concerned with the somatic evolutionary process of neoplastic progression (carcinogenesis). However, this is not the process that kills us. Because the transition from localized disease to metastatic disease is essentially the transition from clinically manageable to unmanageable disease, most cancer deaths could be prevented if we could prevent those neoplasms from metastasizing in the first place. There are many open questions in the evolution of metastasis. In Chap. 8, Schiffman et al. discuss why metastasis is so lethal, how to prevent it and suggest ways of studying the evolution of metastasis.

In the following chapter, Gatenby takes up the implications of the evolutionary foundations of cancer for improving cancer therapy. How can we deal with, and perhaps even use, the evolutionary nature of neoplasms to our advantage? He reviews the lessons of applied ecology for the management of cancers. This is some of the most exciting work in cancer therapy today.

Organismal-Level Evolution in Cancer

The final section of the book shifts focus to the relationship between cancer and the evolution of multicellular organisms. Greaves and Aktipis address the hypothesis that a mismatch between the environment to which were are adapted, due to thousands of years of selection, and our modern environment leads to increased cancer rates. Though there are significant challenges in determining what those ancestral environments were, this is an attractive avenue of research because changing our environment (or modulating its effects on our biology) is relatively tractable. As a form of cancer prevention, this approach is also attractive because it can intervene before neoplasms have evolved high levels of genetic diversity and metastasis—that is, before they become clinically unmanageable.

In the following chapter, Nedelcu and Caulin take up Peto's paradox and the question of how the selective effects of cancers on their hosts have led to the evolution of cancer suppression mechanisms in multicellular organisms. Evolution has already solved the problem of cancer prevention, multiple times, everytime a species evolved to be larger and at least as long lived as humans. For each solution, evolution has had to account for the various trade-offs between cancer suppression and the other components of fitness. Evolution's solution to cancer prevention should be a gold mine of leads for cancer prevention in humans, with one caveat: it may be difficult to translate a germline genetic alteration in a large, long-lived species into a cancer prevention intervention in humans. But that has yet to be tried.

Finally Greaves concludes the book by tackling the problem of how to deal with the evolutionary resilience of cancer. He argues that there likely is no magic bullet for curing cancer. With such an evolvable system, even combinations of drugs may be inadequate. This suggests that we should shift attention and effort away from curing cancer to preventing it before it becomes an intractable problem. Such an emphasis then brings questions of the causation, detection, and intervention to the fore. Of course, even if we make great strides with cancer prevention, some people

will still develop cancers, and we will still be faced with the Herculean task of treating the disease. Greaves argues that, in addition to the innovations discussed by Gatenby, there is promise in targeting the tumor's ecosystem ("drain the swamp") and in slowing the pace of evolution to control the disease rather than eliminate it. I heartily second these points.

Tempe, AZ, USA Carlo C. Maley

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Contents

Chapter 1
The Evolutionary Foundations of Cancer Research

Carlo C. Maley

Abstract Cancer biology rests on the foundation of evolutionary biology and ecology. This is true both at the cellular and organismal level. Natural selection acts at the level of cells within a multicellular body, leading to the expansion of clones with survival or reproductive advantages. Which specific mutations or epigenetic alterations provide an advantage depends on the complex ecologies of the microenvironments within the tissue. These ecologies are poorly understood but include both the competing neoplastic cells as well as fibroblasts, lymphocytes, endothelial cells, extracellular matrix, nutrients, cytokines, etc. While these ecologies structure the selective pressures of somatic evolution, the dynamics of that somatic evolution are also poorly understood. At the organismal level, cancer was the primary problem that had to be overcome in order for a multicellular body to evolve. Sister cells had to be forced to stop proliferating on their own, and devote their energies to the reproduction and survival of the multicellular body. Cancer has been an important selective force, shaping multicellular bodies ever since. In this chapter I review the evolutionary theory of cancer, the history of that theory, and provide a brief discussion of additional important open questions in cancer biology. I also provide advice on experimental designs that allow us to study the evolution and ecology of cancer.

Keywords Somatic evolution • Acquired therapeutic resistance • Neoplastic progression • Theory of cancer

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1.1 The Importance of Evolution in Cancer

Evolutionary theory provides the theoretical foundation for cancer biology. It explains both how we get cancer and why it has been so hard to cure. These are two of the most important problems in all cancer biology. Evolution occurs not just at the organismal level, but also at the cell level. Cells are born and die. They accumulate somatic mutations during our lifetimes, some of which alter the rate at which those cells proliferate and die. Thus a cell and its progeny (a "clone") that have acquired a mutation that increases their survival or proliferation rate, will typically increase in frequency within our tissues (called a "clonal expansion"). In fact, all the hallmarks of cancer [1], which are supposed to be the general properties across all cancers, are phenotypes that enhance the proliferation or survival rate of cells. It is now clear that these phenotypes are general across cancers because they are the end result of natural selection at the cell level. The fact that this somatic evolutionary process is ultimately doomed by the death of the host does not negate the fact that evolution occurred at the cell level for hundreds, and perhaps thousands of cell generations [2, 3]. That evolution cannot be dismissed, because it often, in the end, kills us.

By the time a cancer patient presents in the clinic, her tumor likely has 10^9 to 10^{12} cells, with probably 10's of thousands of genetic alterations in each cell [4, 5], and a huge amount of diversity between those cells [6, 7], though this is poorly understood at the moment. The clinical observation has been that when a neoplasm recurs after therapy, it generally no longer responds to the initial therapy. Evidence has shown that this is often because the initial therapy selected for mutations that were present among the diverse cells at diagnosis but conferred therapeutic resistance to the neoplastic cell [8–15]. These surviving cells then regenerated the neoplasm and passed on their resistance phenotype to their daughter cells, leading to a recurrent, resistant neoplasm. This evolutionary mechanism of resistance is general to any selective pressure applied to a tumor. Every anti-cancer drug that has ever been invented selects for resistance, even the anti-angiogenic drugs that were thought to target the non-neoplastic (and thus non-evolving) endothelial cells. It was discovered that anti-angiogenic drugs select for neoplastic cells that use an alternative signal for angiogenesis that is not targeted by the drug [16]. It is quite possible that every anti-cancer drug that ever will be invented will also suffer this fate. This should shift our attention to how to prevent and manage therapeutic resistance.

The evolutionary theory of cancer has withstood over 40 years of experiment and clinical observation since Nowell's seminal publication [17]. The fact that somatic evolution occurs in neoplastic progression and acquired therapeutic resistance is not controversial. What is controversial are the dynamics of that process and what we should do about it. This presents us with wonderful clinical and scientific opportunities. We have a guiding theory for cancer, suggesting many avenues for progress. In most cases, these avenues remain unlit and unexplored. These opportunities are the inspiration for this book. Each chapter aims to focus attention both on what is known about an aspect of the evolutionary and ecological foundations of cancer, but also, more importantly, what is unknown, and suggests experiments for discovering how cancer works and how we can control it.

For the last four decades, cancer biology has been dominated by molecular biology. This work has led to many important insights and drugs that have cured people. However, molecular biology studies the proximal explanations for why cancer acts the way it does. In one case, a translocation or amplification of a proto-oncogene may cause aberrant proliferation. In another case, a genetic deletion or epigenetic silencing may prevent apoptosis from clearing a mutant cell. However, all of this work rests on the foundation of the ultimate cause of the aberration. Why do we observe these alterations and not others? Why do our therapies so often fail? The answer to these questions rest on the foundations of evolutionary and ecological theory that describe the dynamics and constraints that lead to the phenomena of cancer.

1.2 Previous Work: The History of the Evolutionary Theory of Cancer

The history of the evolutionary theory of cancer, near as I have been able to reconstruct it, really starts with the hematopoietic oncologists in the 1960's studying chromosome spreads of leukemic blast cells. Chromosome spreads, like the microscope, revealed a heretofore unseen world. With this genetic assay of single cells, people like DeGouchy, Nowell and Rowley, were able to see chromosomal aberrations, like the translocation between chromosomes 9 and 22, that characterize chronic myeloid leukemia [18–21]. But crucially, with the hematopoietic diseases, it was feasible to collect longitudinal blood samples and discover that later in progression, the leukemic cells bore not only the t(9:22) translocation, but also additional aberrations, including whole chromosome deletions, duplications and further translocations. In other words, there appeared to be "descent with modification" in the leukemic cells. Furthermore, not every cell bore identical lesions, and so the leukemias were actually composed of a diversity of cells, unified by common ancestry. The blood was full of these leukemic cells, indicating a pathological increase in the proliferation rate (or decrease in the death rate) of the cells. Thus, all the components of evolution were visible under the microscope: variation in the cell population that was passed on to daughter cells at division, some of which seemed to be associated with a proliferative advantage to the cells. In 1975 John Cairns published a paper pointing out that the tissue architecture of epithelia, divided into proliferative units like intestinal crypts, with small numbers of stem cells in each unit, should limit the selective consequences of carcinogenic mutations [22]. A year later, in 1976, Peter Nowell published the evolutionary theory of cancer in *Science* [17]. And then… nothing happened.

In retrospect, it appears that the evolutionary theory of cancer developed in the cultural background of the modern synthesis [23] of Darwin's theory of natural selection, Mendelian genetics, and population genetics. The beauty with which these theories fit together, and their mutual support, gave rise to Dobzhansky's famous saying "Nothing in biology makes sense except in the light of evolution."[24] The same can be said of cancer. At the time when he wrote that essay, in 1973, Dobzhansky himself was ill with a chronic lymphocytic leukemia that claimed his life 2 years later.