Introduction to Cancer Biology

A Concise Journey from Epidemiology through Cell and Molecular Biology to Treatment and Prospects

This concise overview of the fundamental concepts of cancer biology is ideal for those with little or no background in the field. A summary of global cancer patterns introduces students to the general principles of how cancers arise and the risk factors involved. By focusing on fundamental examples of the signalling pathways within cells, the functional effects of DNA damage are explained. Later chapters then build on this foundation to provide a comprehensive summary of the major signalling pathways that affect tumour development. Current therapeutic strategies are reviewed, along with a discussion of methods for tumour detection and biomarker identification. Finally, the impact of whole genome sequencing is discussed, bringing students up to date with key recent developments in the field. From basic principles to insights from cutting-edge research, this book will enable the reader to move into the cancer field with confidence. The online material that accompanies this book can be found at www.cambridge.org/hesketh.

Robin Hesketh has been a member of the Biochemistry Department at the University of Cambridge for over twenty-five years. He has taught at all undergraduate levels from first-year medicine to fourth-year biochemistry on a wide range of cell and molecular biology topics with a particular focus on cancer. His major research area is the development of anti-angiogenic strategies for the treatment of cancer. He is also the author of the popular science book *Betrayed by Nature: The War on Cancer* (2012).

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No cancer book should fail to acknowledge the vast, anonymous army of those who have confronted cancer and in so doing found the resolution to participate in medical research. Over the years they have made an immense contribution to our knowledge of cancer and, as we move into the era of personal genome sequencing, their role has become even more significant.

The scientific story rests, of course, on the wonderful labours of so many who have built the massive archive that represents our current state of knowledge. Its telling in this book has also drawn on countless hours of discussion with colleagues over many years, as well as on their lectures and published work. In addition I am profoundly grateful to more generations of students than I care to count for their stimulating input, ranging from questions eliciting a long pause, a big gulp and 'Mmm. . .' to comments on the clarity (or otherwise) of my lecture slides and handouts. The number who deserve acknowledgement thus runs into thousands, represented here, I'm afraid, only by the small number of specific citations I've been able to include.

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FOREWORD

In 1971, President Richard Nixon famously committed the intellectual and technological might of the USA to its great "war on cancer," signing in the National Cancer Act and making eradication of the disease both a national imperative and an international cause célèbre. Other than the space race, few if any peace-time endeavours have consumed such prodigious resources over such a protracted time-scale. Yet 40+ years and billions of dollars later, cancer still kills over one third of all people in what some fondly call the "developed" world. To many, this manifest failure is inexplicable and to a small fringe clear evidence that a cure has been found but is being suppressed for some nefarious end by an international conspiracy of governments and pharmaceutical companies. After all, rumours routinely circulate of natural products or extracts with amazing anti-cancer therapeutic efficacy but whose use is, for some unfathomable reason, shunned by the Western medical elite. The truth, however, is far less sensational but far more intriguing: cancers have emerged as an unexpectedly complex and diverse ensemble of diseases driven by mutations in processes that lie at the heart of the fundamental questions of biology – how cells, tissues and organisms self-build, self-assemble, self-maintain and self-repair. To comprehend cancer is no less daunting a task than comprehending the very organizational principles that underpin biology.

Discussions of cancer are further confounded by the misleading mythology that enshrouds it and endows it with both strategic foresight and murderous intent. Cancers are said to skulk unseen in our bodies - sometimes for decades – waiting to lash out, sicken, invade and kill. Then, as cancers spread and invade they are said to "progress" – a word loaded with directional purpose and carrying the clear implication that the disease is out to get you. In response to treatment, cancers "fight back," developing resistance and then returning with renewed and deadly vigour. All the time, the relationship between patient and cancer is depicted as a battle, literally to the death. Unfortunately, such language is not just counterproductive fearmongering – it is also plain wrong and appalling biology to boot. Cancers are not single entities but diverse, heterogenous ensembles of independently evolving clones. The rules governing cancers are the same as those that govern any evolutionary process – random variation in huge numbers of replicating individuals fuels selection for ever-fitter variants. In the case of cancers, the individuals are tumour cells and fitter means faster growth. A cardinal feature of natural selection is that we see only the winners – we have no idea how often cancers start but die out and the prodigious tumour cell death that chemo or radiotherapy of primary tumours usually triggers counts for little in the face of a small number of resistant residual clones that subsequently regenerate the disease and precipitate relapse.

Foreword

In this comprehensive new book on the molecular basis of cancer, Robin Hesketh offers us both illumination and demystification. Chapter 1 offers us a lucid and comprehensive survey of worldwide cancer incidence, but immediately confronts us with the still largely unexplained conundrum that the frequencies of so many cancers differ dramatically between cultures and nations. Some insight is offered in Chapter 2, which addresses the general issue of causes of the genetic changes that precipitate cancers. Even setting aside the witting depredations of tobacco and solar UV, the sinister truth is that our bodies and our environment are awash with all manner of carcinogens and mutagens that relentlessly pummel our DNA and epigenome. Mutations are inevitable: and so, as night follows day, is cancer. Chapter 3 lifts the lid on one of life's greatest underlying principles – biology is all about moving information around. Large, long-lived organisms like humans are comprised of a vast, heterogenous colony of self-assembling, self-organizing, self-diagnosing and self-repairing cells, each of which appears to know "who" it is, where it belongs and how it is supposed to behave. The key to unlocking this particular mystery is the processing and transduction machinery within each cell that receives, coordinates and interprets the signals that give cells their instructions. And exactly how this signal processing machinery gets corrupted in cancers is the theme of Chapter 4. Cancers are unique puzzles because they are diseases of misregulation: they arise by mutations in the genes that regulate key cellular processes – growth, proliferation, repair and survival, differentiation, movement and migration resulting in cells that are too many, in the wrong place, doing the wrong thing and at the wrong time. Understanding how such mutations cause cancer offers insights into how normal cells and tissues self assemble, maintain their architectures and regenerate when damaged.

The 1980s and 1990s were heady days in cancer research, when almost every month seemed to herald another dramatic example of the convergence between cell signaling/intracellular regulatory pathways and the proteins encoded by the ever-lengthening list of oncogenes and tumour suppressor genes mutated in various cancers. A fundamental principle of cancer biology with profound explicatory power had, indeed, been uncovered: mutations in various oncogenes and tumour suppressors loosened the shackles of intracellular regulators and brakes, propelling cancer cells into their pathological autonomy. Thereafter, additional traits would gradually accumulate that further augmented their potential to grow and spread. Many of these "hallmarks" affected cell autonomous properties, such as refractoriness to growth inhibitory signals and to programmed cell death and the switch to biosynthetic metabolism and aerobic glycolysis that Warburg had noted back in the 1930s. But oncologists and pathologists had long known that cancers are not merely monocultures of rogue cancer cells but complex, aberrant tissues. In the 1860s, Virchow noted the dramatic infiltration of tumours by leukocytes and other inflammatory cells, opining that cancers resembled "wounds that do not heal," while the remarkable vascular infiltration of many solid tumours led Judah Folkmann in the 1970s to formulate his groundbreaking notions on the necessity of angiogenesis for macroscopic tumour growth and dissemination. More recently, the pivotal role played by both fibroblasts and stroma in the initiation, maintenance, spread and therapeutic responses of cancers has emerged. Such observations highlight an important principle of the biology of multicellular organisms.

Foreword

To crudely paraphrase the 17th century satirist John Donne: "no cell is an island, entire of itself." Somatic cells may appear physically discrete down the microscope but everything about their biology is obligatorily social – their proliferation, differentiation, migration, metabolic state and, indeed, very survival are all dictated by extracellular signals. And while cancer cells have, indeed, lost some of these social constraints, they remain deeply reliant on the signals from, and activities of, neighbouring normal cells both for sustenance and to remodel tissue stroma and vasculature. It is therefore appropriate that Chapter 5 takes the time to consider not only what defines a cancer cell but also what defines a tumour.

The final chapters, 6, 7 and 8 make an especially intriguing trio. Having dealt in Chapter 3 with the nuts and bolts of how information is conveyed across cells and tissues, Chapter 6 takes us further down the rabbit hole to the deeper understanding that such signaling "pathways" are organized into networks – complex, self-regulating and self-correcting ensembles more akin to the internet than to telephone cables. Biologists understand such integration as an inevitable consequence of evolution – the potently creative mix of variation and selection painstakingly incorporating any tweaks, fixes, patches, feedback and integration with other processes that confers greater fitness. Ascertaining how such networks "function" is daunting for two reasons. First, they tend to respond as an integrated whole rather than as discrete but interconnected functional units. Where information is relayed in such a diffuse, iterative and parallel manner, where even the distinction between output and input is blurred, it can prove impossible to pin down cause-and-effect relationships. Second, evolution has a predilection for employing functional networks as general purpose signaling machines, redeploying them in a variety of other roles in other tissues. Perhaps of greatest significance to cancer therapy, however, is that such networks typically exhibit remarkable robustness, stability and uniformity of output despite perturbation, damage and variability and inconsistency in input. Given this, it is hardly surprising that even our newest cancer drugs, notwithstanding the unparalleled specificity and efficacy with which they inhibit their targets, frequently elicit unforeseen side effects and often lose efficacy as cancers progress and patients relapse. Finally, Chapter 8 is our ticket on the post-genomic roller coaster, a ride at once both entrancing and terrifying. State of the art technologies can now garner and catalogue extraordinary masses of data: whole cancer genomes can be sequenced and every dent or scratch in the DNA documented; the entire gamut of genes turned on or off at any juncture can be defined, compiled and presented in glorious, multicoloured ontogenies; and every protein present in a cell or tissue can be itemized, characterized and quantified. The devastating conclusion we distill from recent detailed analyses of individual cancers is that each person's cancer is different from every other, each with its own peculiar ensemble of mutations and epigenetic changes. Worse yet, recent studies reveal that a tapestry of interwoven diverse clonal lineages resides even within each single tumour. This is daunting, yes, but not altogether surprising. After all, the engine that powers the evolution of cancers is random heritable variation at (we now appreciate) both the genetic and epigenetic level and such variation, fueled as it is by intrinsic and environmental forces, is an inescapable fact of life. Our task now is find productive ways to use this information to improve cancer therapy.

Foreword

The most obvious strategy is to personalize cancer treatment – to take advantage of the speed and plummeting costs of state-of-the-art genomic technologies to define the molecular architecture of each patient's cancer and build a treatment regimen around that architecture – is personalized therapy. In so doing, it will be essential to identify where the robustness and functional redundancy resides in oncogenic pathways and networks, and to map within those networks how and where resistance arises in response to targeted therapies. Ultimately, to avoid the evolution of drug resistance and the all-too-familiar spectre of patient relapse we may need to develop strategies that specifically target functionally non-redundant processes, since these cannot be circumvented by adaptive compensation or evolution. Here, we may be heartened by one of the conclusions from Chapter 6 – that most of the diverse mutations in human cancers in the end converge on a relatively small number of core pathways (e.g. Ras, Myc, E2F/RB1, p53, NF-κβ, STAT3, TGFβ). It seems that underneath the glittering diversity of cancers there lies a deep commonality – and maybe the potential for novel therapeutic strategies in the future.

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INTRODUCTION

The aim of this book is to provide an introduction to the science of cancer for those coming to the topic for the first time – be they students or graduates or post-doctoral scientists moving into the field of oncology. That is, to paint a picture of what we think happens to cells and molecules in the making of cancers, how it bears on diagnosis and prognosis, and where the science is taking us in terms of treatment. To scientists and non-scientists alike, cancer can seem almost the ultimately daunting subject. It's true that cancers are the most complex diseases that afflict us and it is arguable that no two cases are identical, if all the biochemical changes involved are identified. However, while at some point we will face that problem – indeed we shall see that its very complexity may offer some advantage in the therapeutic battle against the disease – it's now clear that the underlying principles by which cancers arise are remarkably consistent and conceptually straightforward.

By keeping that in mind it is possible to advance through the story by the following relatively simple steps:

1. Consider some facts about the frequency with which cancers arise across the world and what the distribution patterns of different types of cancer, that is the epidemiology, tell us about the underlying causes.
2. Review the major risk factors. Some of these are beyond our control: for the others we consider possible measures to reduce the risk of getting the disease. This takes us from cancer statistics to the underlying science, and a discussion of why the causes can sometimes be difficult to confirm and why there is such variation in treatment efficacy between and even within countries.
3. The fundamental feature of cancer is the perturbation of normal cellular control, most critically of the machinery that regulates cell growth and division – the cell cycle – and we consider next how cells respond to environmental cues, focusing on one major signalling pathway.
4. Mutations are the driving force in cancer progression and the critical targets are the central pathways that regulate the cell cycle. In this chapter we consider mutations: the nature of the alterations that can occur in DNA and how they can affect protein and, hence, cellular function. Although many genes may be targets, there are only three basic mutational mechanisms and we use a minimal number of examples as illustrations.
5. These mutational changes convert cells from normal to aberrant, cancerous behaviour. In this chapter we define what makes a tumour cell in terms of the characteristics that differentiate them from normal cells. These emerge as eight major features associated with the development of primary cancers and the progression to a malignant phenotype. Of these, the most critical is the capacity to metastasise,

that is, for cells to migrate from primary tumours through the body to colonise secondary sites.

6. This leads to a more comprehensive view of the aberrations that can occur in intracellular signalling pathways to promote cancer. The initial focus is on a core of pathways, parts of which are abnormal in virtually all cancers. The discussion then expands to consider all the major signalling routes from the plasma membrane to the nucleus and the associations that some of these have with specific types of cancer. This reveals a complex interacting 'information network' of proteins and raises the question of how cells make sense of such complex signalling inputs to enable them to mount a discrete response.
7. The penultimate chapter reviews the progress in both diagnosis, monitoring and therapy in the latter part of the twentieth century and the remarkable advances that have already occurred in the first decade of this century, highlighting the extraordinary scientific diversity that is being brought to bear on cancer.
8. The final chapter focuses on the impact of the revolution in DNA sequencing that has seen the birth of 'personalised medicine' and has already wrought drastic changes in our approach to cancer research, diagnosis and treatment.

The intention therefore is to provide a book that will be the ideal companion to most student courses on cancer. The starting level required is not much more than knowing what a molecule is and having a general concept of a cell. The chapters that introduce cell signalling and mutations are designed to be as easy as possible by describing only sufficient specific examples to illustrate the key points. Similarly, the chapter discussing the behavioural changes associated with the switch from normal to tumour concentrates on the cell biology, keeping specific mentions of genes and proteins to a minimum. The emphasis therefore is on the principles, with diagrams and photographs to help convey the key points without becoming submerged in detail, as can so easily happen in this field. To avoid appearing to over-simplify, Chapter 6 comprises a basic summary of the central molecular defences against cancer but then reviews the major signalling pathways involved in some detail. This confers a reasonably comprehensive perspective and it also opens the way to discussing therapeutic strategies, a field that is considered in the following chapter in a review that takes us from the introduction of the first specific drugs to the current situation. The last chapter deals with genomics and the sequencing revolution that has taken us into the world of 'personalised medicine'. This has dramatically enlarged the scope for therapeutic intervention and we end with a summary of the prospects for cancer treatment as we move into this new era.

In addition to a glossary (the terms therein being emboldened on first appearance in the text), there are five appendices that provide supporting reference sources: Appendix A describes how tumours are graded and staged; Appendix B provides a list of molecular targets for currently available anti-cancer drugs; Appendices C and D summarise the main classes of oncoproteins and tumour suppressor genes; and Appendix E summarises the principal features of the ten types of cancer that predominate in terms of global mortality.

Introduction

The encouraging message is that if we limit the amount of detail we attempt to absorb, the essential principles of cancer become easy to grasp – in contrast, say, to the problems our physicist colleagues have in trying to explain theories of quantum gravity. The enduring message is that, although cancer remains as fascinating as ever from a scientific point of view, the progress that has been achieved has replaced at least some of its mystery with effective treatments and that each passing year sees an increase in the proportion of individuals who are afflicted with cancer and yet triumph.

The online materials that accompany this books include chapter-by-chapter multiple-choice questions, short-answer questions and essay titles for students. Answers and suggested key points for essays are available for instructors. These can be found at www.cambridge.org/hesketh.

Gene nomenclature

The HUGO Gene Nomenclature Committee (HGNC: www.genenames.org/index.html) assigns unique symbols to human genes. Gene names are written in italicised capitals; the protein that they encode is non-italicised: *EGFR* (gene)/EGFR (protein). They are pronounced phonetically when possible (SRC is *sarc*, MYC *mick*, ABL *able*). Viral forms are prefixed by v- (e.g. v-*src*). For some genes that have commonly used informative names both are shown (e.g. *SLC2A1*/GLUT1 and *SLC2A5*/GLUT3).