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Stella Pelengaris, PhD, was a Senior Research Fellow in Molecular Medicine in the Department of Biological Sciences at the University of Warwick and Warwick Medical School. While working at the Imperial Cancer Research Fund, she established a series of unique model systems for studying the role of c-Myc and apoptosis in cancer initiation and reversal. From 1999 to 2008 she and Michael Khan jointly ran the Cancer Research Group at the University of Warwick, where, in collaboration with Gerard Evan, they confirmed the inherent tumor suppressor activity of c-Myc (apoptosis) as a major barrier to oncogenic activity of c-Myc. Stella is now director of Pharmalogos Ltd, in which capacity she provides advice to biotechnology and pharmaceutical companies on promising novel targets for future oncology therapy developments.

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Preface to the Second Edition

Based on our extensive experience of teaching undergraduates and postgraduates, it became clear that no single current resource covered in detail the cellular and molecular changes that give rise to cancer alongside the basic principles of biology and clinical practice, without which these cannot be readily understood. We had not intended to write a textbook at this stage in our careers, but realized that there was a real need for such a work for undergraduates, medical students, and even established researchers in the field. Very few cancer molecular biology textbooks were available that started at the beginning, using a format and language easy to digest, and included not only a comprehensive description of all aspects of cancer biology but also important chapters on diagnosis, treatment, and care of cancer patients.

Much has changed since the first edition and we have responded to the explosion in knowledge around targeted therapies and how these are developed and tested. Moreover, the emergent field of systems biology has impacted strongly on cancer biology, and may well revolutionize the way in which we view, study, and treat cancer in the near future, in particular with the inextricable association with concepts such as individualized and tailored therapies. We follow a similar structure to the first edition, but all chapters have been extensively revised, new chapters have been added, and an even stronger up-front emphasis has been placed on first presenting easy-to-digest models served up in plain English.

Students are first introduced to an overview of the cancer cell and important new concepts and those which are only just emerging (Chapter 1), and of selected human cancers (Chapter 2), following which the textbook covers in depth those key cellular processes of greatest relevance to cancer. Thus, Chapters 3–14 cover the full range of cancer-relevant biology, including highly topical and important areas such as apoptosis, telomeres, DNA damage and repair, cell adhesion, angiogenesis, immunity, epigenetics, and the proteasome, as well as traditionally important areas such cell-cycle control, growth regulation, oncogenes, and tumor suppressors. A major improvement on the first edition has been the inclusion of a detailed account of how cancer drugs are developed and brought to market. Moreover, the great strides forward in targeted treatments have allowed us to introduce Chapter 16, specifically to link the subject of each of the scientific chapters to classes of newly available treatments or to those in various stages of development. The result is that the science is put firmly into the context of treating cancer patients – the relevance becomes crystal clear.

The book then gives a description of cancer diagnosis, treatment, and care of cancer patients, which is not only essential to medical students but also important for cancer researchers and biology students who need to have a broader view of cancer and its impact. Finally, Chapter 20 concludes with a vision of how the future of cancer biology and oncology may be directed by interdisciplinary sciences, such as the exciting field of systems biology and the new technologies that underpin it.

The role of textbooks as information repositories is increasingly under threat. Yet even now that we are well into the new millennium, with students and researchers alike bathed in seemingly limitless available information on the World Wide Web, textbooks still exist. Why is this? With the near-universal availability of Internet access to students and researchers, the most current information is potentially available to any interested party almost instantaneously. No printed source can hope to provide the same immediacy of the latest breakthroughs or experimental findings, although they are free of the distractions of online gambling, 24-hour shopping, and less savory diversions that plague the Internet. However, limitless information creates new problems, namely how to evaluate, correlate, and place into context this wealth of knowledge. More than a million cancer-related publications are referenced on Medline alone, and even for the initiated it can prove daunting to attempt to construct a balanced overview of the many aspects of cell and molecular biology that impact on cancer. Because of these difficulties, one of the key aims of this book is to provide in a single source the necessary framework within which new information can subsequently be aligned and a more comprehensive, but still contextual, understanding of cancer achieved. In particular, we have taken the opportunity to highlight controversial areas and to identify areas of research promise, while establishing potential links between often diverse subdisciplines in a coordinated and accessible way. It is hoped that, having read this book, the reader will be suitably equipped to understand the significance and relevance to cancer of a new publication and be able to place the work into an overall picture of the disease. Moreover, the book should also provide established cancer researchers with valuable insights into the important questions that remain to be addressed.

The issue of references, how many and where to cite, is often difficult to judge for a textbook. One has to balance the flow of the text with the need to give pointers to the reader for further information and to highlight key studies. This textbook can be used by undergraduates in biology and medical students and can be used alongside cancer biology courses structured either for a quarter or semester system. Moreover, the book will be of value to those preparing for professional exams in medicine and oncology and for established cancer researchers seeking a single-source overview of all aspects of cancer.
Features

We have included a number of features to facilitate the use of this textbook to teach cancer biology:

- Each chapter begins with a series of bullet points which explain the key concepts and illustrate areas of controversy in plain English. This is the platform on which the more complicated and detailed processes and models will be built throughout the rest of the chapter.
- Each chapter builds on concepts learned in previous chapters and is organized in a similar fashion, starting with an introduction and ending with a “Conclusions and future directions” section, a list of key outstanding questions remaining in the field, suggestions for further reading, and questions for student review.
- All the chapters contain textboxes that provide additional and relevant information as it relates to a described concept and are fully illustrated throughout.

Reviews of the First Edition

“Pelengaris, Khan, and the contributing authors are to be applauded. The Molecular Biology of Cancer is a comprehensive and readable presentation of the many faces of cancer from molecular mechanisms to clinical therapies and diagnostics. This book will be welcomed by neophyte students, established scientists in other fields, and curious physicians.” Dean Felsher, Stanford University

“The explosion of information on the molecular biology of cancer, and its widespread and immediate availability via the internet, provides major challenges for those engaged in cancer treatment and research. A single up-to-date reference textbook on this topic is needed more than ever. This book will go a long way towards meeting this need, providing a valuable resource for a range of individuals and departments.” Stan Kaye, Royal Marsden Hospital, London
Acknowledgments

An enormous number of talented scientists contributed to the knowledge described in this textbook. We acknowledge the many colleagues past and present whose important work could not be referenced in the text due to space constraints. In addition, we apologize if we failed to adequately identify contributions in the reference section at the end of this text. This oversight was not intentional, but rather a reflection of the overwhelming number of contributors to this field.

We thank mentors past and present for their help and encouragement: Martin Raff and Anne Mudge for making cell biology interesting and intelligible and Gerard Evan for introducing us to the world of cancer research. We thank our friends and colleagues who took time from their hectic research and clinical commitments to contribute to this book. In addition to those mentioned in the first edition, we especially thank our dedicated research team, Sylvie, Luxian, Yi-Fang, Elena, and Liam for bearing with us while we were writing and editing this book and for their patient reading and suggestions for improving the text. A special thanks is due to David Epstein FRS, our friend and colleague, for taking on too many tasks while we were occupied with this venture as well as for reading several chapters. We also greatly appreciate the suggestions and the gentle way in which these were presented by our friend Anthony Parker. Finally, we thank freelance project manager Nik Prowse and freelance copy-editors Cheryl Adam and Harriet Stewart-Jones, who have painstakingly teased out our many abuses of English and have helped us eliminate every tortured metaphor and incomprehensible sentence. Any that remain are entirely our fault. We are also very grateful to Rosie Hayden and Kelvin Matthews at Wiley-Blackwell for the belief and support of this exciting adventure.

We also acknowledge the contributions of our outside reviewers: Stewart Martin of Nottingham University; Brian Keith of the University of Pennsylvania; S.J. Assinder of the University of Wales, Bangor; Satya Narayan of the University of Florida; Mary Jane Niles of the University of California, San Francisco; Fiona Yull of Vanderbilt University, as well as those who have chosen to remain anonymous.

Reviewing is an enormous and time-consuming activity. We greatly appreciate the time spent by our reviewers, generating insightful and helpful comments.

For the cover figure showing a multiplexed protein expression image of colorectal cancer we owe a big thank you to our friends and collaborators Adnan Mujahid, Shan-E-Ahmed Raza, Professor David Epstein FRS, and Dr Nasir Rajpoot, from the Department of Computer Science at University of Warwick, and to the much-missed former doctoral student Dr Sylvie Abouna.

Dedication

This book is dedicated to our parents, whose unceasing support and encouragement made this work possible. A much loved father who recently finally lost his brave struggle with lung cancer would be particularly proud of this legacy. We also thank our daughter Charlotte for providing the perfect balance to academic work, namely a very happy and always entertaining family life. Many friends have helped and encouraged us through this process and we particularly thank Anthony Parker, David Epstein, and Liam Jones for their tactful and valuable comments.
About the Companion Website

This book is accompanied by a companion website: www.wiley.com/go/pelengaris/molecularbiologyofcancer

The website includes:

- References for each chapter
- Powerpoints of all figures and tables from the book for downloading
Introduction

By doubting we come to enquiry, and by enquiring we pursue the truth.

Abelard, 1079–1140

The legend went, unconfirmed and unaccredited, but still propagated.

Charlotte Bronte

Everybody said so. Far be it from me to assert that what everybody says must be true. Everybody is, often, as likely to be wrong as right.

Charles Dickens

Much has changed since the last edition. If you inadvisably type the word “cancer” into PubMed you will now be rewarded with over 2.5 million papers and reviews, a figure increasing at a rate of around 4000 per month, making a complete nonsense of any pretensions to keep up to date. Yet, some bold conclusions may be drawn from this overflowing font of knowledge.

The world of cancer remains one of relentless clonal competition and selection – a cellular “Tumor’s Got Talent.” Yet cancer cells, performing from their rewritten genomic libretto, are no longer the unchallenged divas of the tumor opera. The stroma, previously regarded as the backdrop against which portentous cellular events were enacted, has now finally gained recognition for staging the whole performance. Moreover, just as no rousing aria is possible without appropriate cooperation between stage and pit, so few cells will hit a high C and fulfill their malignant potential without the incendiary score orchestrated by chronic inflammation, both prefiguring and fomenting the development of most epithelial cancers.

Caught in the slipstream of inflammatory cells and mediators, junior cancer cells are propelled to their fate by the accretion of liberating epimutations. Through chronic inflammation, normal conformist cell behaviors may be cast aside. Paradoxically, those same liberating forces may also offer a chink in cancer’s armour, an Achilles’ heel that if correctly exploited could leave the cancer cells ripe for sacrifice on the altar of their own oncogenes.

We are also now much more aware of how a cancer cell may be fashioned not by occasional seismic molecular events but often by the infinitely subtle calibrations of cellular behavior played out over many years. These shifts occur under the auspices of inherited and sequentially acquired mutations. New high-throughput molecular techniques are enabling us to read this curriculum vitae of the cancer cell. Following the molecular clues leads us inexorably to an identification of the culpable mutations, at least where we avoid *cum hoc ergo propter hoc* fallacies by supporting conjecture with appropriate functional studies and clinical trials. We are increasingly able to differentiate propitious and “mission critical” molecular alterations from irrelevant bystanders; the practical benefit is the reduced list from which will be drawn our new treatment targets.

Successful deployment of pharmaceutical hardware requires a knowledge not only of what to target but also who to target. Thus, among the cancer cells themselves, all is not as it was. We are now seeking to identify the hardliners and the agents provocateurs – those responsible for inciting and maintaining the cancer and therefore arguably the engine for malignant behavior. This cancer elite includes the elusive so-called “cancer stem cells” (CSCs), referencing their perceived molecular and functional similarity to normal stem cells. These pernicious cells, along with the epithelial–mesenchymal transition (EMT), the molecular plan that directed their evolution, are likely to become the key targets for new cancer therapies. By implication, does this suggest that other tumor cells will henceforth be relegated to the position of subsidiary drones, meagre ciphers that will automatically reconform to the template of acceptable cell behavior once CSCs are no longer there to throw them out of kilter? We must wait and see.

Another important concept concerns the relative clinical importance of the primary tumor as compared to the infinitely more dangerous distant colonies that have been seeded from it. Patients rarely die because their primary tumors enlarge; they die because some cancer cells desire Lebensraum. Sallying forth from their ancestral homeland, cancer cells establish footholds within immediately adjacent territories but also in more distant and alien environments that are connected to the primary tumor by vessels and lymphatics. The road to hell is paved with endothelial cells. Initially precarious and potentially vulnerable to an effective counterattack, these estranged voyagers will eventually give rise to an increasingly malign and radicalized cadre of invasive...