Contents

Contributors, vii Preface to the Second Edition, ix Reviews of the First Edition, x Acknowledgments and Dedication, xi About the Companion Website, xii

Introduction, 1

1 Overview of Cancer Biology, 3

Michael Khan and Stella Pelengaris Introduction, 5 Cancer incidence and epidemiology, 8 Towards a definition of cancer, 8 Causes of cancer, 16 Cancer is a genetic disease, 21 Cancers (and Darwin's finches) evolve by mutation and natural selection, 21 Blame the parents - inherited single gene defects and susceptibility to cancer, 21 The cancer "roadmap" - What kinds of genes are epimutated in cancer?, 23 Viruses and the beginnings of cancer biology, 25 Hens and teeth or bears and woods? The hens have it - cancer is rare, 25 The barriers to cancer, 25 What is the secret of cancer developme ... "timing", 28 Location, location, location – the cancer environment: nanny or spartan state, 28 Cancer goes agricultural, 29 Cancer superhighways - blood vessels and lymphatics, 31 On your bike and turn the lights off before you go, 31 Catching cancer, 31 Hammering the hallmarks, 32 Painting a portrait of cancer, 33 The drugs don't work, 34 Mechanism of origin rather than cell of origin - towards a new functional taxonomy of cancer, 35 Is it worth it?, 36 Conclusions and future directions, 36 Bibliography, 37 Appendix 1.1 History of cancer, 40 2 The Burden of Cancer, 43

William P. Steward and Anne L. Thomas

Introduction, 43 Lung cancer, 45

Breast cancer, 49 Colorectal cancer, 53 Carcinoma of the prostate, 56 Renal carcinoma, 57 Skin cancer, 58 Carcinoma of the cervix, 60 Hematological malignancies, 60 Conclusions and future directions, 63 Outstanding questions, 63 Bibliography, 64 Questions for student review, 66

3 Nature and Nurture in Oncogenesis, 67

Michael Khan and Stella Pelengaris

Introduction, 69 Risk factors, 73 Preventing cancers, 76 Cancer genetics - in depth, 78 Cancer genomics, 87 Gene-environment interactions, 89 Mutations and treatment, 89 Chemoprevention of cancer, 90 Risk factors act in combination, 90 Environmental causes of cancer, 93 The clinical staging and histological examination of cancer, 101 Screening and biomarkers, 102 Somatic gene mutations, epigenetic alterations and multistage tumorigenesis, 105 Conclusions and future directions, 107 Outstanding questions, 107 Bibliography, 107 Questions for student review, 109

4 DNA Replication and the Cell Cycle, 111

Stella Pelengaris and Michael Khan

Introduction, 112 The cell cycle - overview, 114 Phases of the cell cycle, 120 The cell-cycle engine: cyclins and kinases, 123 Regulation by degradation, 126 Regulation by transcription, 129 MicroRNAs and the cell cycle, 131 Chromatin, 131 DNA replication and mitosis, 131 Checkpoints - putting breaks on the cell-cycle engine, 135 The DNA damage response (DDR), 136

The checkpoints, 136 Cell-cycle entry and its control by extracellular signals, 138 Changes in global gene expression during the cell cycle, 139 Cell cycle and cancer, 139 Drugging the cell cycle in cancer therapies, 141 Conclusions and future directions, 142 Outstanding questions, 143 Bibliography, 143 Questions for student review, 144

5 Growth Signaling Pathways and the New Era of Targeted Treatment of Cancer, 146

Stella Pelengaris and Michael Khan

Introduction, 147 Growth factor regulation of the cell cycle, 150 Growth homeostasis and tissue repair and regeneration, 151 Regulated and deregulated growth, 155 Cellular differentiation, 157 Tissue growth and the "angiogenic switch", 158 Cancers and nutrients, 158 Growth factor signaling pathways, 160 A detailed description of signal transduction pathways and their subversion in cancer, 160 Translational control and growth, 184 Conclusions and future directions, 185 Outstanding questions, 185 Bibliography, 186 Questions for student review, 187

6 Oncogenes, 188

Stella Pelengaris and Michael Khan Introduction, 189 The oncogenes, 189 The discovery of oncogenes ushers in the new era of the molecular biology of cancer, 191 Overview of oncogenes, 191 Types of oncogenes, 193 Oncogene collaboration - from cell culture to animal models, 199 The c-MYC oncogene, 199 The RAS superfamily, 213 SRC - the oldest oncogene, 228 BCR-ABL and the Philadelphia chromosome, 232 The BCL-2 family, 235 Biologically targeted therapies in cancer and the concept of "oncogene addiction", 235 Conclusions and future directions, 235 Outstanding questions, 236 Bibliography, 236 Questions for student review, 238

7 Tumor Suppressors, 239

Martine F. Roussel

Introduction, 239 The "two-hits" hypothesis: loss of heterozygosity (LOH), 240

Haploinsufficiency in cancer, 240 Epigenetic events, 242 Definition of a tumor suppressor, 242 The retinoblastoma protein family, 242 p53/TP53, 250 INK4a/ARF, 254 The p53 and RB pathways in cancer, 257 Senescence and immortalization: Role of RB and p53, 258 Tumor suppressors and the control of cell proliferation, 258 Tumor suppressors and control of the DNA damage response and genomic stability, 260 The microRNAs and tumor suppressors, 260 Conclusions and future directions, 263 Acknowledgments, 263 Outstanding questions, 264 Bibliography, 264 Questions for student review, 265

8 Cell Death, 266

Stella Pelengaris and Michael Khan Introduction, 267 An historical perspective, 267 Apoptosis in context, 267 Apoptosis as a barrier to cancer formation, 271 Apoptosis versus necrosis, 271 Cell death by necrosis - not just inflammatory, 272 The pathways to apoptosis, 272 The apoptosome - "wheel of death", 274 Caspases - the initiators and executioners of apoptosis, 274 The IAP family - inhibitors of apoptosis and much more, 276 The central role of MOMP and its regulators in apoptosis - the BCL-2 family, 279 Mitochondrial outer membrane permeabilization (MOMP), 281 Endoplasmic reticulum stress, 282 Stress-inducible heat shock proteins, 282 Tumor suppressor p53, 282 Oncogenic stress: MYC-induced apoptosis, 283 Autophagy – a different kind of cell death and survival, 287 Cell death in response to cancer therapy, 290 Exploiting cell death (and senescence) in cancer control, 290 Conclusions and future directions, 292 Outstanding questions, 293 Bibliography, 293 Questions for student review, 294

9 Senescence, Telomeres, and Cancer Stem Cells, 295

Maria A. Blasco and Michael Khan

Introduction, 296 Senescence, 298 Conclusions and future directions, 310 Outstanding questions, 310 Bibliography, 311 Questions for student review, 312

10 Genetic Instability, Chromosomes, and Repair, 314

Michael Khan

Introduction, 316 Telomere attrition and genomic instability, 321 Sensing DNA damage, 323 Repairing DNA damage, 325 Checkpoints, 336 Microsatellites and minisatellites, 343 Chaperones and genomic instability, 344 Cancer susceptibility syndromes involving genetic instability, 345 Genomic instability and colon cancer, 346 Conclusions and future directions, 346 Outstanding questions, 347 Bibliography, 347 Questions for student review, 349

11 There Is More to Cancer than Genetics: Regulation of Gene and Protein Expression by Epigenetic Factors, Small Regulatory RNAs, and Protein Stability, 350

Stella Pelengaris and Michael Khan

Introduction, 351 The language of epigenetics, 353 Epigenetics, 353 Methylation of DNA, 359 Acetylation of histones and other posttranslational modifications, 360 Epigenetics and cancer, 362 CIMP and MIN and the "mutator phenotype", 365 Imprinting and loss of imprinting, 366 Clinical use of epigenetics, 367 Regulation of translation, 368 Noncoding RNA and RNA interference, 369 Therapeutic and research potential of RNAi, 371 Treatments based on miRNA, 373 Regulating the proteins, 373 Therapeutic inhibition of the proteasome, 376 Receptor degradation, 377 Wrestling with protein transit - the role of SUMO and the promyelocytic leukemia (PML) body, 377 Conclusions and future directions, 380 Outstanding questions, 380 Bibliography, 381 Questions for student review, 382

12 Cell Adhesion in Cancer, 383

Charles H. Streuli

Introduction, 383
Adhesive interactions with the extracellular matrix, 384
Cell-cell interactions, 393
Critical steps in the dissemination of metastases, 395
E-cadherin downregulation in cancer leads to migration, 399
Epithelial-mesenchymal transitions, 401
Integrins, metalloproteinases, and cell invasion, 402
Survival in an inappropriate environment, 404 Conclusions, 406 Outstanding questions, 406 Bibliography, 407 Questions for student review, 409

13 Tumor Immunity and Immunotherapy, 410

Cassian Yee

Introduction, 410 Endogenous immune response, 411 Effector cells in tumor immunity, 413 Tumor antigens, 417 Antigen-specific therapy of cancer, 420 Clinical trials in vaccine therapy, 422 Cytokine therapy of cancer, 423 Tumor immune evasion, 424 Clinical trials in immunomodulatory therapy, 425 Conclusions, 425 Bibliography, 426 Questions for student review, 427

14 Tumor Angiogenesis, 429

Christiana Ruhrberg

Introduction, 429
General principles of new vessel growth, 430
Pathological neovascularization: tumor vessels, 430
Basic concepts in tumor angiogenesis: the angiogenic switch, 432
Vascular growth and differentiation factors: stimulators of the angiogenic switch, 432
Role of inhibitors in angiogenesis, 436
Clinical outcomes and future directions, 436
Acknowledgments, 437
Bibliography, 437
Questions for student review, 437

15 Cancer Chemistry: Designing New Drugs for Cancer Treatment, 438

Ana M. Pizarro and Peter J. Sadler

Introduction, 439
Historical perspective, 439
The drug discovery process and preclinical development of a drug, 442
Questions remaining, 457
Conclusions and future directions, 457
Bibliography, 458
Questions for student review, 459

16 Biologically Targeted Agents from Bench to Bedside, 461

Michael Khan, Peter Sadler, Ana M. Pizarro, and Stella Pelengaris Introduction, 463 Targeted therapies, 465 Cancer cell heterogeneity, 466 Finding the molecular targets, 468 Tumor regression in mice by inactivating single oncogenes, 468 Targeted cancer therapies, 473 Targeting oncogenes to treat cancer?, 473 Contents

The concept of synthetic lethality and collateral vulnerability, 475 Clinical progress in biological and molecular targeted therapies, 476 Molecular targeted drugs - an inventory, 479 DNA damage responses, 490 Transcription factors, 491 Targeting epigenetic regulation of gene expression, 492 Hitting the extrinsic support network and preventing spread, 493 Gene therapy, antisense, and siRNA, 495 Resistance to targeted therapies - intrinsic resistance and emergence of secondary pathways and tumor escape, 497 Negative feedback loops and failure of targeted therapies, 500 Biomarkers to identify optimal treatments and tailored therapies, 501 Pharmacogenetics and pharmacogenomics, 505 Clinical trials in cancer, 506 Conclusions and future directions, 506 Bibliography, 507 Questions for student review, 508

17 The Diagnosis of Cancer, 509

Anne L. Thomas, Bruno Morgan, and William P. Steward Introduction, 509 Clinical manifestations, 510 Investigations in oncological practice, 511 Non-invasive imaging techniques, 516 Future novel uses of imaging, 521 Proteomics and microarrays, 523 Circulating tumor cells, 523 Disease staging, 523 Conclusions and future directions, 524 Bibliography, 524 Questions for student review, 525

18 Treatment of Cancer: Chemotherapy and Radiotherapy, 526

Anne L. Thomas, J.P. Sage, and William P. Steward

Introduction, 526 Radiotherapy physics, 526 Radiobiology, 527 Treatment planning, 528 Recent advances, 529 Chemoradiation, 530 Conclusion, 540 Bibliography, 542 Questions for student review, 543

19 Caring for the Cancer Patient, 544

Nicky Rudd and Esther Waterhouse

Introduction, 544 Key concepts, 544 Communication with the cancer patient, 544 When is palliative care appropriate for cancer patients?, 545

Palliative care assessment, 545 Symptom control, 545 Respiratory symptoms, 547 Nausea and vomiting, 547 Bowel obstruction, 548 Constipation, 549 Fatigue, 549 Cachexia and anorexia, 549 Psychological problems, 549 The dying patient, 550 Supportive care, 550 An example of the care of a cancer patient, 551 Questions remaining, 551 Conclusions and future directions, 551 Underlying problems, 551 Comment, 551 Underlying problems, 552 Bibliography, 552 Questions for student review, 553

20 Systems Biology of Cancer, 554

Walter Schubert, Norbert C.J. de Wit, and Peter Walden

Introduction, 556 Information flow in cells, 556 Model organisms and cancer models, 557 Array-based technologies: genomics, epigenomics, and transcriptomics, 559 SNPs, the HapMap, and the identification of cancer genes, 559 Cancer mRNA expression analysis, 562 CGH arrays, CpG island microarrays, and ChIP-on-Chip, 564 Next-generation sequencing, 564 Proteomics, 566 Posttranslational modifications, 567 Protein complexes and cellular networks, 569 Clinical applications of proteomics, 570 Toponomics: investigating the protein network code of cells and tissues, 571 Processing the images from the cyclical imaging procedures, 571 Structure, code, and semantics of the toponome: a high-dimensional combinatorial problem, 573 Detecting a cell surface protein network code: lessons from a tumor cell, 575 The molecular face of cells in diseases, 576 Individualized medicine and tailored therapies, 576 Discussion and conclusion, 579 Bibliography, 579 Internet resources, 581 Questions for student review, 582 Appendix 20.1 Techniques for the generation of genetically altered mouse models of cancer, 582

Glossary, 585 Answers to Questions, 597 Index, 603