

Contents

Chapter 1	The Biology and Genetics of Cells and Organisms	1
Chapter 2	The Nature of Cancer	25
Chapter 3	Tumor Viruses	57
Chapter 4	Cellular Oncogenes	91
Chapter 5	Growth Factors and Their Receptors	119
Chapter 6	Cytoplasmic Signaling Circuitry Programs Many of the Traits of Cancer	159
Chapter 7	Tumor Suppressor Genes	209
Chapter 8	pRb and Control of the Cell Cycle Clock	255
Chapter 9	p53 and Apoptosis: Master Guardian and Executioner	307
Chapter 10	Eternal Life: Cell Immortalization and Tumorigenesis	357
Chapter 11	Multistep Tumorigenesis	399
Chapter 12	Maintenance of Genomic Integrity and the Development of Cancer	463
Chapter 13	Dialogue Replaces Monologue: Heterotypic Interactions and the Biology of Angiogenesis	527
Chapter 14	Moving Out: Invasion and Metastasis	587
Chapter 15	Crowd Control: Tumor Immunology and Immunotherapy	655
Chapter 16	The Rational Treatment of Cancer	725
	Abbreviations	A:1
	Glossary	G:1
	Index	I:1

List of Headings

Chapter 1

The Biology and Genetics of Cells and Organisms	1
1.1 Mendel establishes the basic rules of genetics	2
1.2 Mendelian genetics helps to explain Darwinian evolution	4
1.3 Mendelian genetics governs how both genes and chromosomes behave	7
1.4 Chromosomes are altered in most types of cancer cells	10
1.5 Mutations causing cancer occur in both the germ line and the soma	11
1.6 Genotype embodied in DNA sequences creates phenotype through proteins	15
1.7 Gene expression patterns also control phenotype	19
1.8 Transcription factors control gene expression	21
1.9 Metazoa are formed from components conserved over vast evolutionary time periods	22
1.10 Gene cloning techniques revolutionized the study of normal and malignant cells	23

Chapter 2

The Nature of Cancer	25
2.1 Tumors arise from normal tissues	26
2.2 Tumors arise from many specialized cell types throughout the body	28
2.3 Some types of tumors do not fit into the major classifications	34
2.4 Cancers seem to develop progressively	34
2.5 Tumors are monoclonal growths	39
2.6 Cancers occur with vastly different frequencies in different human populations	43
2.7 The risks of cancers often seem to be increased by assignable influences including lifestyle	45
2.8 Specific chemical agents can induce cancer	46
2.9 Both physical and chemical carcinogens act as mutagens	48
2.10 Mutagens may be responsible for some human cancers	52
2.11 Synopsis and prospects	54
Key concepts	55
Thought questions	56
Additional reading	56

Chapter 3

Tumor Viruses	57
3.1 Peyton Rous discovers a chicken sarcoma virus	58
3.2 Rous sarcoma virus is discovered to transform infected cells in culture	61
3.3 The continued presence of RSV is needed to maintain transformation	63
3.4 Viruses containing DNA molecules are also able to induce cancer	65
3.5 Tumor viruses induce multiple changes in cell phenotype including acquisition of tumorigenicity	69
3.6 Tumor virus genomes persist in virus-transformed cells by becoming part of host cell DNA	71
3.7 Retroviral genomes become integrated into the chromosomes of infected cells	73
3.8 A version of the <i>src</i> gene carried by RSV is also present in uninfected cells	75
3.9 RSV exploits a kidnapped cellular gene to transform cells	77
3.10 The vertebrate genome carries a large group of proto-oncogenes	80
3.11 Slowly transforming retroviruses activate proto-oncogenes by inserting their genomes adjacent to these cellular genes	82
3.12 Some retroviruses naturally carry oncogenes	84
3.13 Synopsis and prospects	86
Key concepts	88
Thought questions	90
Additional reading	90

Chapter 4

Cellular Oncogenes	91
4.1 Can cancers be triggered by the activation of endogenous retroviruses?	92
4.2 Transfection of DNA provides a strategy for detecting nonviral oncogenes	93
4.3 Oncogenes discovered in human tumor cell lines are related to those carried by transforming retroviruses	98
4.4 Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure	103

4.5	Variations on a theme: the <i>myc</i> oncogene can arise via at least three additional distinct mechanisms	107
4.6	A diverse array of structural changes in proteins can also lead to oncogene activation	111
4.7	Synopsis and prospects	112
	Key concepts	115
	Thought questions	117
	Additional reading	117

Chapter 5

Growth Factors, Receptors, and Cancer 119

5.1	Normal metazoan cells control each other's lives	121
5.2	The Src protein functions as a tyrosine kinase	123
5.3	The EGF receptor functions as a tyrosine kinase	126
5.4	An altered growth factor receptor can function as an oncoprotein	129
5.5	A growth factor gene can become an oncogene: the case of <i>sis</i>	132
5.6	Transphosphorylation underlies the operations of receptor tyrosine kinases	135
5.7	Yet other types of receptors enable mammalian cells to communicate with their environment	141
5.8	Integrin receptors sense association between the cell and the extracellular matrix	147
5.9	The Ras protein, an apparent component of the downstream signaling cascade, functions as a G protein	150
5.10	Synopsis and prospects	153
	Key concepts	156
	Thought questions	158
	Additional reading	158

Chapter 6

Cytoplasmic Signaling Circuitry Programs Many of the Traits of Cancer 159

6.1	A signaling pathway reaches from the cell surface into the nucleus	161
6.2	The Ras protein stands in the middle of a complex signaling cascade	164
6.3	Tyrosine phosphorylation controls the location and thereby the actions of many cytoplasmic signaling proteins	166
6.4	SH2 groups explain how growth factor receptors activate Ras and acquire signaling specificity	171
6.5	A cascade of kinases forms one of three important signaling pathways downstream of Ras	173

6.6	A second pathway downstream of Ras controls inositol lipids and the Akt/PKB kinase	176
6.7	A third Ras-regulated pathway acts through Ral, a distant cousin of Ras	183
6.8	The Jak-STAT pathway allows signals to be transmitted from the plasma membrane directly to the nucleus	185
6.9	Cell adhesion receptors emit signals that converge with those released by growth factor receptors	186
6.10	The Wnt- β -catenin pathway contributes to cell proliferation	189
6.11	G-protein-coupled receptors can also drive normal and neoplastic proliferation	191
6.12	Four other signaling pathways contribute in various ways to normal and neoplastic proliferation	193
6.13	Synopsis and prospects	197
	Key concepts	204
	Thought questions	207
	Additional reading	207

Chapter 7

Tumor Suppressor Genes	209	
7.1	Cell fusion experiments indicate that the cancer phenotype is recessive	210
7.2	The recessive nature of the cancer cell phenotype requires a genetic explanation	213
7.3	The retinoblastoma tumor provides a solution to the genetic puzzle of tumor suppressor genes	214
7.4	Incipient cancer cells invent ways to eliminate wild-type copies of tumor suppressor genes	216
7.5	The <i>Rb</i> gene often undergoes loss of heterozygosity in tumors	219
7.6	Loss-of-heterozygosity events can be used to find tumor suppressor genes	221
7.7	Many familial cancers can be explained by inheritance of mutant tumor suppressor genes	224
7.8	Promoter methylation represents an important mechanism for inactivating tumor suppressor genes	226
7.9	Tumor suppressor genes and proteins function in diverse ways	232
7.10	The NF1 protein acts as a negative regulator of Ras signaling	233
7.11	Apc facilitates egress of cells from colonic crypts	235
7.12	Von Hippel-Lindau disease: pVHL modulates the hypoxic response	241
7.13	Synopsis and prospects	247
	Key concepts	252
	Thought questions	253
	Additional reading	253

Chapter 8

pRb and Control of the Cell Cycle Clock	255
8.1 External signals influence a cell's decision to enter into the active cell cycle	256
8.2 Cells make decisions about growth and quiescence during a specific period in the G ₁ phase	261
8.3 Cyclins and cyclin-dependent kinases constitute the core components of the cell cycle clock	262
8.4 Cyclin-Cdk complexes are also regulated by Cdk inhibitors	268
8.5 Viral oncoproteins reveal how pRb blocks advance through the cell cycle	273
8.6 pRb is deployed by the cell cycle clock to serve as a guardian of the restriction point gate	277
8.7 E2F transcription factors enable pRb to implement growth-versus-quiescence decisions	278
8.8 A variety of mitogenic signaling pathways control the phosphorylation state of pRb	282
8.9 The Myc oncoprotein perturbs the decision to phosphorylate pRb and thereby deregulates control of cell cycle progression	284
8.10 TGF- β prevents phosphorylation of pRb and thereby blocks cell cycle progression	288
8.11 pRb function and the controls of differentiation are closely linked	292
8.12 Control of pRb function is perturbed in most if not all human cancers	296
8.13 Synopsis and prospects	300
Key concepts	304
Thought questions	305
Additional reading	305

Chapter 9

p53 and Apoptosis: Master Guardian and Executioner	307
9.1 Papovaviruses lead to the discovery of p53	308
9.2 <i>p53</i> is discovered to be a tumor suppressor gene	310
9.3 Mutant versions of p53 interfere with normal p53 function	311
9.4 p53 protein molecules usually have short lifetimes	314
9.5 A variety of signals cause p53 induction	315
9.6 DNA damage and deregulated growth signals cause p53 stabilization	317
9.7 Mdm2 and ARF battle over the fate of p53	318
9.8 ARF and p53-mediated apoptosis protect against cancer by monitoring intracellular signaling	323

9.9	p53 functions as a transcription factor that halts cell cycle advance in response to DNA damage and attempts to aid in the repair process	325
9.10	p53 often ushers in the apoptotic death program	329
9.11	p53 inactivation provides advantage to incipient cancer cells at a number of steps in tumor progression	331
9.12	Inherited mutant alleles affecting the p53 pathway predispose one to a variety of tumors	332
9.13	Apoptosis is a complex program that often depends on mitochondria	334
9.14	Two distinct signaling pathways can trigger apoptosis	342
9.15	Cancer cells invent numerous ways to inactivate some or all of the apoptotic machinery	346
9.16	Synopsis and prospects	350
	Key concepts	354
	Thought questions	355
	Additional reading	356

Chapter 10

	Eternal Life: Cell Immortalization and Tumorigenesis	357
10.1	Normal cell populations register the number of cell generations separating them from their ancestors in the early embryo	358
10.2	Cancer cells need to become immortal in order to form tumors	361
10.3	Cell-physiologic stresses impose a limitation on replication	365
10.4	The proliferation of cultured cells is also limited by the telomeres of their chromosomes	368
10.5	Telomeres are complex molecular structures that are not easily replicated	373
10.6	Incipient cancer cells can escape crisis by expressing telomerase	376
10.7	Telomerase plays a key role in the proliferation of human cancer cells	381
10.8	Some immortalized cells can maintain telomeres without telomerase	383
10.9	Telomeres play different roles in the cells of laboratory mice and in human cells	386
10.10	Telomerase-negative mice show both decreased and increased cancer susceptibility	388
10.11	The mechanisms underlying cancer pathogenesis in telomerase-negative mice may also operate during the development of human tumors	392
10.12	Synopsis and prospects	393
	Key concepts	397
	Thought questions	398
	Additional reading	398

Chapter 11

Multi-Step Tumorigenesis	399
11.1 Most human cancers develop over many decades of time	400
11.2 Histopathology provides evidence of multi-step tumor formation	403
11.3 Colonic growths accumulate genetic alterations as tumor progression proceeds	408
11.4 Multi-step tumor progression helps to explain familial polyposis and field cancerization	412
11.5 Cancer development seems to follow the rules of Darwinian evolution	413
11.6 Tumor stem cells further complicate the Darwinian model of clonal succession and tumor progression	416
11.7 A linear path of clonal succession oversimplifies the reality of cancer	420
11.8 The Darwinian model of tumor development is difficult to validate experimentally	423
11.9 Multiple lines of evidence reveal that normal cells are resistant to transformation by a single mutated gene	424
11.10 Transformation usually requires collaboration between two or more mutant genes	427
11.11 Transgenic mice provide models of oncogene collaboration and multi-step cell transformation	429
11.12 Human cells are constructed to be highly resistant to immortalization and transformation	431
11.13 Nonmutagenic agents, including those favoring cell proliferation, make important contributions to tumorigenesis	435
11.14 Toxic and mitogenic agents can act as human tumor promoters	439
11.15 Chronic inflammation often serves to promote tumor progression in mice and humans	441
11.16 Inflammation-dependent tumor promotion operates through defined signaling pathways	444
11.17 Tumor promotion is likely to be a critical determinant of the rate of tumor progression in many human tissues	452
11.18 Synopsis and prospects	453
Key concepts	460
Thought questions	461
Additional reading	462

Chapter 12

Maintenance of Genomic Integrity and the Development of Cancer	463
12.1 Tissues are organized to minimize the progressive accumulation of mutations	464

12.2	Stem cells are the likely targets of the mutagenesis that leads to cancer	466
12.3	Apoptosis, drug pumps, and DNA replication mechanisms offer tissues a way to minimize the accumulation of mutant stem cells	470
12.4	Cell genomes are threatened by errors made during DNA replication	475
12.5	Cell genomes are under constant attack from endogenous biochemical processes	479
12.6	Cell genomes are under occasional attack from exogenous mutagens and their metabolites	483
12.7	Cells deploy a variety of defenses to protect DNA molecules from attack by mutagens	490
12.8	Repair enzymes fix DNA that has been altered by mutagens	493
12.9	Inherited defects in nucleotide-excision repair, base-excision repair, and mismatch repair lead to specific cancer susceptibility syndromes	499
12.10	A variety of other DNA repair defects confer increased cancer susceptibility through poorly understood mechanisms	505
12.11	The karyotype of cancer cells is often changed through alterations in chromosome structure	510
12.12	The karyotype of cancer cells is often changed through alterations in chromosome number	511
12.13	Synopsis and prospects	517
	Key concepts	524
	Thought questions	525
	Additional reading	525

Chapter 13

	Dialogue Replaces Monologue: Heterotypic Interactions and the Biology of Angiogenesis	527
13.1	Normal and neoplastic epithelial tissues are formed from interdependent cell types	530
13.2	The cells forming cancer cell lines develop without heterotypic interactions and deviate from the behavior of cells within human tumors	536
13.3	Tumors resemble wounded tissues that do not heal	537
13.4	Stromal cells are active contributors to tumorigenesis	548
13.5	Macrophages represent important participants in activating the tumor-associated stroma	551
13.6	Endothelial cells and the vessels that they form ensure tumors adequate access to the circulation	556
13.7	Tripping the angiogenic switch is essential for tumor expansion	563
13.8	The angiogenic switch initiates a highly complex process	567

13.9	Angiogenesis is normally suppressed by physiologic inhibitors	571
13.10	Certain anti-angiogenesis therapies hold great promise for treating cancer	574
13.11	Synopsis and prospects	581
	Key concepts	585
	Thought questions	585
	Additional reading	586

Chapter 14

Moving Out: Invasion and Metastasis 587

14.1	Travel of cancer cells from a primary tumor to a site of potential metastasis depends on a series of complex biological steps	589
14.2	Colonization represents the most complex and challenging step of the invasion–metastasis cascade	594
14.3	The epithelial–mesenchymal transition and associated loss of E-cadherin expression enable carcinoma cells to become invasive	597
14.4	The epithelial–mesenchymal transition is often induced by stromal signals	605
14.5	EMTs are programmed by transcription factors that orchestrate key steps of embryogenesis	615
14.6	Extracellular proteases play key roles in invasiveness	621
14.7	Small Ras-like GTPases control cellular processes including adhesion, cell shape, and cell motility	624
14.8	Metastasizing cells can use lymphatic vessels to disperse from the primary tumor	631
14.9	A variety of factors govern the organ sites in which disseminated cancer cells form metastases	634
14.10	Metastasis to bone requires the subversion of osteoblasts and osteoclasts	638
14.11	Metastasis suppressor genes contribute to regulating the metastatic phenotype	642
14.12	Occult micrometastases threaten the long-term survival of cancer patients	645
14.13	Synopsis and prospects	646
	Key concepts	652
	Thought questions	653
	Additional reading	653

Chapter 15

Crowd Control: Tumor Immunology and Immunotherapy 655

15.1	The immune system functions in complex ways to destroy foreign invaders and abnormal cells in the body's tissues	656
------	--	-----

15.2	The adaptive immune response leads to antibody production	659
15.3	Another adaptive immune response leads to the formation of cytotoxic cells	663
15.4	The innate immune response does not require prior sensitization	666
15.5	The need to distinguish self from non-self results in immune tolerance	668
15.6	Regulatory T cells are able to suppress major components of the adaptive immune response	669
15.7	The immunosurveillance theory is born and then suffers major setbacks	669
15.8	Use of genetically altered mice leads to a resurrection of the immunosurveillance theory	673
15.9	The human immune system plays a critical role in warding off various types of human cancer	675
15.10	Subtle differences between normal and neoplastic tissues may allow the immune system to distinguish between them	681
15.11	Immune recognition of tumors may be delayed until relatively late in tumor progression	683
15.12	Tumor-specific transplantation antigens often provoke a potent immune response	685
15.13	Tumor-associated transplantation antigens may also evoke anti-tumor immunity	687
15.14	Cancer cells can evade immune detection by suppressing cell surface display of tumor antigens	689
15.15	Cancer cells protect themselves from NK-mediated attack	695
15.16	Tumor cells launch counterattacks on immunocytes	697
15.17	Cancer cells become intrinsically resistant to various forms of killing used by the immune system	701
15.18	Cancer cells attract regulatory T cells to fend off attacks by other lymphocytes	703
15.19	Passive immunization with Herceptin can be used to kill breast cancer cells	704
15.20	Passive immunization with antibody can be used to treat B-cell tumors	708
15.21	Passive immunization can be achieved by transfer of immunocytes from one individual to another	713
15.22	Patients' immune systems can be mobilized to attack their tumors	714
15.23	Synopsis and prospects	720
	Key concepts	722
	Thought questions	723
	Additional reading	724

Chapter 16

The Rational Treatment of Cancer	725
16.1 The development and clinical use of effective therapies will depend on accurate diagnosis of disease	727
16.2 Successful anti-cancer drugs can elicit several responses from tumor cells	732
16.3 Functional considerations dictate that only a subset of the defective proteins in cancer cells are attractive targets for drug development	734
16.4 The biochemistry of proteins also determines whether they are attractive targets for intervention	737
16.5 Pharmaceutical chemists can generate and explore the biochemical properties of a wide array of potential drugs	744
16.6 Drug candidates must be tested on cell models as an initial measurement of their utility in whole organisms	747
16.7 Studies of a drug's action in laboratory animals are an essential part of pre-clinical testing	748
16.8 Promising candidate drugs must be subjected to rigorous and extensive clinical trials in Phase I trials in humans	751
16.9 Phase II and III trials provide credible indications of clinical efficacy	752
16.10 Tumors often develop resistance to initially effective therapy	755
16.11 Gleevec development has paved the way for the development of many other highly targeted compounds	757
16.12 EGF receptor antagonists may be useful for treating a wide variety of tumor types	765
16.13 Proteasome inhibitors yield unexpected therapeutic benefit	769
16.14 A sheep teratogen may be useful as a highly potent anti-cancer drug	776
16.15 mTOR, a master regulator of cell physiology, represents an attractive target for anti-cancer therapy	782
16.16 Synopsis and prospects: Challenges and opportunities on the road ahead	787
Key concepts	794
Thought questions	795
Additional reading	795