

Detailed Contents

Chapter 1: The Biology and Genetics of Cells and Organisms	1	3.5	Tumor viruses induce multiple changes in cell phenotype including acquisition of tumorigenicity	82
1.1 Mendel establishes the basic rules of genetics	2	3.6	Tumor virus genomes persist in virus-transformed cells by becoming part of host-cell DNA	83
1.2 Mendelian genetics helps to explain Darwinian evolution	4	3.7	Retroviral genomes become integrated into the chromosomes of infected cells	87
1.3 Mendelian genetics governs how both genes and chromosomes behave	7	3.8	A version of the <i>src</i> gene carried by RSV is also present in uninfected cells	89
1.4 Chromosomes are altered in most types of cancer cells	10	3.9	RSV exploits a kidnapped cellular gene to transform cells	91
1.5 Mutations causing cancer occur in both the germ line and the soma	11	3.10	The vertebrate genome carries a large group of proto-oncogenes	93
1.6 Genotype embodied in DNA sequences creates phenotype through proteins	14	3.11	Slowly transforming retroviruses activate proto-oncogenes by inserting their genomes adjacent to these cellular genes	94
1.7 Gene expression patterns also control phenotype	19	3.12	Some retroviruses naturally carry oncogenes	97
1.8 Histone modification and transcription factors control gene expression	21	3.13	Synopsis and prospects	99
1.9 Heritable gene expression is controlled through additional mechanisms	24	Key concepts		101
1.10 Unconventional RNA molecules also affect the expression of genes	25	Thought questions		102
1.11 Metazoa are formed from components conserved over vast evolutionary time periods	27	Additional reading		102
1.12 Gene cloning techniques revolutionized the study of normal and malignant cells	28	Chapter 4: Cellular Oncogenes		103
Additional reading	29	4.1	Can cancers be triggered by the activation of endogenous retroviruses?	104
Chapter 2: The Nature of Cancer	31	4.2	Transfection of DNA provides a strategy for detecting nonviral oncogenes	105
2.1 Tumors arise from normal tissues	32	4.3	Oncogenes discovered in human tumor cell lines are related to those carried by transforming retroviruses	108
2.2 Tumors arise from many specialized cell types throughout the body	34	4.4	Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure	113
2.3 Some types of tumors do not fit into the major classifications	40	4.5	Variations on a theme: the <i>myc</i> oncogene can arise via at least three additional distinct mechanisms	117
2.4 Cancers seem to develop progressively	45	4.6	A diverse array of structural changes in proteins can also lead to oncogene activation	124
2.5 Tumors are monoclonal growths	50	4.7	Synopsis and prospects	127
2.6 Cancer cells exhibit an altered energy metabolism	53	Key concepts		128
2.7 Cancers occur with vastly different frequencies in different human populations	55	Thought questions		130
2.8 The risks of cancers often seem to be increased by assignable influences including lifestyle	58	Additional reading		130
2.9 Specific chemical agents can induce cancer	59	Chapter 5: Growth Factors, Receptors, and Cancer		131
2.10 Both physical and chemical carcinogens act as mutagens	60	5.1	Normal metazoan cells control each other's lives	133
2.11 Mutagens may be responsible for some human cancers	64	5.2	The <i>Src</i> protein functions as a tyrosine kinase	135
2.12 Synopsis and prospects	66	5.3	The EGF receptor functions as a tyrosine kinase	138
Key concepts	68	5.4	An altered growth factor receptor can function as an oncoprotein	141
Thought questions	69	5.5	A growth factor gene can become an oncogene: the case of <i>sis</i>	144
Additional reading	69	5.6	Transphosphorylation underlies the operations of receptor tyrosine kinases	146
Chapter 3: Tumor Viruses	71	5.7	Yet other types of receptors enable mammalian cells to communicate with their environment	153
3.1 Peyton Rous discovers a chicken sarcoma virus	72	5.8	Nuclear receptors sense the presence of low-molecular-weight lipophilic ligands	159
3.2 Rous sarcoma virus is discovered to transform infected cells in culture	75	5.9	Integrin receptors sense association between the cell and the extracellular matrix	161
3.3 The continued presence of RSV is needed to maintain transformation	77			
3.4 Viruses containing DNA molecules are also able to induce cancer	79			

Detailed contents

5.10	The Ras protein, an apparent component of the downstream signaling cascade, functions as a G protein	165	7.11	Apc facilitates egress of cells from colonic crypts	259
5.11	Synopsis and prospects	169	7.12	Von Hippel–Lindau disease: pVHL modulates the hypoxic response	265
	Key concepts	172	7.13	Synopsis and prospects	268
	Thought questions	174		Key concepts	272
	Additional reading	174		Thought questions	273
				Additional reading	273
Chapter 6: Cytoplasmic Signaling Circuitry Programs Many of the Traits of Cancer			Chapter 8: pRb and Control of the Cell Cycle Clock		
6.1	A signaling pathway reaches from the cell surface into the nucleus	177	8.1	Cell growth and division is coordinated by a complex array of regulators	276
6.2	The Ras protein stands in the middle of a complex signaling cascade	180	8.2	Cells make decisions about growth and quiescence during a specific period in the G ₁ phase	281
6.3	Tyrosine phosphorylation controls the location and thereby the actions of many cytoplasmic signaling proteins	182	8.3	Cyclins and cyclin-dependent kinases constitute the core components of the cell cycle clock	283
6.4	SH2 and SH3 groups explain how growth factor receptors activate Ras and acquire signaling specificity	188	8.4	Cyclin–CDK complexes are also regulated by CDK inhibitors	288
6.5	Ras-regulated signaling pathways: A cascade of kinases forms one of three important signaling pathways downstream of Ras	189	8.5	Viral oncoproteins reveal how pRb blocks advance through the cell cycle	294
6.6	Ras-regulated signaling pathways: a second downstream pathway controls inositol lipids and the Akt/PKB kinase	193	8.6	pRb is deployed by the cell cycle clock to serve as a guardian of the restriction-point gate	298
6.7	Ras-regulated signaling pathways: a third downstream pathway acts through Ral, a distant cousin of Ras	201	8.7	E2F transcription factors enable pRb to implement growth-versus-quiescence decisions	299
6.8	The Jak–STAT pathway allows signals to be transmitted from the plasma membrane directly to the nucleus	202	8.8	A variety of mitogenic signaling pathways control the phosphorylation state of pRb	304
6.9	Cell adhesion receptors emit signals that converge with those released by growth factor receptors	204	8.9	The Myc protein governs decisions to proliferate or differentiate	306
6.10	The Wnt– β -catenin pathway contributes to cell proliferation	206	8.10	TGF- β prevents phosphorylation of pRb and thereby blocks cell cycle progression	311
6.11	G-protein-coupled receptors can also drive normal and neoplastic proliferation	209	8.11	pRb function and the controls of differentiation are closely linked	314
6.12	Four additional “dual-address” signaling pathways contribute in various ways to normal and neoplastic proliferation	212	8.12	Control of pRb function is perturbed in most if not all human cancers	318
6.13	Well-designed signaling circuits require both negative and positive feedback controls	216	8.13	Synopsis and prospects	323
6.14	Synopsis and prospects	217		Key concepts	327
	Key concepts	227		Thought questions	328
	Thought questions	228		Additional reading	329
	Additional reading	228	Chapter 9: p53 and Apoptosis: Master Guardian and Executioner		
Chapter 7: Tumor Suppressor Genes			9.1	Papovaviruses lead to the discovery of p53	332
7.1	Cell fusion experiments indicate that the cancer phenotype is recessive	232	9.2	p53 is discovered to be a tumor suppressor gene	334
7.2	The recessive nature of the cancer cell phenotype requires a genetic explanation	234	9.3	Mutant versions of p53 interfere with normal p53 function	335
7.3	The retinoblastoma tumor provides a solution to the genetic puzzle of tumor suppressor genes	235	9.4	p53 protein molecules usually have short lifetimes	338
7.4	Incipient cancer cells invent ways to eliminate wild-type copies of tumor suppressor genes	238	9.5	A variety of signals cause p53 induction	339
7.5	The <i>Rb</i> gene often undergoes loss of heterozygosity in tumors	241	9.6	DNA damage and deregulated growth signals cause p53 stabilization	341
7.6	Loss-of-heterozygosity events can be used to find tumor suppressor genes	243	9.7	Mdm2 destroys its own creator	342
7.7	Many familial cancers can be explained by inheritance of mutant tumor suppressor genes	248	9.8	ARF and p53-mediated apoptosis protect against cancer by monitoring intracellular signaling	348
7.8	Promoter methylation represents an important mechanism for inactivating tumor suppressor genes	249	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	352
7.9	Tumor suppressor genes and proteins function in diverse ways	254	9.10	p53 often ushers in the apoptotic death program	355
7.10	The NF1 protein acts as a negative regulator of Ras signaling	255	9.11	p53 inactivation provides advantage to incipient cancer cells at a number of steps in tumor progression	359
			9.12	Inherited mutant alleles affecting the p53 pathway predispose one to a variety of tumors	360
			9.13	Apoptosis is a complex program that often depends on mitochondria	361
			9.14	Both intrinsic and extrinsic apoptotic programs can lead to cell death	371
			9.15	Cancer cells invent numerous ways to inactivate some or all of the apoptotic machinery	376
			9.16	Necrosis and autophagy: two additional forks in the road of tumor progression	379

9.17	Synopsis and prospects	381	11.15	Chronic inflammation often serves to promote tumor progression in mice and humans	486
	Key concepts	387	11.16	Inflammation-dependent tumor promotion operates through defined signaling pathways	490
	Thought questions	388	11.17	Tumor promotion is likely to be a critical determinant of the rate of tumor progression in many human tissues	498
	Additional reading	389	11.18	Synopsis and prospects	501
Chapter 10: Eternal Life: Cell Immortalization and Tumorigenesis				Key concepts	506
10.1	Normal cell populations register the number of cell generations separating them from their ancestors in the early embryo	392		Thought questions	507
10.2	Cancer cells need to become immortal in order to form tumors	394		Additional reading	508
10.3	Cell-physiologic stresses impose a limitation on replication	398	Chapter 12: Maintenance of Genomic Integrity and the Development of Cancer		
10.4	The proliferation of cultured cells is also limited by the telomeres of their chromosomes	404	12.1	Tissues are organized to minimize the progressive accumulation of mutations	512
10.5	Telomeres are complex molecular structures that are not easily replicated	409	12.2	Stem cells may or may not be targets of the mutagenesis that leads to cancer	515
10.6	Incipient cancer cells can escape crisis by expressing telomerase	412	12.3	Apoptosis, drug pumps, and DNA replication mechanisms offer tissues a way to minimize the accumulation of mutant stem cells	517
10.7	Telomerase plays a key role in the proliferation of human cancer cells	417	12.4	Cell genomes are threatened by errors made during DNA replication	519
10.8	Some immortalized cells can maintain telomeres without telomerase	419	12.5	Cell genomes are under constant attack from endogenous biochemical processes	523
10.9	Telomeres play different roles in the cells of laboratory mice and in human cells	423	12.6	Cell genomes are under occasional attack from exogenous mutagens and their metabolites	527
10.10	Telomerase-negative mice show both decreased and increased cancer susceptibility	425	12.7	Cells deploy a variety of defenses to protect DNA molecules from attack by mutagens	535
10.11	The mechanisms underlying cancer pathogenesis in telomerase-negative mice may also operate during the development of human tumors	429	12.8	Repair enzymes fix DNA that has been altered by mutagens	538
10.12	Synopsis and prospects	433	12.9	Inherited defects in nucleotide-excision repair, base-excision repair, and mismatch repair lead to specific cancer susceptibility syndromes	544
	Key concepts	436	12.10	A variety of other DNA repair defects confer increased cancer susceptibility through poorly understood mechanisms	549
	Thought questions	437	12.11	The karyotype of cancer cells is often changed through alterations in chromosome structure	555
	Additional reading	437	12.12	The karyotype of cancer cells is often changed through alterations in chromosome number	558
Chapter 11: Multi-Step Tumorigenesis			12.13	Synopsis and prospects	564
11.1	Most human cancers develop over many decades of time	440		Key concepts	572
11.2	Histopathology provides evidence of multi-step tumor formation	442		Thought questions	573
11.3	Cells accumulate genetic and epigenetic alterations as tumor progression proceeds	449		Additional reading	574
11.4	Multi-step tumor progression helps to explain familial polyposis and field cancerization	453	Chapter 13 Dialogue Replaces Monologue: Heterotypic Interactions and the Biology of Angiogenesis		
11.5	Cancer development seems to follow the rules of Darwinian evolution	455	13.1	Normal and neoplastic epithelial tissues are formed from interdependent cell types	579
11.6	Tumor stem cells further complicate the Darwinian model of clonal succession and tumor progression	458	13.2	The cells forming cancer cell lines develop without heterotypic interactions and deviate from the behavior of cells within human tumors	585
11.7	A linear path of clonal succession oversimplifies the reality of cancer: intra-tumor heterogeneity	463	13.3	Tumors resemble wounded tissues that do not heal	587
11.8	The Darwinian model of tumor development is difficult to validate experimentally	467	13.4	Experiments directly demonstrate that stromal cells are active contributors to tumorigenesis	600
11.9	Multiple lines of evidence reveal that normal cells are resistant to transformation by a single mutated gene	468	13.5	Macrophages and myeloid cells play important roles in activating the tumor-associated stroma	604
11.10	Transformation usually requires collaboration between two or more mutant genes	470	13.6	Endothelial cells and the vessels that they form ensure tumors adequate access to the circulation	607
11.11	Transgenic mice provide models of oncogene collaboration and multi-step cell transformation	474	13.7	Tripping the angiogenic switch is essential for tumor expansion	615
11.12	Human cells are constructed to be highly resistant to immortalization and transformation	475	13.8	The angiogenic switch initiates a highly complex process	619
11.13	Nonmutagenic agents, including those favoring cell proliferation, make important contributions to tumorigenesis	480	13.9	Angiogenesis is normally suppressed by physiologic inhibitors	622
11.14	Toxic and mitogenic agents can act as human tumor promoters	484	13.10	Anti-angiogenesis therapies can be employed to treat cancer	626

Detailed contents

13.11 Synopsis and prospects	634	15.13 Cancer cells can evade immune detection by suppressing cell-surface display of tumor antigens	761
Key concepts	638	15.14 Cancer cells protect themselves from destruction by NK cells and macrophages	765
Thought questions	639	15.15 Tumor cells launch counterattacks on immunocytes	769
Additional reading	639	15.16 Cancer cells become intrinsically resistant to various forms of killing used by the immune system	773
Chapter 14: Moving Out: Invasion and Metastasis	641	15.17 Cancer cells attract regulatory T cells to fend off attacks by other lymphocytes	774
14.1 Travel of cancer cells from a primary tumor to a site of potential metastasis depends on a series of complex biological steps	643	15.18 Passive immunization with monoclonal antibodies can be used to kill breast cancer cells	778
14.2 Colonization represents the most complex and challenging step of the invasion–metastasis cascade	652	15.19 Passive immunization with antibody can also be used to treat B-cell tumors	781
14.3 The epithelial–mesenchymal transition and associated loss of E-cadherin expression enable carcinoma cells to become invasive	657	15.20 Transfer of foreign immunocytes can lead to cures of certain hematopoietic malignancies	785
14.4 Epithelial–mesenchymal transitions are often induced by contextual signals	662	15.21 Patients' immune systems can be mobilized to attack their tumors	786
14.5 Stromal cells contribute to the induction of invasiveness	669	15.22 Synopsis and prospects	791
14.6 EMTs are programmed by transcription factors that orchestrate key steps of embryogenesis	672	Key concepts	793
14.7 EMT-inducing transcription factors also enable entrance into the stem cell state	677	Thought questions	795
14.8 EMT-inducing TFs help drive malignant progression	680	Additional reading	795
14.9 Extracellular proteases play key roles in invasiveness	685	Chapter 16: The Rational Treatment of Cancer	797
14.10 Small Ras-like GTPases control cellular processes such as adhesion, cell shape, and cell motility	689	16.1 The development and clinical use of effective therapies will depend on accurate diagnosis of disease	800
14.11 Metastasizing cells can use lymphatic vessels to disperse from the primary tumor	695	16.2 Surgery, radiotherapy, and chemotherapy are the major pillars on which current cancer therapies rest	806
14.12 A variety of factors govern the organ sites in which disseminated cancer cells form metastases	699	16.3 Differentiation, apoptosis, and cell cycle checkpoints can be exploited to kill cancer cells	813
14.13 Metastasis to bone requires the subversion of osteoblasts and osteoclasts	703	16.4 Functional considerations dictate that only a subset of the defective proteins in cancer cells are attractive targets for drug development	815
14.14 Metastasis suppressor genes contribute to regulating the metastatic phenotype	709	16.5 The biochemistry of proteins also determines whether they are attractive targets for intervention	818
14.15 Occult micrometastases threaten the long-term survival of cancer patients	711	16.6 Pharmaceutical chemists can generate and explore the biochemical properties of a wide array of potential drugs	822
14.16 Synopsis and prospects	713	16.7 Drug candidates must be tested on cell models as an initial measurement of their utility in whole organisms	825
Key concepts	719	16.8 Studies of a drug's action in laboratory animals are an essential part of pre-clinical testing	826
Thought questions	720	16.9 Promising candidate drugs are subjected to rigorous clinical tests in Phase I trials in humans	829
Additional reading	721	16.10 Phase II and III trials provide credible indications of clinical efficacy	831
Chapter 15: Crowd Control: Tumor Immunology and Immunotherapy	723	16.11 Tumors often develop resistance to initially effective therapy	833
15.1 The immune system functions to destroy foreign invaders and abnormal cells in the body's tissues	724	16.12 Gleevec paved the way for the development of many other highly targeted compounds	834
15.2 The adaptive immune response leads to antibody production	726	16.13 EGF receptor antagonists may be useful for treating a wide variety of tumor types	844
15.3 Another adaptive immune response leads to the formation of cytotoxic cells	729	16.14 Proteasome inhibitors yield unexpected therapeutic benefit	850
15.4 The innate immune response does not require prior sensitization	736	16.15 A sheep teratogen may be useful as a highly potent anti-cancer drug	855
15.5 The need to distinguish self from non-self results in immune tolerance	736	16.16 mTOR, a master regulator of cell physiology, represents an attractive target for anti-cancer therapy	861
15.6 Regulatory T cells are able to suppress major components of the adaptive immune response	737	16.17 B-Raf discoveries have led to inroads into the melanoma problem	864
15.7 The immunosurveillance theory is born and then suffers major setbacks	739	16.18 Synopsis and prospects: challenges and opportunities on the road ahead	866
15.8 Use of genetically altered mice leads to a resurrection of the immunosurveillance theory	742	Key concepts	874
15.9 The human immune system plays a critical role in warding off various types of human cancer	745	Thought questions	875
15.10 Subtle differences between normal and neoplastic tissues may allow the immune system to distinguish between them	751	Additional reading	875
15.11 Tumor transplantation antigens often provoke potent immune responses	756		
15.12 Tumor-associated transplantation antigens may also evoke anti-tumor immunity	758		