## Contents

Chapter 1:	The Biology and Genetics of Cells and Organisms	1
Chapter 2:	The Nature of Cancer	31
Chapter 3:	Tumor Viruses	71
Chapter 4:	Cellular Oncogenes	103
Chapter 5:	Growth Factors, Receptors, and Cancer	131
Chapter 6:	Cytoplasmic Signaling Circuitry Programs Many of the Traits of Cancer	175
Chapter 7:	Tumor Suppressor Genes	231
Chapter 8:	pRb and Control of the Cell Cycle Clock	275
Chapter 9:	p53 and Apoptosis: Master Guardian and Executioner	331
Chapter 10:	Eternal Life: Cell Immortalization and Tumorigenesis	391
Chapter 11:	Multi-Step Tumorigenesis	439
Chapter 12:	Maintenance of Genomic Integrity and the Development of Cancer	511
Chapter 13:	Dialogue Replaces Monologue: Heterotypic Interactions and the Biology of Angiogenesis	577
Chapter 14:	Moving Out: Invasion and Metastasis	641
Chapter 15:	Crowd Control: Tumor Immunology and Immunotherapy	723
Chapter 16:	The Rational Treatment of Cancer	797
Abbreviation	S man a chicles attention rate (22) Translating barylation ander its optimistical receptor to tookie kineses	A:1
Glossary		G:1
Index		I:1

## Detailed Contents

C	Chapter 1: The Biology and Genetics of Cells and		3.5	Tumor viruses induce multiple changes in cell phenoty	oe .
C	Organisms	1		including acquisition of tumorigenicity	8
	*Summer of the state of the sta		3.6	Tumor virus genomes persist in virus-transformed cells	
1.	1 Mendel establishes the basic rules of genetics	2		by becoming part of host-cell DNA	8
1.		1 4	3.7	Retroviral genomes become integrated into the	U
1.			3.7		
1.		7		chromosomes of infected cells	8
	chromosomes behave	7	3.8	A version of the src gene carried by RSV is also present	
1.				in uninfected cells	8
	cells	10	3.9	RSV exploits a kidnapped cellular gene to transform	
1.	5 Mutations causing cancer occur in both the		1000	cells	9
- 50	germ line and the soma	11	210		,
4		11	3.10	The vertebrate genome carries a large group of proto-	-
1.				oncogenes	9
	phenotype through proteins	14	3.11	Slowly transforming retroviruses activate proto-	
1.	7 Gene expression patterns also control phenotype	19		oncogenes by inserting their genomes adjacent to	
1.	8 Histone modification and transcription factors control			these cellular genes	9
	gene expression	21	3.12	Some retroviruses naturally carry oncogenes	9
1.					
	additional mechanisms	24	3.13	Synopsis and prospects	9
4		24		oncepts	10
1.	10 Unconventional RNA molecules also affect the	100	Thoug	ght questions	10.
	expression of genes	25	Addit	ional reading	10.
1.	11 Metazoa are formed from components conserved over				
	vast evolutionary time periods	27			
1	12 Gene cloning techniques revolutionized the study of	~.	Chap	ter 4: Cellular Oncogenes	103
1.		20	1	A American when D.S.A. Jeruin defines ARMAR Healthan	-
	normal and malignant cells	28	4.1	Can cancers be triggered by the activation of	
A	dditional reading	29		endogenous retroviruses?	10
			4.2	Transfection of DNA provides a strategy for detecting	200
0	1 . 27	0.4	1.4		10
C	hapter 2: The Nature of Cancer	31	100	nonviral oncogenes	10:
2	1 T	22	4.3	Oncogenes discovered in human tumor cell lines are	
2.		32		related to those carried by transforming retroviruses	10
2.	, 1		4.4	Proto-oncogenes can be activated by genetic changes	
	throughout the body	34		affecting either protein expression or structure	113
2	3 Some types of tumors do not fit into the major		4.5	Variations on a theme: the myc oncogene can arise	
	classifications	40	1.5		111
2.		45		via at least three additional distinct mechanisms	11
2.	110		4.6	A diverse array of structural changes in proteins can	
		50		also lead to oncogene activation	12
2.		53	4.7	Synopsis and prospects	127
2.	7 Cancers occur with vastly different frequencies in		Key co	oncepts	128
		55		th questions	130
2.	8 The risks of cancers often seem to be increased by				
	The state of the s	50	Additi	ional reading	130
21		58			
2.		59	Chan	tor 5: Crowth Factors Pagentors and Canana	121
2.		60	Chap	ter 5: Growth Factors, Receptors, and Cancer	131
2.	11 Mutagens may be responsible for some human cancers	64	5.1	Normal metazoan cells control each other's lives	133
2.	10 0 1	66			
	Fig. Factor and the second part of the second part		5.2	The Src protein functions as a tyrosine kinase	135
Th		68	5.3	The EGF receptor functions as a tyrosine kinase	138
Λ.	ought questions	69	5.4	An altered growth factor receptor can function as an	
T)	dditional reading	69		oncoprotein	141
			5.5	A growth factor gene can become an oncogene:	
0			3.3	the case of sis	1.4
C.	hapter 3: Tumor Viruses	71	-/		144
2 -	D D		5.6	Transphosphorylation underlies the operations of	
3.	J	72		receptor tyrosine kinases	146
3.2	sacoma viras is discovered to transform infected		5.7	Yet other types of receptors enable mammalian cells	
	cells in culture	75		to communicate with their environment	153
3.3	The continued presence of RSV is needed to maintain	10	5.8	Nuclear receptors sense the presence of low-molecular-	
	transformation	77	5.0		
3.4		11		weight lipophilic ligands	159
-	Thuses containing DIVA molecules are also able to	-	5.9	Integrin receptors sense association between the cell	13
	induce cancer	79		and the extracellular matrix	161

## xviii Detailed contents

5.10	The Ras protein, an apparent component of the		7.11	Apc facilitates egress of cells from colonic crypts	259
5.10	downstream signaling cascade, functions as a G protein		7.12	Von Hippel-Lindau disease: pVHL modulates the	
5.11	Synopsis and prospects	169		hypoxic response	265
Key co	oncepts	172	7.13	Synopsis and prospects	268
	ht questions	174	Key co	oncepts	272
	onal reading	174		tht questions	273
2 Kuuru	ona reading			ional reading	273
Chap	ter 6: Cytoplasmic Signaling Circuitry Programs		C1	0 Pt 10 1 Ct 0 TO 1 Ct 1	275
-	of the Traits of Cancer	175	Chap	eter 8: pRb and Control of the Cell Cycle Clock	275
6.1	A signaling pathway reaches from the cell surface into	177	8.1	Cell growth and division is coordinated by a complex array of regulators	276
6.2	the nucleus The Ras protein stands in the middle of a complex	177	8.2	Cells make decisions about growth and quiescence during a specific period in the G <sub>1</sub> phase	281
6.3	signaling cascade Tyrosine phosphorylation controls the location and	180	8.3	Cyclins and cyclin-dependent kinases constitute the	
0.5	thereby the actions of many cytoplasmic signaling	100	8.4	core components of the cell cycle clock Cyclin–CDK complexes are also regulated by CDK	283
6.4	proteins SH2 and SH3 groups explain how growth factor	182		inhibitors	288
	receptors activate Ras and acquire signaling specificity	188	8.5	Viral oncoproteins reveal how pRb blocks advance through the cell cycle	294
6.5	Ras-regulated signaling pathways: A cascade of kinases forms one of three important signaling pathways		8.6	pRb is deployed by the cell cycle clock to serve as a	298
	downstream of Ras	189	8.7	guardian of the restriction-point gate E2F transcription factors enable pRb to implement	
6.6	Ras-regulated signaling pathways: a second downstream pathway controls inositol lipids and the		8.8	growth-versus-quiescence decisions A variety of mitogenic signaling pathways control	299
6.7	Akt/PKB kinase Ras-regulated signaling pathways: a third downstream	193		the phosphorylation state of pRb	304
	pathway acts through Ral, a distant cousin of Ras	201	8.9	The Myc protein governs decisions to proliferate or differentiate	306
6.8	The Jak-STAT pathway allows signals to be transmitted from the plasma membrane directly to		8.10	TGF-β prevents phosphorylation of pRb and thereby blocks cell cycle progression	311
	the nucleus	202	8.11	pRb function and the controls of differentiation are	
6.9	Cell adhesion receptors emit signals that converge with those released by growth factor receptors	204	8.12	closely linked Control of pRb function is perturbed in most if not	314
6.10	The Wnt-β-catenin pathway contributes to cell	206		all human cancers	318
	proliferation	200	8.13	Synopsis and prospects	323
6.11	G-protein-coupled receptors can also drive normal	200		oncepts	327
	and neoplastic proliferation	209	Thoug	ght questions	328
6.12	Four additional "dual-address" signaling pathways contribute in various ways to normal and neoplastic		Addit	ional reading	329
	proliferation	212	-		
6.13	Well-designed signaling circuits require both negative		Chap	oter 9: p53 and Apoptosis: Master Guardian and	
0.440	and positive feedback controls	216		utioner	331
614	Synopsis and prospects	217			222
		227	9.1	Papovaviruses lead to the discovery of p53	332
	oncepts	228	9.2	p53 is discovered to be a tumor suppressor gene	334
	tht questions ional reading	228	9.3	Mutant versions of p53 interfere with normal p53 function	335
			9.4	p53 protein molecules usually have short lifetimes	338
01	- m c	221		A variety of signals cause p53 induction	339
-	ter 7: Tumor Suppressor Genes	231	9.5 9.6	DNA damage and deregulated growth signals cause	
7.1	Cell fusion experiments indicate that the cancer	222		p53 stabilization	341
7.2	The recessive nature of the cancer cell phenotype	232	9.7 9.8	Mdm2 destroys its own creator ARF and p53-mediated apoptosis protect against	342
	requires a genetic explanation	234		cancer by monitoring intracellular signaling	348
7.3	The retinoblastoma tumor provides a solution to the genetic puzzle of tumor suppressor genes	235	9.9	p53 functions as a transcription factor that halts cell cycle advance in response to DNA damage and	
7.4	Incipient cancer cells invent ways to eliminate wild-	238	0.40	attempts to aid in the repair process	352 355
7.5	type copies of tumor suppressor genes The <i>Rb</i> gene often undergoes loss of heterozygosity		9.10 9.11	p53 often ushers in the apoptotic death program p53 inactivation provides advantage to incipient	
7.6	in tumors Loss-of-heterozygosity events can be used to find	241		cancer cells at a number of steps in tumor progression Inherited mutant alleles affecting the p53 pathway	359
	tumor suppressor genes	243	9.12	predispose one to a variety of tumors	360
7.7	Many familial cancers can be explained by inheritance	240	9.13	Apoptosis is a complex program that often depends	201
7.8	of mutant tumor suppressor genes Promoter methylation represents an important	248	9.14	on mitochondria  Both intrinsic and extrinsic apoptotic programs can	361
	mechanism for inactivating tumor suppressor genes	249		lead to cell death	371
7.9	Tumor suppressor genes and proteins function in diverse ways	254	9.15	Cancer cells invent numerous ways to inactivate some or all of the apoptotic machinery	376
7.10	The NF1 protein acts as a negative regulator of Ras	5.9	9.16	Necrosis and autophagy: two additional forks in the	

9.17	Synopsis and prospects	381	11.15	Chronic inflammation often serves to promote tumor	
Key concepts		387	****	progression in mice and humans	48
Thought questions		388	11.16	Inflammation-dependent tumor promotion operates	
Addit	ional reading	389		through defined signaling pathways	49
			11.17		
Chan	ter 10: Eternal Life: Cell Immortalization and		44.40	of the rate of tumor progression in many human tissues	
Tumorigenesis		391		Synopsis and prospects	50
Tume	ongenesis	371		oncepts	500
10.1	Normal cell populations register the number of cell			tht questions	50
	generations separating them from their ancestors in		Addit	ional reading	508
	the early embryo	392			
10.2	Cancer cells need to become immortal in order to form		Chap	ter 12: Maintenance of Genomic Integrity and the	
	tumors	394		lopment of Cancer	511
10.3	Cell-physiologic stresses impose a limitation on				
-	replication	398	12.1	Tissues are organized to minimize the progressive	24.7
10.4	The proliferation of cultured cells is also limited by the			accumulation of mutations	512
	telomeres of their chromosomes	404	12.2	Stem cells may or may not be targets of the	
10.5	Telomeres are complex molecular structures that are not			mutagenesis that leads to cancer	515
	easily replicated	409	12.3	Apoptosis, drug pumps, and DNA replication	
10.6	Incipient cancer cells can escape crisis by expressing			mechanisms offer tissues a way to minimize the	
	telomerase	412		accumulation of mutant stem cells	517
10.7	Telomerase plays a key role in the proliferation of		12.4	Cell genomes are threatened by errors made during	
10.7	human cancer cells	417		DNA replication	519
10.8	Some immortalized cells can maintain telomeres	411	12.5	Cell genomes are under constant attack from	
10.0	without telomerase	419		endogenous biochemical processes	523
100	A LOCATION CONTRACTOR OF THE PARTY OF THE PA	417	12.6	Cell genomes are under occasional attack from	
10.9	Telomeres play different roles in the cells of laboratory	122		exogenous mutagens and their metabolites	527
10 10	mice and in human cells	423	12.7	Cells deploy a variety of defenses to protect DNA	
10.10	Telomerase-negative mice show both decreased and	105		molecules from attack by mutagens	535
1011	increased cancer susceptibility	425	12.8	Repair enzymes fix DNA that has been altered by	
10.11	The mechanisms underlying cancer pathogenesis in			mutagens	538
	telomerase-negative mice may also operate during the		12.9	Inherited defects in nucleotide-excision repair,	
	development of human tumors	429		base-excision repair, and mismatch repair lead to	
10.12	Synopsis and prospects	433		specific cancer susceptibility syndromes	544
	ncepts	436	12.10	A variety of other DNA repair defects confer increased	3.1
	ht questions	437	12.10	cancer susceptibility through poorly understood	
Additi	onal reading	437		mechanisms	549
			12.11	The karyotype of cancer cells is often changed through	347
Chant	11. M.1: Can Tanai	120	12.11	alterations in chromosome structure	555
Chapi	ter 11: Multi-Step Tumorigenesis	439	12.12	The karyotype of cancer cells is often changed through	333
11.1	Most human cancers develop over many decades of		12,12	alterations in chromosome number	558
		440	12 13	Synopsis and prospects	564
11.2	Histopathology provides evidence of multi-step tumor		Key co		572
		442		ht questions	573
11.3	Cells accumulate genetic and epigenetic alterations	NOT US		onal reading	574
		449	Additi	onar reading	3/4
11.4	Multi-step tumor progression helps to explain familial				
		453	Chapt	ter 13 Dialogue Replaces Monologue: Heterotypic	
11.5	Cancer development seems to follow the rules of	133	Intera	ctions and the Biology of Angiogenesis	577
		455			
11.6	Tumor stem cells further complicate the Darwinian	433	13.1	Normal and neoplastic epithelial tissues are formed	
11.0	model of closel every and transfer the Darwinian	450		from interdependent cell types	579
11.7		458	13.2	The cells forming cancer cell lines develop without	
11./	A linear path of clonal succession oversimplifies the	1/2		heterotypic interactions and deviate from the behavior	
11.8		463		of cells within human tumors	585
11.0	The Darwinian model of tumor development is difficult		13.3	Tumors resemble wounded tissues that do not heal	587
11.9		467	13.4	Experiments directly demonstrate that stromal cells	
11.9	Multiple lines of evidence reveal that normal cells are			are active contributors to tumorigenesis	600
11 10		468	13.5	Macrophages and myeloid cells play important roles	
11.10	Transformation usually requires collaboration between			in activating the tumor-associated stroma	604
11 11		470	13.6	Endothelial cells and the vessels that they form ensure	
11.11	Transgenic mice provide models of oncogene			tumors adequate access to the circulation	607
11.10		474	13.7	Tripping the angiogenic switch is essential for tumor	
11.12	Human cells are constructed to be highly resistant				615
11.10		475	13.8	The angiogenic switch initiates a highly complex	
11.13	Nonmutagenic agents, including those favoring				619
	cell proliferation, make important contributions to		13.9	Angiogenesis is normally suppressed by physiologic	
11.11		480			622
11.14	Toxic and mitogenic agents can act as human tumor		13 10	Anti-angiogenesis therapies can be employed to	

13.11	Synopsis and prospects	634	15.13	Cancer cells can evade immune detection by	
Key co		638	10,10	suppressing cell-surface display of tumor antigens	761
		639	15 14	Cancer cells protect themselves from destruction by	701
Thought questions Additional reading		639	1.7.17	NK cells and macrophages	765
reductional reading		037	15 15	Tumor cells launch counterattacks on immunocytes	769
Chan	ter 14: Moving Out: Invasion and Metastasis	641		Cancer cells become intrinsically resistant to various	101
Chapter 14. Woving Out. Invasion and Wetastasis		041	15,10	forms of killing used by the immune system	773
14.1	Travel of cancer cells from a primary tumor to a site		15.17		115
	of potential metastasis depends on a series of complex		15.17		774
	biological steps	643	15.18	attacks by other lymphocytes	114
14.2	Colonization represents the most complex and		15.18	Passive immunization with monoclonal antibodies	770
	challenging step of the invasion-metastasis cascade	652	15 10	can be used to kill breast cancer cells	778
14.3	The epithelial-mesenchymal transition and associated		15.19	Passive immunization with antibody can also be	701
	loss of E-cadherin expression enable carcinoma cells		15.00	used to treat B-cell tumors	781
	to become invasive	657	15.20	Transfer of foreign immunocytes can lead to cures	705
14.4	Epithelial-mesenchymal transitions are often induced		47.04	of certain hematopoietic malignancies	785
	by contextual signals	662	15.21	Patients' immune systems can be mobilized to	=0.0
14.5	Stromal cells contribute to the induction of			attack their tumors	786
	invasiveness	669		Synopsis and prospects	791
14.6	EMTs are programmed by transcription factors that			oncepts	793
	orchestrate key steps of embryogenesis	672		ht questions	795
14.7	EMT-inducing transcription factors also enable		Additi	onal reading	795
	entrance into the stem cell state	677			
14.8	EMT-inducing TFs help drive malignant progression	680	Chan	ter 16: The Rational Treatment of Cancer	797
14.9	Extracellular proteases play key roles in invasiveness	685	Спар	ter 10. The Rational Treatment of Cancer	111
14.10	Small Ras-like GTPases control cellular processes		16.1	The development and clinical use of effective	
	such as adhesion, cell shape, and cell motility	689		therapies will depend on accurate diagnosis of disease	800
14.11	Metastasizing cells can use lymphatic vessels to		16.2	Surgery, radiotherapy, and chemotherapy are the	
	disperse from the primary tumor	695		major pillars on which current cancer therapies rest	806
14.12	A variety of factors govern the organ sites in which	-	16.3	Differentiation, apoptosis, and cell cycle checkpoints	
	disseminated cancer cells form metastases	699		can be exploited to kill cancer cells	813
14.13	Metastasis to bone requires the subversion of	1077	16.4	Functional considerations dictate that only a subset	177
11110	osteoblasts and osteoclasts	703	10.1	of the defective proteins in cancer cells are attractive	
14.14		2134		targets for drug development	815
+	the metastatic phenotype	709	16.5	The biochemistry of proteins also determines whether	010
14.15	Occult micrometastases threaten the long-term		10.5	they are attractive targets for intervention	818
11110	survival of cancer patients	711	16.6	Pharmaceutical chemists can generate and explore	OIG
14.16		713	10.0	the biochemical properties of a wide array of potential	
Key co		719		drugs	822
	ht questions	720	16.7	Drug candidates must be tested on cell models as an	ULL
	onal reading	721	10.7	initial measurement of their utility in whole	
A				organisms	825
Chapt	er 15: Crowd Control: Tumor Immunology		16.8	Studies of a drug's action in laboratory animals are	023
*	nmunotherapy	723	10.0	an essential part of pre-clinical testing	826
HILL II	moraup ide	, 20	16.9	Promising candidate drugs are subjected to rigorous	020
15.1	The immune system functions to destroy foreign		10.7	clinical tests in Phase I trials in humans	829
	invaders and abnormal cells in the body's tissues	724	16.10		02)
15.2	The adaptive immune response leads to antibody		10.10	Phase II and III trials provide credible indications of clinical efficacy	831
	production	726	16 11	Tumors often develop resistance to initially effective	0.51
15.3	Another adaptive immune response leads to the		16.11		833
	formation of cytotoxic cells	729	1/ 12	therapy	033
15.4	The innate immune response does not require prior		10.12	Gleevec paved the way for the development of many	024
	sensitization	736	16.12	other highly targeted compounds	834
15.5	The need to distinguish self from non-self results in		16.13	EGF receptor antagonists may be useful for treating	011
	immune tolerance	736	1/14	a wide variety of tumor types	844
15.6	Regulatory T cells are able to suppress major		16.14	Proteasome inhibitors yield unexpected therapeutic	050
	components of the adaptive immune response	737	1/15	benefit	850
15.7	The immunosurveillance theory is born and then		16.15	A sheep teratogen may be useful as a highly potent	OFF
	suffers major setbacks	739	1/1/	anti-cancer drug	855
15.8	Use of genetically altered mice leads to a resurrection		10.10	mTOR, a master regulator of cell physiology,	0/1
	of the immunosurveillance theory	742	47.47	represents an attractive target for anti-cancer therapy	861
15.9	The human immune system plays a critical role in		16.17	B-Raf discoveries have led to inroads into the	001
	warding off various types of human cancer	745	11.10	melanoma problem	864
15.10	Subtle differences between normal and neoplastic	Ten	16.18	Synopsis and prospects: challenges and opportunities	
	tissues may allow the immune system to distinguish		**	on the road ahead	866
	between them	751	Key co		874
15.11	Tumor transplantation antigens often provoke potent	13.9		ht questions	875
SSA	immune responses	756	Additi	onal reading	875
15.12	Tumor-associated transplantation antigens may	M. EL			