

the biology of
CANCER
SECOND EDITION

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 |
| Abbreviations | | A:1 |
| Glossary | | G:1 |
| Index | | I:1 |

List of Key Techniques

- Apoptotic cells: Various detection techniques (Figure 9.19)
- Apoptotic cells: Detection by the TUNEL assay (Supplementary Sidebar 9.2 )
- Chromatin immunoprecipitation (Supplementary Sidebar 8.3 )
- Circulating tumor cells: Detection using microfluidic devices (Supplementary Sidebar 14.3 )
- Comparative genomic hybridization (CGH) (Supplementary Sidebar 11.4 )
- DNA sequence polymorphisms: Detection by polymerase chain reaction (Supplementary Sidebar 7.3 )
- Embryonic stem cells: Derivation of pluripotent mouse cell lines (Supplementary Sidebar 8.1 )
- Fluorescence-activated cell sorting (FACS) (Supplementary Sidebar 11.1 )
- Gene cloning strategies (Supplementary Sidebar 1.5 )
- Gene cloning: Isolation of genes encoding melanoma antigens (Supplementary Sidebar 15.11 )
- Gene cloning: Isolation of transfected human oncogenes (Figure 4.7)
- Gene knock-in and knock-out: Homologous recombination with mouse germ-line genes (Supplementary Sidebar 7.7 )
- Histopathological staining techniques (Supplementary Sidebar 2.1 )
- Knocking down gene expression with shRNAs and siRNAs (Supplementary Sidebar 1.4 )
- Laser-capture microdissection (Supplementary Sidebar 13.5 )
- Mapping of DNA methylation sites: Use of sequence-specific polymerase chain reaction (Supplementary Sidebar 7.4 )
- Mapping of an oncogene-activating mutation (Figure 4.8)
- Mapping of tumor suppressor genes via restriction fragment length polymorphisms (Figure 7.13)
- Monoclonal antibodies (Supplementary Sidebar 11.1 )
- Mutagenicity measurement: The Ames test (Figure 2.27)
- Probe construction: The *src*-specific DNA probe (Figure 3.20)
- Reproductive cloning (Supplementary Sidebar 1.2 )
- Retroviral vector construction (Supplementary Sidebar 3.3 )
- Screening for mutant oncoproteins (Figure 16.25)
- Skin carcinoma induction in mice (Figure 11.30)
- Southern and Northern blotting (Supplementary Sidebar 4.3 )
- Telomerase activity measurements: The TRAP assay (Supplementary Sidebar 10.1 )
- Transfection of DNA (Figure 4.1)
- Transgenic mice: Creating tumor-prone strains (Figure 9.23A)

 Can be found on the DVD-ROM accompanying the book.

Detailed Contents

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

| | | |
|------|--|-----|
| 5.10 | The Ras protein, an apparent component of the downstream signaling cascade, functions as a G protein | 165 |
| 5.11 | Synopsis and prospects | 169 |
| | Key concepts | 172 |
| | Thought questions | 174 |
| | Additional reading | 174 |

Chapter 6: Cytoplasmic Signaling Circuitry Programs Many of the Traits of Cancer 175

| | | |
|------|--|-----|
| 6.1 | A signaling pathway reaches from the cell surface into the nucleus | 177 |
| 6.2 | The Ras protein stands in the middle of a complex signaling cascade | 180 |
| 6.3 | Tyrosine phosphorylation controls the location and thereby the actions of many cytoplasmic signaling proteins | 182 |
| 6.4 | SH2 and SH3 groups explain how growth factor receptors activate Ras and acquire signaling specificity | 188 |
| 6.5 | Ras-regulated signaling pathways: A cascade of kinases forms one of three important signaling pathways downstream of Ras | 189 |
| 6.6 | Ras-regulated signaling pathways: a second downstream pathway controls inositol lipids and the Akt/PKB kinase | 193 |
| 6.7 | Ras-regulated signaling pathways: a third downstream pathway acts through Ral, a distant cousin of Ras | 201 |
| 6.8 | The Jak-STAT pathway allows signals to be transmitted from the plasma membrane directly to the nucleus | 202 |
| 6.9 | Cell adhesion receptors emit signals that converge with those released by growth factor receptors | 204 |
| 6.10 | The Wnt- β -catenin pathway contributes to cell proliferation | 206 |
| 6.11 | G-protein-coupled receptors can also drive normal and neoplastic proliferation | 209 |
| 6.12 | Four additional “dual-address” signaling pathways contribute in various ways to normal and neoplastic proliferation | 212 |
| 6.13 | Well-designed signaling circuits require both negative and positive feedback controls | 216 |
| 6.14 | Synopsis and prospects | 217 |
| | Key concepts | 227 |
| | Thought questions | 228 |
| | Additional reading | 228 |

Chapter 7: Tumor Suppressor Genes 231

| | | |
|------|--|-----|
| 7.1 | Cell fusion experiments indicate that the cancer phenotype is recessive | 232 |
| 7.2 | The recessive nature of the cancer cell phenotype requires a genetic explanation | 234 |
| 7.3 | The retinoblastoma tumor provides a solution to the genetic puzzle of tumor suppressor genes | 235 |
| 7.4 | Incipient cancer cells invent ways to eliminate wild-type copies of tumor suppressor genes | 238 |
| 7.5 | The <i>Rb</i> gene often undergoes loss of heterozygosity in tumors | 241 |
| 7.6 | Loss-of-heterozygosity events can be used to find tumor suppressor genes | 243 |
| 7.7 | Many familial cancers can be explained by inheritance of mutant tumor suppressor genes | 248 |
| 7.8 | Promoter methylation represents an important mechanism for inactivating tumor suppressor genes | 249 |
| 7.9 | Tumor suppressor genes and proteins function in diverse ways | 254 |
| 7.10 | The NF1 protein acts as a negative regulator of Ras signaling | 255 |

| | | |
|------|--|-----|
| 7.11 | ApC facilitates egress of cells from colonic crypts | 259 |
| 7.12 | Von Hippel-Lindau disease: pVHL modulates the hypoxic response | 265 |
| 7.13 | Synopsis and prospects | 268 |
| | Key concepts | 272 |
| | Thought questions | 273 |
| | Additional reading | 273 |

Chapter 8: pRb and Control of the Cell Cycle Clock 275

| | | |
|------|---|-----|
| 8.1 | Cell growth and division is coordinated by a complex array of regulators | 276 |
| 8.2 | Cells make decisions about growth and quiescence during a specific period in the G ₁ phase | 281 |
| 8.3 | Cyclins and cyclin-dependent kinases constitute the core components of the cell cycle clock | 283 |
| 8.4 | Cyclin-CDK complexes are also regulated by CDK inhibitors | 288 |
| 8.5 | Viral oncoproteins reveal how pRb blocks advance through the cell cycle | 294 |
| 8.6 | pRb is deployed by the cell cycle clock to serve as a guardian of the restriction-point gate | 298 |
| 8.7 | E2F transcription factors enable pRb to implement growth-versus-quiescence decisions | 299 |
| 8.8 | A variety of mitogenic signaling pathways control the phosphorylation state of pRb | 304 |
| 8.9 | The Myc protein governs decisions to proliferate or differentiate | 306 |
| 8.10 | TGF- β prevents phosphorylation of pRb and thereby blocks cell cycle progression | 311 |
| 8.11 | pRb function and the controls of differentiation are closely linked | 314 |
| 8.12 | Control of pRb function is perturbed in most if not all human cancers | 318 |
| 8.13 | Synopsis and prospects | 323 |
| | Key concepts | 327 |
| | Thought questions | 328 |
| | Additional reading | 329 |

Chapter 9: p53 and Apoptosis: Master Guardian and Executioner 331

| | | |
|------|---|-----|
| 9.1 | Papovaviruses lead to the discovery of p53 | 332 |
| 9.2 | p53 is discovered to be a tumor suppressor gene | 334 |
| 9.3 | Mutant versions of p53 interfere with normal p53 function | 335 |
| 9.4 | p53 protein molecules usually have short lifetimes | 338 |
| 9.5 | A variety of signals cause p53 induction | 339 |
| 9.6 | DNA damage and deregulated growth signals cause p53 stabilization | 341 |
| 9.7 | Mdm2 destroys its own creator | 342 |
| 9.8 | ARF and p53-mediated apoptosis protect against cancer by monitoring intracellular signaling | 348 |
| 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 |
| 9.10 | p53 often ushers in the apoptotic death program | 355 |
| 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 | 391 | 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 | 511 |
| 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 | 439 | 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 | 577 |
| 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 |

| | | | | | |
|--|---|------------|---|--|------------|
| 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 | | | |