Brief Contents

PART 1 Fundamentals and Foundations 1

CHAPTER 1 Introduction to Cells and Cell Research 1

CHAPTER 2 Physical Principles Underlying Cell Structure and Function 40

CHAPTER 3 Fundamentals of Molecular Biology 84

PART 2 The Flow of Genetic Information 135

CHAPTER 4 Genes and Genomes 135

CHAPTER 5 Replication, Maintenance, and Rearrangements of Genomic DNA 162

CHAPTER 6 RNA Synthesis and Processing 199

CHAPTER 7 Transcriptional Regulation and Epigenetics 230

CHAPTER 8 Protein Synthesis, Processing, and Regulation 263

CHAPTER 9 Genomics, Proteomics, and Systems Biology 304

PART 3 Subcellular Structures and Functions 336

CHAPTER 10 The Nucleus 336

CHAPTER 11 Protein Processing and Sorting: The Endoplasmic Reticulum, Golgi Apparatus, and Lysosomes 365

CHAPTER 12 Mitochondria, Chloroplasts, and Peroxisomes 411

CHAPTER 13 The Cytoskeleton and Cell Movement 458

CHAPTER 14 The Plasma Membrane 502

CHAPTER 15 Cell Walls, the Extracellular Matrix, and Cell Interactions 542

PART 4 Cell Regulation 563

CHAPTER 16 Cell Signaling 563

CHAPTER 17 The Cell Cycle 598

CHAPTER 18 Cell Renewal and Cell Death 630

CHAPTER 19 Cancer 660

Contents

PART 1 Fundamentals and Foundations 1

1 Introduction to Cells and Cell Research 1

1.1 The Origin and Evolution of Cells 2

How did the first cell arise? 2
The evolution of metabolism 4
Prokaryotes 5
Eukaryotic cells 6
The origin of eukaryotes 8
The development of multicellular organisms 10

1.2 Experimental Models in Cell Biology 14

E. coli 15
Yeasts 15
Caenorhabditis elegans and *Drosophila melanogaster* 16
Arabidopsis thaliana 17
Vertebrates 18
Animal cell culture 19
Key Experiment HeLa Cells: The First Human Cell Line 21
Viruses 21
Molecular Medicine Viruses and Cancer 22

1.3 Tools of Cell Biology: Microscopy and Subcellular Fractionation 24

Light microscopy 24
Fluorescence microscopy 27
Sharpening the focus and seeing cells deeper within living tissue 29
Super-resolution microscopy: Breaking the diffraction barrier 31
Electron microscopy 32
Subcellular fractionation 34

DATA ANALYSIS PROBLEM 37
SUGGESTED READING 38

2 Physical Principles Underlying Cell Structure and Function 40

2.1 Chemical Bonds, Thermodynamics, and ATP 40

Atoms and molecules interact through chemical bonds 41
The laws of thermodynamics and free energy changes govern chemical reactions 44
Cells use ATP as an energy source to drive energetically unfavorable reactions 45

2.2 Organic Molecules of Cells 48

Carbohydrates 49
Lipids 51
Nucleic acids 53
Proteins 58
Key Experiment The Folding of Polypeptide Chains 63

2.3 Enzymes as Biological Catalysts 68
The catalytic activity of enzymes 68
Mechanisms of enzymatic catalysis 69
Coenzymes 71
Regulation of enzyme activity 73

2.4 Cell Membranes 75
Membrane lipids 76
Membrane proteins 77
Key Experiment The Structure of Cell Membranes 78
Transport across cell membranes 79
DATA ANALYSIS PROBLEM 82
SUGGESTED READING 83

3 Fundamentals of Molecular Biology 84

3.1 Heredity, Genes, and DNA 84
Discoveries indicate genes and chromosomes contain the genetic material 85
Identification of DNA as the genetic material 87
Determination of DNA structure 89
DNA structure explains DNA replication 90

3.2 Expression of Genetic Information 92
The role of messenger RNA 93
The genetic code 93
A basic model of gene expression 95
RNA viruses and reverse transcription 97
Key Experiment The DNA Provirus Hypothesis 98

3.3 Recombinant DNA Technology 100
Restriction endonucleases 100
Generating recombinant DNA molecules 101
DNA sequencing 106
Generating recombinant proteins from cloned genes 108

3.4 Techniques to Detect and Examine Nucleic Acids and Proteins 110
Amplification of DNA by the polymerase chain reaction 110
Nucleic acid hybridization 112
Antibodies as probes for proteins 114
Antibody-based techniques 115

3.5 Techniques to Study Gene Function in Eukaryotes 118
Gene transfer in plants and animals 119
Mutagenesis of cloned DNAs 122
GFP-fusion proteins 124
Introducing mutations into cellular genes 125
Genome engineering by the CRISPR/Cas system 127
Key Experiment CRISPR-Cas9 as a Programmable Tool for Genome Editing 129
Targeting mRNA 130
DATA ANALYSIS PROBLEM 133
SUGGESTED READING 134

PART 2 The Flow of Genetic Information 135

4 Genes and Genomes 135

4.1 The Structure of Eukaryotic Genes 135
Introns and exons 137
Key Experiment The Discovery of Introns 139
Roles of introns 141

4.2 Noncoding Sequences 143
Noncoding RNAs 143
Key Experiment The ENCODE Project 145
Repetitive sequences 147
Gene duplication and pseudogenes 150

4.3 Chromosomes and Chromatin 152
Chromatin 153
Centromeres 156
Telomeres 158
DATA ANALYSIS PROBLEM 160
SUGGESTED READING 161

5 Replication, Maintenance, and Rearrangements of Genomic DNA 162

5.1 DNA Replication 162
DNA polymerases 163
The replication fork 164
The fidelity of replication 170
Origins and the initiation of replication 171
Telomeres and telomerase: Maintaining the ends of chromosomes 176
Key Experiment Telomerase Is a Reverse Transcriptase 177

5.2 DNA Repair 179
Direct reversal of DNA damage 180
Excision repair 181
Translesion DNA synthesis 185
Molecular Medicine Colon Cancer and DNA Repair 186
Repair of double-strand breaks 187

5.3 DNA Rearrangements and Gene Amplification 191
Antibody genes 191
Gene amplification 196
DATA ANALYSIS PROBLEM 198
SUGGESTED READING 198

6 RNA Synthesis and Processing 199

6.1 Transcription in Bacteria 199
Bacterial RNA polymerase 200
Bacterial promoters 200
Elongation and termination 202

6.2 Transcription in Eukaryotes 204
Eukaryotic RNA polymerases 204
General transcription factors and transcription by RNA polymerase II 204
Transcription by RNA polymerases I and III 208

6.3 RNA Processing and Turnover 212
Processing of ribosomal and transfer RNAs 212
Processing of mRNA in eukaryotes 215
Splicing mechanisms 217
Key Experiment The Discovery of snRNPs 220
Alternative splicing 222
Molecular Medicine Splicing Therapy for Duchenne Muscular Dystrophy 224
RNA editing 225
RNA degradation 226
DATA ANALYSIS PROBLEM 227
SUGGESTED READING 229

7 Transcriptional Regulation and Epigenetics 230

7.1 Gene Regulation in *E. coli* 230
The *lac* operon: The prototype for transcriptional regulation 230
The *lac* repressor: A prototype for negative control of transcription 231
Catabolite activator protein: A prototype for positive control of transcription 233
Concurrent mechanisms link transcription to multiple parameters 234

7.2 Transcription Factors in Eukaryotes 235
cis-acting regulatory sequences: Promoters and enhancers 236

Transcription factor binding sites 240
Transcription factors 243
Key Experiment Isolation of a Eukaryotic Transcription Factor 244
Regulation of elongation 246

7.3 Chromatin and Epigenetics 248
Histone modifications 249
Key Experiment The Role of Histone Modification 251
Chromatin remodeling factors 254
Histones and epigenetic inheritance 255
DNA methylation 256
Noncoding RNAs 258
SUGGESTED READING 260
DATA ANALYSIS PROBLEM 261

8 Protein Synthesis, Processing, and Regulation 263

8.1 Translation of mRNA 263
Transfer RNAs 264
The ribosome 264
The organization of mRNAs and the initiation of translation 267
The process of translation 269
Regulation of translation 273

8.2 Protein Folding and Processing 278
Chaperones and protein folding 278
Protein misfolding diseases 281
Enzymes that catalyze protein folding 283
Molecular Medicine Alzheimer's Disease 283
Protein cleavage 285
Attachment of carbohydrates and lipids 286

8.3 Regulation of Protein Function and Stability 288
Regulation by small molecules 289
Protein phosphorylation and other modifications 290
Key Experiment The Discovery of Tyrosine Kinases 294
Protein–protein interactions 295
Protein degradation 297
Cascades of protein regulation 299
DATA ANALYSIS PROBLEM 301
SUGGESTED READING 303

9 Genomics, Proteomics, and Systems Biology 304

9.1 Genomics and Transcriptomics 304
The human genome 305
Key Experiment The Human Genome 306
The genomes of other vertebrates 308
Next-generation sequencing and personal genomes 310
Global analysis of gene expression 314

9.2 Proteomics 316
Identification of cell proteins 317
Global analysis of protein localization 318
Protein interactions 319

9.3 Systems Biology 323
Systematic screens of gene function 324
Regulation of gene expression 325
Networks 326
Synthetic biology 328
Molecular Medicine COVID-19 and Synthetic Biology 331
DATA ANALYSIS PROBLEM 333
SUGGESTED READING 335

PART 3 Subcellular Structures and Functions 336

10 The Nucleus 336

10.1 The Nuclear Envelope and Traffic between the Nucleus and the Cytoplasm 336

Structure of the nuclear envelope 336

Molecular Medicine Nuclear Lamina Diseases 340

The nuclear pore complex 340

Selective transport of proteins to and from the nucleus 343

Key Experiment Identification of Nuclear Localization Signals 344

Transport of RNAs 348

Regulation of nuclear protein import 349

10.2 The Organization of Chromatin 350

Chromosome territories 351

Chromatin localization and transcriptional activity 352

Replication factories and transcription hubs 355

10.3 Nuclear Bodies 356

The nucleolus and rRNA 357

Polycomb bodies: Centers of transcriptional repression 360

Cajal bodies and nuclear speckles: Processing and storage of snRNPs 360

DATA ANALYSIS PROBLEM 362

SUGGESTED READING 364

11 Protein Processing and Sorting: The Endoplasmic Reticulum, Golgi Apparatus, and Lysosomes 365

11.1 The Endoplasmic Reticulum 366

The rough endoplasmic reticulum and protein secretion 366

Targeting proteins to the rough endoplasmic reticulum 368

Key Experiment The Signal Hypothesis 369

Insertion of transmembrane proteins into the rough ER membrane 373

Protein folding and processing in the rough ER 379

Quality control in the rough ER 381

The smooth ER and lipid synthesis 385

Export of proteins and lipids from the ER 386

11.2 The Golgi Apparatus 389

Organization of the Golgi 389

Protein glycosylation within the Golgi 390

Lipid and polysaccharide metabolism in the Golgi 392

Protein sorting and export from the Golgi apparatus 393

11.3 The Mechanism of Vesicular Transport 396

Assembly of vesicle coat proteins drives vesicle budding 398

GTP-binding proteins coordinate vesicle budding and cargo recruitment 400

Tethering factors and SNAREs mediate vesicle docking and fusion 401

11.4 Lysosomes 402

Acid hydrolases: The degradative enzymes of lysosomes 403

Molecular Medicine Gaucher Disease 403

Lysosome formation is coupled to endocytosis 404

Autophagy is a critical function of lysosomes 404

DATA ANALYSIS PROBLEM 409

SUGGESTED READING 410

12 Mitochondria, Chloroplasts, and Peroxisomes 411

12.1 Mitochondrial Structure, Composition, and Dynamics 411
Structure and composition of mitochondria 412
Mitochondrial dynamics 414

12.2 Oxidative Catabolism of Glucose and Fatty Acids 417
Glycolysis 417
The citric acid cycle 419
Fatty acid oxidation 421

12.3 Oxidative Phosphorylation 422
Overview of oxidative phosphorylation through chemiosmotic coupling 422
Key Experiment The Chemiosmotic Theory 424
Mechanisms of the electron transport chain 425
Coupling of proton flow to ATP production by ATP synthase 427

12.4 Mitochondrial Assembly and Maintenance 429
The genetic system of mitochondria 430
Molecular Medicine Mitochondrial Replacement Therapy 431
Import of nuclear-encoded mitochondrial proteins 432
Mitochondrial lipids 436
Transport of metabolites across the inner membrane 436

12.5 Chloroplasts and Other Plastids 438
Chloroplast structure and composition 439
Photosynthesis 442
The chloroplast genome 446
Import and sorting of chloroplast proteins 446
Other plastids 449

12.6 Peroxisomes 451
Functions of peroxisomes 452
Peroxisome assembly 453
DATA ANALYSIS PROBLEM 456
SUGGESTED READING 457

13 The Cytoskeleton and Cell Movement 458

13.1 Structure and Organization of Actin Filaments 458
Assembly and organization of actin filaments 459
Association of actin filaments with the plasma membrane 462
Microvilli 465
Cell surface protrusions and cell movement 466

13.2 Myosin Motors 469
Muscle contraction 469
Contractile assemblies of actin and myosin in nonmuscle cells 473
Unconventional myosins 474

13.3 Microtubules 476
Structure and dynamic organization of microtubules 476
Assembly of microtubules 480
MAPs and the organization of microtubules 481

13.4 Microtubule Motors and Movement 483
Microtubule motor proteins 483
Key Experiment The Isolation of Kinesin 484
Cargo transport and intracellular organization 486
Cilia and flagella 487
Microtubules during mitosis 490

13.5 Intermediate Filaments 492
Intermediate filament proteins 493
Assembly of intermediate filaments 494
Intracellular organization of intermediate filaments 495
Key Experiment Function of Intermediate Filaments 497
DATA ANALYSIS PROBLEM 499
SUGGESTED READING 501

14 The Plasma Membrane 502

14.1 Structure of the Plasma Membrane 502
The lipid bilayer 502
Plasma membrane proteins 506
Plasma membrane domains 510

14.2 Transport of Small Molecules 513
Facilitated diffusion and carrier proteins 514
Ion channels 514
Active transport driven by ATP hydrolysis 525
Active transport driven by ion gradients 528
Molecular Medicine Cystic Fibrosis 529

14.3 Internalization of Large Molecules by Endocytosis 531
Phagocytosis 532
Clathrin-mediated endocytosis 533
Key Experiment The LDL Receptor 535
DATA ANALYSIS PROBLEM 539
SUGGESTED READING 541

15 Cell Walls, the Extracellular Matrix, and Cell Interactions 542

15.1 Cell Walls 542
Bacterial cell walls 542
Eukaryotic cell walls 543

15.2 The Extracellular Matrix and Cell–Matrix Interactions 546
Matrix structural proteins 546
Matrix polysaccharides 548
Adhesion proteins 550
Cell–matrix interactions 551
Key Experiment The Characterization of Integrin 551

15.3 Cell–Cell Interactions 554
Adhesion junctions 554
Tight junctions 556
Gap junctions 557
Molecular Medicine Gap Junction Diseases 558
Plasmodesmata 559
Tunneling nanotubes 560
DATA ANALYSIS PROBLEM 561
SUGGESTED READING 562

PART 4 Cell Regulation 563

16 Cell Signaling 563

16.1 Signaling Molecules and Their Receptors 563
Modes of cell–cell signaling 564
Steroid hormones and the nuclear receptor superfamily 565
Signaling by other small molecules 567
Peptide hormones and growth factors 568

16.2 G Proteins and Cyclic AMP 570
G proteins and G protein-coupled receptors 570

Key Experiment G Protein-Coupled Receptors and Odor Detection 571
The cAMP pathway: Second messengers and protein phosphorylation 574

16.3 Tyrosine Kinases and Signaling by the MAP Kinase and PI 3-Kinase Pathways 577
Receptor tyrosine kinases 578
Nonreceptor tyrosine kinases 579
MAP kinase pathways 582
Molecular Medicine Cancer: Signal Transduction and the *ras* Oncogenes 583
The PI 3-kinase/Akt and mTOR pathways 586

16.4 Receptors Coupled to Transcription Factors 591
The TGF-β/Smad pathway 591
NF-κB signaling 591
The Wnt and Notch pathways 592

16.5 Signaling Dynamics and Networks 594
Feedback loops and signaling dynamics 594
Networks and crosstalk 595
DATA ANALYSIS PROBLEM 596
SUGGESTED READING 597

17 The Cell Cycle 598

17.1 The Eukaryotic Cell Cycle 598
The cell cycle consists of four sequential phases 599
Extracellular signals and cell growth regulate progression through the cell cycle 600
Cell cycle checkpoints 602

17.2 Regulators of Cell Cycle Progression 604
Cdk1 and cyclin B: The prototype regulators of cell cycle progression 604
Key Experiment The Discovery of MPF 605
Key Experiment The Identification of Cyclin 607
Families of cyclins and cyclin-dependent kinases 609
Growth factors and the regulation of G_1 Cdks 610
S phase and regulation of DNA replication 612
DNA damage checkpoints 615

17.3 The Events of M Phase 617
Stages of mitosis 617
Mitotic kinases drive entry into mitosis 619
The spindle assembly checkpoint controls the metaphase-to-anaphase transition and exit from mitosis 623
Cytokinesis 625
DATA ANALYSIS PROBLEM 627
SUGGESTED READING 629

18 Cell Renewal and Cell Death 630

18.1 Stem Cells and the Maintenance of Adult Tissues 630
Proliferation of differentiated cells 631
Stem cells 632
Medical applications of adult stem cells 637

18.2 Pluripotent Stem Cells, Cellular Reprogramming, and Regenerative Medicine 639
Embryonic stem cells 639
Key Experiment Culture of Embryonic Stem Cells 641
Somatic cell nuclear transfer 642
Induced pluripotent stem cells 643
Transdifferentiation of somatic cells 645

18.3 Programmed Cell Death 647
The hallmarks of apoptosis 647
Caspases: The executioners of apoptosis 649

Key Experiment Identification of Genes Required for Programmed Cell Death 650
Central regulators of apoptosis: The Bcl-2 family 651
Signaling pathways that regulate apoptosis 653
Alternative pathways of programmed cell death 656
DATA ANALYSIS PROBLEM 657
SUGGESTED READING 659

19 Cancer 660

19.1 The Development and Causes of Cancer 660
Types of cancer 660
The development of cancer 661
Properties of cancer cells 662
Causes of cancer 665

19.2 Oncogenes 667
Retroviral oncogenes 668
Proto-oncogenes 669
Key Experiment The Discovery of Proto-Oncogenes 670
Oncogenes in human cancer 671
Functions of oncogene products 674

19.3 Tumor Suppressor Genes 679
Identification of tumor suppressor genes 680
Functions of tumor suppressor gene products 683
Cancer genomics 685

19.4 Molecular Approaches to Cancer Treatment 687
Prevention and early detection 687
Oncogene-targeted drugs 688
Molecular Medicine Imatinib: Cancer Treatment Targeted against the *bcr/abl* Oncogene 691
Immunotherapy 692
DATA ANALYSIS PROBLEM 696
SUGGESTED READING 698

Appendix 699
Answers 701
Glossary 732
References 749
Index 753