# Contents

2

2

3

5

6

6

8

9

10

10

10

11

13

13

15

15

15

17

18

19

20

36

Chapter 1 Cells, Genomes, and the Diversity of Life

THE UNIVERSAL FEATURES OF LIFE ON EARTH All Cells Store Their Hereditary Information in the Form of

**Double-Strand DNA Molecules** 

All Cells Replicate Their Hereditary Information by Templated Polymerization

All Cells Transcribe Portions of Their DNA into RNA Molecules All Cells Use Proteins as Catalysts

All Cells Translate RNA into Protein in the Same Way Each Protein Is Encoded by a Specific Gene

Life Requires a Continual Input of Free Energy

The Expression Levels of All the Genes of an Organism	
Can Be Determined	37
Arabidopsis Has Been Chosen as a Model Plant	38
The World of Animal Cells Is Mainly Represented by a Worm,	
a Fly, a Fish, a Mouse, and a Human	38
Studies in the Fruit Fly Drosophila Provide a Key to Vertebrate	
Development	39
The Frog and the Zebrafish Provide Highly Accessible	
Vertebrate Models	40
The Mouse Is the Predominant Mammalian Model Organism	41
The COVID-19 Pandemic Has Focused Scientists	
on the SARS-CoV-2 Coronavirus	42

All Cells Function as Biochemical Factories All Cells Are Enclosed in a Plasma Membrane Across

Which Nutrients and Waste Materials Must Pass Cells Operate at a Microscopic Scale Dominated by

**Random Thermal Motion** 

A Living Cell Can Exist with 500 Genes Summary

GENOME DIVERSIFICATION AND THE TREE OF LIFE

The Tree of Life Has Three Major Domains: Eukaryotes,

Bacteria, and Archaea

Eukaryotes Make Up the Domain of Life That Is Most

Familiar to Us

On the Basis of Genome Analysis, Bacteria Are the Most

Diverse Group of Organisms on the Planet Archaea: The Most Mysterious Domain of Life Organisms Occupy Most of Our Planet

Cells Can Be Powered by a Wide Variety of Free-Energy Sources Some Cells Fix Nitrogen and Carbon Dioxide for Other Cells Genomes Diversify Over Evolutionary Time, Producing

New Types of Organisms New Genes Are Generated from Preexisting Genes Gene Duplications Give Rise to Families of Related Genes Within a Single Genome

on the SARS-CoV-2 Coronavirus Humans Are Unique in Reporting on Their Own Peculiarities To Understand Cells and Organisms Will Require Mathematics, Computers, and Quantitative Information Summary Problems References **Chapter 2 Cell Chemistry and Bioenergetics** THE CHEMICAL COMPONENTS OF A CELL Water Is Held Together by Hydrogen Bonds Four Types of Noncovalent Attractions Help Bring Molecules Together in Cells Some Polar Molecules Form Acids and Bases in Water A Cell Is Formed from Carbon Compounds Cells Contain Four Major Families of Small Organic Molecules The Chemistry of Cells Is Dominated by Macromolecules with Remarkable Properties Noncovalent Bonds Specify Both the Precise Shape of a Macromolecule and Its Binding to Other Molecules Summary CATALYSIS AND THE USE OF ENERGY BY CELLS

72

44

44

45

46

47

The Function of a Gene Can Often Be Deduced from		Dialogical Order k
Its Nucleotide Sequence	20	Hoat Eporar f
More Than 200 Gene Families Are Common to All		Cells Obtain Ener
Summer Comains of Life	21	Oxidation and Rec
Summary	21	Enzymes Lower th
EUKARYOTES AND THE ORIGIN OF THE EUKARYOTIC CELL	22	Chemical Rea
Eukaryotic Cells Contain a Variety of Organelles	23	Enzymes Can Driv
Mitochondria Evolved from a Symbiotic Bacterium		Reaction Path
Captured by an Ancient Archaeon	25	How Enzymes Fin
Chioroplasts Evolved from a Symbiotic Photosynthetic		Rapidity of Mo
Eukanyotos Hovo Llubrid Osna Ancient Eukaryotic Cell	26	The Free-Energy (
Eukaryotic Genomes Are Rig	27	Whether It Ca
Eukarvotic Genomes Are Bigh in Regulatory DNA	20	The Concentration
Eukarvotic Genomes Define the Program of Multicellular	20	Change and a
Development	29	The Standard Free
Many Eukarvotes Live as Solitary Cells	30	to Compare th
Summary	31	The Equilibrium Co
MODEL ORGANISMS	01	Each Other
Mutations Reveal the Euroctions of Genes	31	Activated Carrier
Molecular Biology Began with a Spotlight on One Bacterium	52	The Formation of
and Its Viruses	33	an Energetica
The Focus on E. coli as a Model Organism Has Accelerated		ATP Is the Most W
Many Subsequent Discoveries	35	Energy Stored in A

Cell Metabolism Is Organized by Enzymes	5
Biological Order Is Made Possible by the Release of	
Heat Energy from Cells	5
Cells Obtain Energy by the Oxidation of Organic Molecules	6
Oxidation and Reduction Involve Electron Transfers	6:
Enzymes Lower the Activation-Energy Barriers That Block	
Chemical Reactions	6
Enzymes Can Drive Substrate Molecules Along Specific	
Reaction Pathways	6
How Enzymes Find Their Substrates: The Enormous	
Rapidity of Molecular Motions	6
The Free-Energy Change for a Reaction, $\Delta G$ , Determines	
Whether It Can Occur Spontaneously	66
The Concentration of Reactants Influences the Free-Energy	
Change and a Reaction's Direction	6
The Standard Free-Energy Change, ∆G°, Makes It Possible	OTE
to Compare the Energetics of Different Reactions	6
The Equilibrium Constant and $\Delta G^{\circ}$ Are Readily Derived from	NU2 SUM
Each Other	68
The Free-Energy Changes of Coupled Reactions Are Additive	69
Activated Carrier Molecules Are Essential for Biosynthesis	69
The Formation of an Activated Carrier Is Coupled to	10-
an Energetically Favorable Reaction	7(
ATP Is the Most Widely Used Activated Carrier Molecule	7.



#### Energy Stored in ATP Is Often Harnessed to Join

Two Molecules Together

NADH and NADPH Are Important Electron Carriers There Are Many Other Activated Carrier Molecules in Cells The Synthesis of Biological Polymers Is Driven by

ATP Hydrolysis

Summary

HOW CELLS OBTAIN ENERGY FROM FOOD

Glycolysis Is a Central ATP-producing Pathway Glycolysis Illustrates How Enzymes Couple Oxidation

to Energy Storage

Fermentations Produce ATP in the Absence of Oxygen Organisms Store Food Molecules in Special Reservoirs Between Meals, Most Animal Cells Derive Their Energy from Fatty Acids Obtained from Fat Sugars and Fats Are Both Degraded to Acetyl CoA in Mitochondria

The Citric Acid Cycle Generates NADH by Oxidizing Acetyl Groups to CO<sub>2</sub>

Electron Transport Drives the Synthesis of the Majority of the ATP in Most Cells

Many Biosynthetic Pathways Begin with Glycolysis

or the Citric Acid Cycle Animals Must Obtain All the Nitrogen and Sulfur

Thou Mood from Lood

73	Enzymes Speed Reactions by Selectively Stabilizing	
75	Transition States	148
70	Enzymes Can Use Simultaneous Acid and Base Catalysis	148
76	Lysozyme Illustrates How an Enzyme Works	149
18	Tightiy Bound Small Molecules Add Extra Functions to Proteins The Cell Regulates the Catalytic Activities of Its Enzymes	152
80	Allosteric Enzymes Have Two or More Rinding Sites That Interact	155
80	Two Ligands Whose Binding Sites Are Coupled Must Reciprocally	157
83	Symmetrical Protein Assemblies Produce Cooperative Allosteric	157
04 85	Transitions	158
00	Many Changes in Proteins Are Driven by Protein Phosphorylation	159
86	A Eukaryotic Cell Contains a Large Collection of Protein Kinases	150
07	The Regulation of the Src Protein Kinase Reveals How a	159
87	Protein Can Function as a Microprocessor	161
88	Regulatory GTP-binding Proteins Are Switched On and	
00	Off by the Gain and Loss of a Phosphate Group	162
90	Proteins Can Be Regulated by the Covalent Addition	
	of Other Proteins	162
90	An Elaborate Ubiquitin-conjugating System Is Used	100
PANO	to Mark Proteins Drotoin Complexes with Interchangeable Darte Make	163
91	Efficient Lise of Genetic Information	164
92	A GTP-binding Protein Shows How Large Protein	104
112	Movements Can Be Generated from Small Ones	166
114	Motor Proteins Produce Directional Movement in Cells	167
UoT	Proteins Often Form Large Complexes That Function as Protein	
	Machines	167
115	The Disordered Regions in Proteins Are Critical for a	100
115	Set of Different Functions	168
	Scalloids Bring Sets of Interacting Macromolecules Together	170
115	Macromolecules Can Self-assemble to Form Biomolecular	170
121	Condensates	171
121	Classical Studies of Phase Separation Have Relevance	
100	for Biomolecular Condensates	173
120	A Comparison of Three Important Types of Large Biological	320.
124	Assemblies	174
126	That Direct Them to Specific Sites Inside the Cell	175
	A Complex Network of Protein Interactions Linderlies	175
	Cell Function	176
126	Protein Structures Can Be Predicted and New Proteins	
100	Designed	178
120	Summary	179
120	Problems	179
120	References	181
130		
Biole	Chapter 4 DNA, Chromosomes, and Genomes	183
130	THE OTOHOTHOE AND FUNCTION OF DUA	105
131	A DNA Molecule Consists of Two Complementary Chains of	185
133	A DNA Molecule Consists of two Complementary Chains of Nucleotides	185
100	The Structure of DNA Provides a Mechanism for Heredity	187
134	In Eukarvotes, DNA Is Enclosed in a Cell Nucleus	189
136	Summary	189
	CHROMOSOMAL DNA AND ITS PACKAGING	
136	IN THE CHROMATIN FIBER	189
107	Eukaryotic DNA Is Packaged into a Set of Chromosomes	190
137	Chromosomes Contain Long Strings of Genes	191
140	The Nucleotide Sequence of the Human Genome Shows	
140	How Our Genes Are Arranged	193
140	Must Contain a Contromoro Two Tolomoroo	
142	and Replication Origins	195
	DNA Molecules Are Highly Condensed in Chromosomes	197
142	Nucleosomes Are a Basic Unit of Eukaryotic Chromosome	MOG
	Structure	197

They Need from Food
Metabolism Is Highly Organized and Regulated
Summary
Problems
References

# Chapter 3 Proteins

## THE ATOMIC STRUCTURE OF PROTEINS

The Structure of a Protein Is Specified by Its Amino

Acid Sequence

Proteins Fold into a Conformation of Lowest Energy The  $\alpha$  Helix and the  $\beta$  Sheet Are Common Folding Motifs Four Levels of Organization Are Considered to Contribute

to Protein Structure Protein Domains Are the Modular Units from Which Larger

Proteins Are Built

Proteins Also Contain Unstructured Regions

All Protein Structures Are Dynamic, Interconverting Rapidly

Between an Ensemble of Closely Related Conformations

Because of Thermal Energy

Function Has Selected for a Tiny Fraction of the Many

Possible Polypeptide Chains

Proteins Can Be Classified into Many Families

Some Protein Domains Are Found in Many Different Proteins	;
The Human Genome Encodes a Complex Set of Proteins,	

Revealing That Much Remains Unknown Protein Molecules Often Contain More Than One

Polypeptide Chain

Some Globular Proteins Form Long Helical Filaments Protein Molecules Can Have Elongated, Fibrous Shapes Covalent Cross-Linkages Stabilize Extracellular Proteins Protein Molecules Often Serve as Subunits for the Assembly

of Large Structures

Many Structures in Cells Are Capable of Self-Assembly Assembly Factors Often Aid the Formation of Complex

**Biological Structures** 

When Assembly Processes Go Wrong: The Case of

Amyloid Fibrils

Amyloid Structures Can Also Perform Useful Functions in Cells Summary

#### **PROTEIN FUNCTION**

All Proteins Bind to Other Molecules

The Surface Conformation of a Protein Determines Its Chemistry 142 Sequence Comparisons Between Protein Family Members

Highlight Crucial Ligand-binding Sites 142 Proteins Bind to Other Proteins Through Several Types of Interfaces 143

198

200

Antibody Binding Sites Are Especially Versatile The Equilibrium Constant Measures Binding Strength Enzymes Are Powerful and Highly Specific Catalysts Substrate Binding Is the First Step in Enzyme Catalysis

146 146

The Structure of the Nucleosome Core Particle Reveals 144 How DNA Is Packaged 145 Nucleosomes Have a Dynamic Structure and Are Frequently Subjected to Changes Catalyzed by ATP-dependent Chromatin-remodeling Complexes

Attractions Between Nucleosomes Compact the	
Chromatin Fiber	202
Summary	203
THE EFFECT OF CHROMATIN STRUCTURE	202
ON DNA FUNCTION	203
Very Differently in Chromatin	204
Heterochromatin Is Highly Condensed and Restricts	AVIA
Gene Expression	204
The Heterochromatic State Can Spread Along a	
Chromosome and Be Inherited from One Cell Generation	205
to the Next The Core Histories Are Covalently Modified at Many	205
Different Sites	206
Chromatin Acquires Additional Variety Through	1397
the Site-specific Insertion of a Small Set of Histone Variants	208
Covalent Modifications and Histone Variants Can	
Act in Concert to Control Chromosome Functions	208
A Complex of Reader and writer Proteins Can Spread Specific	210
Parrier DNA_Protein Complexes Block the Spread	210
of Reader-Writer Complexes and Thereby Separate	
Neighboring Chromatin Domains	212
Centromeres Have a Special, Inherited Chromatin Structure	213
Some Forms of Chromatin Can Be Directly Inherited	215
The Abnormal Perturbations of Heterochromatin	0.15
That Arise During Tumor Progression Contribute to Many Cancers	215
Summary	217
THE GLOBAL STRUCTURE OF CHROMOSOMES	217
Chromosomes Are Folded Into Large Loops of Chromatin	217
Chromatin Structures	218
Chromosome Loops Decondense When the Genes Within	210
Them Are Expressed	220
Mammalian Interphase Chromosomes Occupy Discrete	
Territories in the Nucleus, with Their Heterochromatin	
and Euchromatin Distributed Differently	220
A Biochemical Technique Called HI-C Reveals Details	001
Chromosomal DNA is Organized into Loops by Large Protein Rings	221
Euchromatin and Heterochromatin Separate Spatially	220
in the Nucleus	225
Mitotic Chromosomes Are Highly Condensed	227
Summary	228
HOW GENOMES EVOLVE	229
Genome Comparisons Reveal Functional DNA Sequences	
by Their Conservation Throughout Evolution	230
Genome Alterations Are Caused by Failures of the	
Normal Mechanisms for Copying and Maintaining	001
The Genome Sequences of Two Species Differ in Proportion	231
to the Length of Time Since They Have Separately Evolved	232
Phylogenetic Trees Constructed from a Comparison of	LUL
DNA Sequences Trace the Relationships of All Organisms	233
A Comparison of Human and Mouse Chromosomes	
Shows How the Structures of Genomes Diverge	234
Rates of DNA Addition and DNA Less in a Lineage	000
Multispecies Sequence Comparisons Identify Many	236
Conserved DNA Sequences of Unknown Function	237
Changes in Previously Conserved Sequences Can	201
Help Decipher Critical Steps in Evolution	238
Mutations in the DNA Sequences That Control Gene	
Expression Have Driven Many of the Evolutionary	
Gene Duplication Aleo Dravidence lunched of Comments	239
Genetic Novelty During Evolution	240
Duplicated Genes Diverge	240
The Evolution of the Globin Gene Family Shows How	ē

We Can Trace Human History by Analyzing Genomes The Sequencing of Hundreds of Thousands of Human	244
Genomes Reveals Much Variation	245
Most of the Variants Observed in the Human Population Are Common Alleles, with at Most a Weak Effect	
on Phenotype	246
Forensic Analyses Exploit Special DNA Sequences with Unusually High Mutation Rates	247
An Understanding of Human Variation Is Critical for	- 11
Summary	248
Problems	249
Reterences	251
Chapter 5 DNA Poplication Popair	
and Recombination	253
THE MAINTENANCE OF DNA SEQUENCES	253
Mutation Rates Are Extremely Low	253
Low Mutation Rates Are Necessary for Life as We Know It Summary	254 255
DNA REPLICATION MECHANISMS	255
Base-pairing Underlies DNA Replication and DNA Repair The DNA Replication Fork Is Asymmetrical	255 256
The High Fidelity of DNA Replication Requires Several	200
Proofreading Mechanisms DNA Replication in the 5'-to-3' Direction Allows Efficient Error	258
Correction	260
A Special Nucleotide-polymerizing Enzyme Synthesizes	260
Special Proteins Help to Open Up the DNA Double Helix	200
A Sliding Ring Holds a Moving DNA Polymerase onto the DNA	261
The Proteins at a Replication Fork Cooperate to Form	202
a Replication Machine	263
and Bacteria	265
A Strand-directed Mismatch Repair System Removes	
Replication Machine	267
The Accidental Incorporation of Ribonucleotides During	260
DNA Topoisomerases Prevent DNA Tangling During	209
Replication	269
THE INITIATION AND COMPLETION OF DNA DEDUCATION	212
IN CHROMOSOMES	272
DNA Synthesis Begins at Replication Origins	272
of DNA Replication	273
Eukaryotic Chromosomes Contain Multiple Origins	070
In Eukaryotes, DNA Replication Takes Place During	213
Only One Part of the Cell Cycle	276
by the Assembly of an Origin Recognition Complex	276
Features of the Human Genome That Specify Origins	077
Properties of the ORC Ensure That Each Region of the	211
DNA Is Replicated Once and Only Once in Each S Phase	277
Termination of DNA Replication Occurs Through the Ordered	219
Disassembly of the Replication Fork	280
Telomeres Are Packaged into Specialized Structures	201
That Protect the Ends of Chromosomes	282
Summary	282
DNA REPAIR	284

DNA Duplications Contribute to the Evolution of Organisms 241 Genes Encoding New Proteins Can Be Created by the Recombination of Exons 242 Neutral Mutations Often Spread to Become Fixed in a Population, with a Probability That Depends on Population Size 243

DNA REPAIR Without DNA Repair, Spontaneous DNA Damage Would Rapidly Change DNA Sequences 286 The DNA Double Helix Is Readily Repaired 288 DNA Damage Can Be Removed by More Than One Pathway 288

Coupling Nucleotide Excision Repair to Transcription Ensures That the Cell's Most Important DNA Is Efficiently Repaired The Chemistry of the DNA Bases Facilitates Damage Detection Special Translesion DNA Polymerases Are Used in Emergencies Double-Strand Breaks Are Efficiently Repaired DNA Damage Delays Progression of the Cell Cycle Summary

290

290

292

292

295

295

296

298

298

299

300

301

302

302

304

305

306

306

307

307

309

309

311

313

#### HOMOLOGOUS RECOMBINATION

Homologous Recombination Has Common Features in All Cells 296 DNA Base-pairing Guides Homologous Recombination 296 Homologous Recombination Can Flawlessly Repair Double-Strand 297 Breaks in DNA

Specialized Processing of Double-Strand Breaks Commits Repair

to Homologous Recombination Strand Exchange Is Directed by the RecA/Rad51 Protein Homologous Recombination Can Rescue Broken and Stalled **DNA Replication Forks** 

DNA Repair by Homologous Recombination Entails Risks

to the Cell

neve Decemble ation la Onvaial fau Maiasia

In Eukaryotes, Transcription Initiation Also Requires Activator,	Attra
Mediator, and Chromatin-modifying Proteins	334
Protoine	335
Transcription Creates Superhelical Tension	335
Transcription Elongation in Eukarvotes Is Tightly Coupled	000
to RNA Processing	337
RNA Capping Is the First Modification of Eukaryotic	
Pre-mRNAs	338
RNA Splicing Removes Intron Sequences from Newly	lent
Transcribed Pre-mRNAs	339
Nucleotide Sequences Signal Where Splicing Occurs	341
RINA Splicing is Performed by the Spliceosome	341
Sories of RNA_RNA Rearrangements	313
Other Properties of Pre-mRNA and Its Synthesis Help to	040
Explain the Choice of Proper Splice Sites	345
RNA Splicing Has Remarkable Plasticity	346
Spliceosome-catalyzed RNA Splicing Evolved from RNA	
Self-splicing Mechanisms	347
RNA-processing Enzymes Generate the 3' End of Eukaryotic	Bain
mRNAs	348
Mature Eukaryotic mRNAs Are Selectively Exported from	240
Noncoding RNAs Are Also Synthesized and Processed in	349
the Nucleus	351
The Nucleolus Is a Ribosome-producing Factory	353
The Nucleus Contains a Variety of Subnuclear Biomolecular	
Condensates	355
Summary	357
FROM RNA TO PROTFIN	358
An mRNA Sequence Is Decoded in Sets of Three Nucleotides	358
tRNA Molecules Match Amino Acids to Codons in mRNA	359
tRNAs Are Covalently Modified Before They Exit from the Nucleus	361
Specific Enzymes Couple Each Amino Acid to Its Appropriate	
tRNA Molecule	361
Editing by tRNA Synthetases Ensures Accuracy	363
Amino Acids are added to the C-terminal End of a Growing Delynoptide Chain	264
The RNA Message Is Decoded in Ribosomes	365
Elongation Factors Drive Translation Forward and Improve	000
Its Accuracy	368
Induced Fit and Kinetic Proofreading Help Biological Processes	
Overcome the Inherent Limitations of Complementary	
Base-Pairing	369
Accuracy in Translation Requires a Large Expenditure of	070
The Ribesome Is a Ribezyme	370
Nucleotide Sequences in mRNA Signal Where to Start Protein	0/1
Synthesis	373
Stop Codons Mark the End of Translation	374
Proteins Are Made on Polyribosomes	375
There Are Minor Variations in the Standard Genetic Code	375
Inhibitors of Prokaryotic Protein Synthesis Are Useful	070
as Antibiotics	376
Quality-Control Mechanisms Act to Prevent Translation	270
Stalled Ribosomes Can Re Rescued	379
The Ribosome Coordinates the Folding, Enzymatic Modification	01.0
and Assembly of Newly Synthesized Proteins	380
and noothing of noving cyntholizou i rotoino	
Molecular Chaperones Help Guide the Folding of Most Proteins	380
Molecular Chaperones Help Guide the Folding of Most Proteins Proper Folding of Newly Synthesized Proteins Is Also Aided by	380
Molecular Chaperones Help Guide the Folding of Most Proteins Proper Folding of Newly Synthesized Proteins Is Also Aided by Translation Speed and Subunit Assembly	380 383
Molecular Chaperones Help Guide the Folding of Most Proteins Proper Folding of Newly Synthesized Proteins Is Also Aided by Translation Speed and Subunit Assembly Proteins That Ultimately Fail to Fold Correctly Are Marked	380 383
Molecular Chaperones Help Guide the Folding of Most Proteins Proper Folding of Newly Synthesized Proteins Is Also Aided by Translation Speed and Subunit Assembly Proteins That Ultimately Fail to Fold Correctly Are Marked for Destruction by Polyubiquitin	380 383 384

Homologous Recombination is Crucial for Meiosis	
Meiotic Recombination Begins with a Programmed	

**Double-Strand Break** 

Holliday Junctions Are Recognized by Enzymes That Drive

**Branch Migration** 

Homologous Recombination Produces Crossovers Between

Maternal and Paternal Chromosomes During Meiosis Homologous Recombination Often Results in Gene Conversion Summary

#### TRANSPOSITION AND CONSERVATIVE SITE-SPECIFIC RECOMBINATION

Through Transposition, Mobile Genetic Elements Can Insert into Any DNA Sequence

DNA-only Transposons Can Move by a Cut-and-Paste

Mechanism

Some DNA-only Transposons Move by Replicating Themselves

Some Viruses Use a Transposition Mechanism to Move

Themselves into Host-Cell Chromosomes Some RNA Viruses Replicate and Express Their Genomes

Without Using DNA as an Intermediate

Retroviral-like Retrotransposons Resemble Retroviruses,

but Cannot Move from Cell to Cell

A Large Fraction of the Human Genome Is Composed

of Nonr	etroviral Retrotransposons	313
Differen	t Organisms	314
Genome Se Transpo	equences Reveal the Approximate Times at Which sable Elements Have Moved	314
Conservativ	e Site-specific Recombination Can Reversibly	315
Conservativ	e Site-specific Recombination Can Be Used to	316
Bacterial Co	onservative Site-specific Recombinases Have Become	ore
Powerfi Summary Problems	ul Tools for Cell and Developmental Biologists	317
References		320
Chapter 6	6 How Cells Read the Genome:	
From	DNA to Protein	321
FROM DNA RNA Molecu	TO RNA ules Are Single-Stranded	<b>323</b> 324
Transcription	n Produces RNA Complementary to One Strand	005
RNA Polyme	erases Carry Out DNA Transcription	325

Cells Produce Different Categories of RNA Molecules 327 Signals Encoded in DNA Tell RNA Polymerase Where to 328 Start and Stop Bacterial Transcription Start and Stop Signals Are Heterogeneous in Nucleotide Sequence 329 Transcription Initiation in Eukaryotes Requires Many Proteins 331 To Initiate Transcription, RNA Polymerase II Requires a Set of General Transcription Factors 332

Sequestered Active Sites Many Proteins Are Controlled by Regulated Destruction There Are Many Steps from DNA to Protein Summary



386



THE RNA WORLD AND THE ORIGINS OF LIFE Single-Strand RNA Molecules Can Fold into Highly Elaborate Structures Ribozymes Can Be Produced in the Laboratory



RNA Can Both Store Information and Catalyze Chemical Reactions How Did Protein Synthesis Evolve? All Present-Day Cells Use DNA as Their Hereditary Material Summary Problems References	391 392 393 393 394 395
Chapter 7 Control of Gene Expression	397
AN OVERVIEW OF GENE CONTROL The Different Cell Types of a Multicellular Organism Contain	397

Different Cell Types Synthesize Different Sets of RNAs and Proteins 398 The Spectrum of mRNAs Present in a Cell Can Be Used

to Accurately Identify the Cell Type 400 External Signals Can Cause a Cell to Change the Expression

Transcription Circuits Allow the Cell to Carry Out Logic Operations Summary	433 434
MECHANISMS THAT REINFORCE CELL MEMORY IN PLANTS AND ANIMALS	435
Patterns of DNA Methylation Can Be Inherited When Vertebrate	125
CG-Rich Islands Are Associated with Many Genes in Mammals	436
A Chromosome-wide Alteration in Chromatin Structure Can Be	438
Inherited The Mammalian X-Inactivation in Females Is Triggered by	440
the Synthesis of a Long Noncoding RNA Stable Patterns of Gene Expression Can Be Transmitted	442
to Daughter Cells	443
Summary	445
POST-TRANSCRIPTIONAL CONTROLS Transcription Attenuation Causes the Premature Termination	445
of Some RNA Molecules Riboswitches Probably Represent Ancient Forms of Gene	445
Control Alternative RNA Splicing Can Produce Different Forms of	446
a Protein from the Same Gene The Definition of a Gene Has Been Modified Since the Discovery	446
of Alternative RNA Splicing	448
Back Splicing Can Produce Circular RNA Molecules	449
A Change in the Site of RNA Transcript Cleavage and Poly-A	
Addition Can Change the C-terminus of a Protein	449
Nucleotides in mRNA Can Be Covalently Modified	450
RNA Editing Can Change the Meaning of the RNA Message The Human AIDS Virus Illustrates How RNA Transport from	451
the Nucleus Can Be Regulated	452
mRNAs Can Be Localized to Specific Regions of the Cytosol	453
The Phosphorylation of an Initiation Factor Regulates	456
Protein Synthesis Globally	457
Initiation at AUG Codons Upstream of the Translation	450
Internal Ribosome Entry Sites Also Provide Opportunities	458
for Translational Control	458
Changes in mRNA Stability Can Control Gene Expression Regulation of mRNA Stability Involves P-bodies and	459
Stress Granules	461
Summany	160

of Its Genes	400
Gene Expression Can Be Regulated at Many of the Steps	101
in the Pathway from DINA to RINA to Protein	401
Summary	402
CONTROL OF TRANSCRIPTION BY SEQUENCE-SPECIFIC DNA-BINDING PROTEINS	402
The Sequence of Nucleotides in the DNA Double Helix Can Be Read by Proteins	402
Transcription Regulators Contain Structural Motifs That Can	102
Dimerization of Transcription Regulators Increases Their	403
Affinity and Specificity for DNA	406
Many Transcription Regulators Bind Cooperatively to DNA Nucleosome Structure Promotes Cooperative Binding	407
of Transcription Regulators	408
DNA-Binding by Transcription Regulators Is Dynamic	409
Summary	410
TRANSCRIPTION REGULATORS SWITCH GENES	1
ON AND OFF	410
The Tryptophan Repressor Switches Genes Off	410
Repressors Turn Genes Off and Activators Turn Them On	411
Both an Activator and a Repressor Control the Lac Operon	412
Complex Switches Centrel Gene Transcription in Eukanyotes	412
A Eukaryotic Gene Control Region Includes Many cis-Regulatory	414
Sequences Eukonyotic Transporintion Degulatore Wark in Oroung	414
Activator Proteins Promote the Assembly of RNA Polymerase	415
at the Start Point of Transcription	416
of Local Chromotin Structure	117
Some Transcription Activators Work by Releasing Paused	417
RNA Polymerase	418
Transcription Activators Work Synergistically	419
of Transate Formation Likely Increases the Efficiency	100
Fukaryotic Transcription Initiation	420
in Several Ways	120
Insulator DNA Sequences Prevent Eukanyotic Transcription	420
Regulators from Influencing Distant Genes	422
Summary	422
MOLECULAR GENETIC MECHANISMS THAT OPEATE	Beril
AND MAINTAIN SPECIALIZED CELL TYPES	423
Complex Genetic Switches That Regulate Drosophila Development	120
Are Built Up from Smaller Modules	423
The Drosophila Eve Gene Is Regulated by Combinatorial Controls Transcription Regulators Are Brought into Play by	424
in a successful biologic into hay by	

unnary	40
EGULATION OF GENE EXPRESSION BY NONCODING RNAs mall Noncoding RNA Transcripts Regulate Many Animal	46
and Plant Genes Through RNA Interference	46
iRNAs Regulate mRNA Translation and Stability	46
NA Interference Also Serves as a Cell Defense Mechanism	46
NA Interference Can Direct Heterochromatin Formation	46
RNAs Protect the Germ Line from Transposable Elements	46
NA Interference Has Become a Powerful Experimental Tool ells Have Additional Mechanisms to Hold Transposons	46
and Integrated Viral Genomes in Check	46
acteria Use Small Noncoding RNAs to Protect Themselves from Viruses	46
ong Noncoding RNAs Have Diverse Functions in the Cell	46
ummary	47
roblems	47
eferences	47

#### Chapter 8 Analyzing Cells, Molecules, and Systems 475

ISOLATING CELLS AND GROWING THEM IN CULTURE 476 Cells Can Be Isolated from Tissues and Grown in Culture 476 Eukaryotic Cell Lines Are a Widely Used Source of Homogeneous Cells 478 Hybridoma Cell Lines Are Factories That Produce Monoclonal Antibodies 478 480 Summary PURIFYING PROTEINS 480 Cells Can Be Separated into Their Component Fractions 480 Cell Extracts Provide Accessible Systems to Study Cell Functions 482 Proteins Can Be Separated by Chromatography 483

Extracellular Signals426Combinatorial Gene Control Creates Many Different Cell Types427Specialized Cell Types Can Be Experimentally Reprogrammed to<br/>Become Pluripotent Stem Cells428Combinations of Master Transcription Regulators Specify Cell<br/>Types by Controlling the Expression of Many Genes429Specialized Cells Must Rapidly Turn Some Genes On and Off430Differentiated Cells Maintain Their Identity431

Immunoprecipitation Is a Rapid Affinity Purification Method Genetically Engineered Tags Provide an Easy Way to Purify	486
Proteins Purified Cell-free Systems Are Required for the Precise Dissection of Molecular Functions	486
Summary	487
ANALYZING PROTEINS Proteins Can Be Separated by SDS Polyacrylamide-Gel	487
Electrophoresis Two-dimensional Gel Electrophoresis Provides Greater Protein	487
Separation Specific Proteins Can Be Detected by Blotting with Antibodies Hydrodynamic Measurements Reveal the Size and Shape	489
of a Protein Complex Mass Spectrometry Provides a Highly Sensitive Method	490
for Identifying Unknown Proteins Sets of Interacting Proteins Can Be Identified by	491
Biochemical Methods	493
Optical Methods Can Monitor Protein Interactions	493
NMR Can Be Used to Determine Protein Structure in Solution	494
Protein Sequence and Structure Provide Clues About Protein Function	497
Summary	498
ANALYZING AND MANIPULATING DNA	498
Restriction Nucleases Cut Large DNA Molecules into	
Specific Fragments	498
Gel Electrophoresis Separates DNA Molecules of Different Sizes Purified DNA Molecules Can Be Specifically Labeled	499
with Radioisotopes or Chemical Markers in Vitro	501
An Entire Conemo Can Be Represented in a DNA Library	503
Hybridization Provides a Powerful but Simple Way to Detect	000
Specific Nucleotide Sequences	505
Genes Can Be Cloned in Vitro Using PCR	506
PCR is Also Used for Diagnostic and Forensic Applications PCR and Synthetic DNA Are Ideal Sources of Specific	507
Gene Sequences for Cloning	510
DNA Cloning Allows Any Protein to Be Produced in Large	
Amounts	511
Next-Generation Sequencing Methods Have Revolutionized	512
To Re Liseful Genome Sequences Must Re Annotated	516
Summary	518
STUDYING GENE FUNCTION AND EXPRESSION	518
Classical Genetic Screens Identify Random Mutants with Specific	/Rim
Abnormalities	519
Mutations Can Cause Loss or Gain of Protein Function	522
Same Gene or Different Genes	523
Gene Products Can Be Ordered in Pathways by Epistasis Analysis	523
Mutations Responsible for a Phenotype Can Be Identified	504
Rapid and Cheap DNA Sequencing Has Revolutionized	524
Human Genetic Studies	524
Linked Blocks of Polymorphisms Have Been Passed Down	FOF
from Our Ancestors Sequence Variants Can Aid the Search for Mutations	525
Associated with Disease	526
Genomics Is Accelerating the Discovery of Rare Mutations	Brito
That Predispose Us to Serious Disease	527
The Cellular Functions of a Known Gene Can Be Studied	JUCI H
with Genome Engineering	527
A DIDDOID ODD LIODTO LIOD HOLEODOILU AITOROD	600

	Expression of Individual Genes Can Be Measured Using	500
	Global Analysis of mRNAs by RNA-seq Provides a Snapshot	536
	of Gene Expression	536
	Genome-wide Chromatin Immunoprecipitation Identifies	Visas
	Sites on the Genome Occupied by Transcription Regulators Ribosome Profiling Reveals Which mRNAs Are Being	538
	Translated in the Cell	538
	Recombinant DNA Methods Have Revolutionized Human Health	539
	Summary	540
1	MATHEMATICAL ANALYSIS OF CELL FUNCTION	542
	Regulatory Networks Depend on Molecular Interactions	543
	Differential Equations Help Us Predict Transient Behavior	545
	Promoter Activity and Protein Degradation Affect the Rate	EAC
	The Time Required to Reach Stoody State Depends on	540
	Protein Lifetime	547
	Quantitative Methods Are Similar for Transcription Repressors	041
	and Activators	548
	Negative Feedback Is a Powerful Strategy in Cell Regulation	549
	Delayed Negative Feedback Can Induce Oscillations	549
	DNA Binding by a Repressor or an Activator Can Be	Sume
	Cooperative	- 551
	Positive Feedback Is Important for Switchlike Responses	EE4
	and Bistability Reductored lo on Important Characteristic of Rielogical	551
	Notworks	553
	Two Transcription Regulators That Bind to the Same Gene	000
	Promoter Can Exert Combinatorial Control	554
	An Incoherent Feed-forward Interaction Generates Pulses	555
	A Coherent Feed-forward Interaction Detects Persistent Inputs	556
	The Same Network Can Behave Differently in Different	
	Cells Because of Stochastic Effects	557
	Several Computational Approaches Can Be Used to Model	FFZ
	the Reactions in Cells Statistical Mathada Ara Critical for the Analysia of Dialogical	557
	Data	558
	Summany	558
	Problems	559
	References	561
	STUD STORE PROBABLY DESTRICT ON TO STORE STORE STORE VISA DE	THOE

563

Chapter 9 Visualizing Cells and Their Molecules	563
LOOKING AT CELLS AND MOLECULES IN THE LIGHT	
MICROSCOPE	563
The Conventional Light Microscope Can Resolve Details	
0.2 µm Apart	564
Photon Noise Creates Additional Limits to Resolution	
When Light Levels Are Low	567
Living Cells Are Seen Clearly in a Phase-Contrast or a	
Differential-Interference-Contrast Microscope	567
Images Can Be Enhanced and Analyzed by Digital Techniques	568
Intact Tissues Are Usually Fixed and Sectioned Before Microscopy	569
Specific Molecules Can Be Located in Cells by Fluorescence	100
Microscopy	570
Antibodies Can Be Used to Detect Specific Proteins	572
Individual Proteins Can Be Fluorescently Tagged in Living Cells	
and Organisms	573
Protein Dynamics Can Be Followed in Living Cells	575
Fluorescent Biosensors Can Monitor Cell Signaling	576
Imaging of Complex Three-dimensional Objects Is Possible	
with the Optical Microscope	5//
The Confocal Microscope Produces Optical Sections by	570
Excluding Out-of-Focus Light	578
Superresolution Fluorescence Techniques Can Overcome	500
Diffraction-limited Resolution	580

Animais and Plants Can be Genetically Altered 220 The Bacterial CRISPR System Has Been Adapted to Edit Genomes in a Wide Variety of Species 530 Large Collections of Engineered Mutations Provide a Tool for Examining the Function of Every Gene in an Organism 531 RNA Interference Is a Simple and Rapid Way to Test Gene Function 533 Reporter Genes Reveal When and Where a Gene Is Expressed 534 In Situ Hybridization Can Reveal the Location of mRNAs and Noncoding RNAs 535

Dimaction-innited nesolution Single-Molecule Localization Microscopy Also Delivers Superresolution 583 Expanding the Specimen Can Offer Higher Resolution, but 585 with a Conventional Microscope Large Multicellular Structures Can Be Imaged Over Time 586 Single Molecules Can Be Visualized by Total Internal Reflection Fluorescence Microscopy 587 588 Summary

CONTENTS XXXI

647

648

649

P-type ATPase Pumps Ca <sup>2+</sup> into the Sarcoplasmic Reticulum in Muscle Cells e Plasma Membrane Na <sup>+</sup> -K <sup>+</sup> Pump Establishes Na <sup>+</sup> and k Gradients Across the Plasma Membrane C Transporters Constitute the Largest Family of Membran Transport Proteins
mmary
ANNELS AND THE ELECTRICAL PROPERTIES OF MEMBRANES
uaporins Are Permeable to Water but Impermeable to lons
Channels Are Ion-selective and Fluctuate Between

CHANNELS AND THE ELECTRICAL PROPERTIES OF MEMBRANES651Aquaporins Are Permeable to Water but Impermeable to lons652Ion Channels Are Ion-selective and Fluctuate Between Open and Closed States653The Membrane Potential in Animal Cells Depends Mainly on K+ Leak Channels and the K+ Gradient Across the Plasma Membrane655The Resting Potential Decays Only Slowly When the Na+-K+ Pump Is Stopped655The Three-dimensional Structure of a Bacterial K+ Channel655
Aquaporins Are Permeable to Water but Impermeable       652         to lons       652         Ion Channels Are Ion-selective and Fluctuate Between       653         Open and Closed States       653         The Membrane Potential in Animal Cells Depends Mainly       655         on K <sup>+</sup> Leak Channels and the K <sup>+</sup> Gradient Across       655         The Resting Potential Decays Only Slowly When the       655         The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel       655
to lons652Ion Channels Are Ion-selective and Fluctuate Between Open and Closed States653The Membrane Potential in Animal Cells Depends Mainly on K+ Leak Channels and the K+ Gradient Across the Plasma Membrane655The Resting Potential Decays Only Slowly When the Na+-K+ Pump Is Stopped655The Three-dimensional Structure of a Bacterial K+ Channel655
Ion Channels Are Ion-selective and Fluctuate Between       653         Open and Closed States       653         The Membrane Potential in Animal Cells Depends Mainly       653         on K <sup>+</sup> Leak Channels and the K <sup>+</sup> Gradient Across       655         the Plasma Membrane       655         The Resting Potential Decays Only Slowly When the       655         Na <sup>+</sup> -K <sup>+</sup> Pump Is Stopped       655         The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel       655
Open and Closed States653The Membrane Potential in Animal Cells Depends Mainly on K+ Leak Channels and the K+ Gradient Across the Plasma Membrane655The Resting Potential Decays Only Slowly When the Na+-K+ Pump Is Stopped655The Three-dimensional Structure of a Bacterial K+ Channel655
The Membrane Potential in Animal Cells Depends Mainly on K <sup>+</sup> Leak Channels and the K <sup>+</sup> Gradient Across the Plasma Membrane 655 The Resting Potential Decays Only Slowly When the Na <sup>+</sup> -K <sup>+</sup> Pump Is Stopped 655 The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel
on K <sup>+</sup> Leak Channels and the K <sup>+</sup> Gradient Across the Plasma Membrane 655 The Resting Potential Decays Only Slowly When the Na <sup>+</sup> -K <sup>+</sup> Pump Is Stopped 655 The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel
the Plasma Membrane The Resting Potential Decays Only Slowly When the Na <sup>+</sup> -K <sup>+</sup> Pump Is Stopped The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel
The Resting Potential Decays Only Slowly When the Na <sup>+</sup> -K <sup>+</sup> Pump Is Stopped 655 The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel
Na <sup>+</sup> -K <sup>+</sup> Pump Is Stopped The Three-dimensional Structure of a Bacterial K <sup>+</sup> Channel
The Three-dimensional Structure of a Bacterial K <sup>+</sup> (Channel
Observed de la constant de la consta
Shows How an Ion Channel Can Work 657
Intechanosensitive Channels Allow Cells to Sense Their Physical
The Europian of a Nouron Depende on Ite Elengated Structure 661
Voltage-gated Cation Channels Generate Action Potentials
in Electrically Excitable Cells 662
Myelination Increases the Speed and Efficiency of Action
Potential Propagation in Nerve Cells 666
Patch-Clamp Recording Indicates That Individual Ion Channels
Open in an All-or-Nothing Fashion 666
Voltage-gated Cation Channels Are Evolutionarily and Structurally
Related 668
Different Neuron Types Display Characteristic Stable Firing
Properties 668
Transmitter-gated Ion Channels Convert Chemical Signals
into Electrical Ones at Chemical Synapses 669
Chemical Synapses Can Be Excitatory or Inhibitory 670
The Acetylcholine Receptors at the Neuromuscular Junction
Are Excitatory Transmitter-gated Cation Channels 6/1
Neurons Contain Many Types of Transmitter-gated Channels 672
Nouromuscular Transmission Involves the Sequential Activation
of Five Different Sets of Ion Channels
Single Neurons Are Complex Computation Devices 674
Neuronal Computation Requires a Combination of at Least

LOOKING AT CELLS AND MOLECULES IN THE ELECTRON	EA off	A P-typ
MICROSCOPE	588	Re
The Electron Microscope Resolves the Fine Structure of the Cell	588	The Pla
Biological Specimens Require Special Preparation for Electron	500	APC Tr
Microscopy	500	ADU II
Heavy Metals Can Provide Additional Contrast	590	Summe
Images of Surfaces Carribe Obtained by Scanning Liection	501	Summe
Microscopy	001	CHAN
Electron Microscope Tomography Allows the Molecular	593	OF
Architecture of Ocilo to De Coerrine Molecular	000	Aquapo
Structures at Atomic Resolution	595	lon Chr
Light Microscopy and Electron Microscopy Are Mutually	Aab P	
Beneficial	597	The Me
Lising Microscopy to Study Cells Always Involves Trade-Offs	598	on
Summary	599	the
Problems	600	The Re
References	601	Na
		The Th
Chapter 10 Membrane Structure	603	Sho
ROUGH THE GOLG! APPARATUBUL	004	Mechar
THE LIPID BILAYER	604	En
Glycerophospholipids, Sphingolipids, and Sterois Are	605	The Fur
the Major Lipius in Cell Membranes	606	Voltage
The Lipid Bilaver Is a Two-dimensional Fluid	608	in E
The Eluidity of a Lipid Bilaver Depends on Its Composition	609	IViyelina
Despite Their Fluidity, Lipid Bilavers Can Form Domains	000	Pot
of Different Compositions	610	Patch-C
Lipid Droplets Are Surrounded by a Phospholipid Monolayer	611	Voltage
The Asymmetry of the Lipid Bilayer Is Functionally Important	612	Rel
Glycolipids Are Found on the Surface of All Eukaryotic Plasma		Differen
Membranes	613	Pro
Summary	614	Transm
MEMBRANE PROTEINS	615	into
Membrane Proteins Can Be Associated with the Lipid Bilayer		Chemic
in Various Ways	615	The Ace
Lipid Anchors Control the Membrane Localization of Some	SUMIT	Are
Signaling Proteins	616	Neuron
In Most Transmembrane Proteins, the Polypeptide Chain	T	Many P
Crosses the Lipid Bilayer in an $\alpha$ -Helical Conformation	617	Neurom
Iransmembrane $\alpha$ Helices Often Interact with One Another	619	of F
Some B Barrels Form Large Channels	619	Single M

630

632

633

634

635

637

E

M

B

Bi

Many Membrane Proteins Are Glycosylated 621 Membrane Proteins Can Be Solubilized and Purified in Detergents 622 Bacteriorhodopsin Is a Light-driven Proton (H<sup>+</sup>) Pump That

Traverses the Lipid Bilayer as Seven  $\alpha$  Helices 625 Membrane Proteins Often Function as Large Complexes 627 Many Membrane Proteins Diffuse in the Plane of the Membrane 627 Cells Can Confine Proteins and Lipids to Specific Domains Within a Membrane 629

The Cortical Cytoskeleton Gives Membranes Mechanical Strength and Restricts Membrane Protein Diffusion Membrane-bending Proteins Deform Bilayers Summary Problems References

# Chapter 11 Small-Molecule Transport and **Electrical Properties of Membranes**

PRINCIPLES OF MEMBRANE TRANSPORT 637 Protein-free Lipid Bilayers Are Impermeable to Ions 638 There Are Two Main Classes of Membrane Transport Proteins: Transporters and Channels 638 Active Transport Is Mediated by Transporters Coupled to an Energy Source 639 Summary 640

Three Kinds of K<sup>+</sup> Channels 675 Long-term Potentiation in the Mammalian Hippocampus Depends on Ca<sup>2+</sup> Entry Through NMDA-Receptor Channels 677 The Use of Channelrhodopsins Has Revolutionized the Study of Neural Circuits 678 679 Summary Problems 680 References 681

# Chapter 12 Intracellular Organization and **Protein Sorting**

HE COMPARTMENTALIZATION OF CELLS	683
I Eukaryotic Cells Have the Same Basic Set of	000
Membrane-enclosed Organelles	683
of Organelles	686
acromolecules Can Be Segregated Without a Surrounding	
Membrane	688
ultivalent Interactions Mediate Formation of Biomolecular	000
Condensates	690
omolecular Condensates Create Biochemical Factories omolecular Condensates Form and Disassemble in Response	690

TRANSPORTERS AND ACTIVE MEMBRANE TRANSPORT 640 Active Transport Can Be Driven by Ion-Concentration Gradients 642 Transporters in the Plasma Membrane Regulate Cytosolic pH 644 An Asymmetric Distribution of Transporters in Epithelial Cells Underlies the Transcellular Transport of Solutes 645 There Are Three Classes of ATP-driven Pumps 646

to Need

Summary



694

683

Proteins Can Move Between Compartments in Different Ways Sorting Signals and Sorting Receptors Direct Proteins to the Correct Cell Address Construction of Most Organelles Requires Information in the Organelle Itself



695

# **XXXII** CONTENTS

THE ENDOPLASMIC RETICULUM	698
The ER Is Structurally and Functionally Diverse	698
Signal Sequences Were First Discovered in Proteins Imported	701
into the Rough ER	701
A Signal-Recognition Particle (SRP) Directs the ER Signal	702
Sequence to a Specific neceptor at the En	102
Aquoous Channel in the Translocator	705
Translocation Across the FR Membrane Does Not Always	100
Require Ongoing Polypeptide Chain Flongation	707
Transmembrane Proteins Contain Hydrophobic Segments	
That Are Recognized Like Signal Sequences	709
Hydrophobic Segments of Multipass Transmembrane Proteins	
Are Interpreted Contextually to Determine Their Orientation	710
Some Proteins Are Integrated into the ER Membrane by a	
Post-translational Mechanism	711
Some Membrane Proteins Acquire a Covalently Attached	enT
Glycosylphosphatidylinositol (GPI) Anchor	712
Translocated Polypeptide Chains Fold and Assemble in the	710
Lumen of the Rough ER	/12
the Addition of a Common M Linked Oligospeeboride	711
Oligossocharidos Aro Llood as Tags to Mark the State of	/ 14
Protein Folding	715
Improperly Folded Proteins Are Exported from the FR and	110
Degraded in the Cytosol	716
Misfolded Proteins in the ER Activate an Unfolded Protein Response	717
The ER Assembles Most Lipid Bilayers	720
Membrane Contact Sites Between the ER and Other Organelles	
Facilitate Selective Lipid Transfer	722
Summary	723
PEROXISOMES	723
Peroxisomes Use Molecular Oxygen and Hydrogen Peroxide	
to Perform Oxidation Reactions	724
Short Signal Sequences Direct the Import of Proteins	1506
into Peroxisomes	724
Summary	726
THE TRANSPORT OF PROTEINS INTO MITOCHONDRIA	
AND CHLOROPLASTS	726
Translocation into Mitochondria Depends on Signal Sequences	707
and Protein Translocators	121
Mitochondrial Proteins Are Imported Post-translationally as	700
Protoin Import le Doworod by ATP Hydrolysis, a Mombrano	120
Potential and Redox Potential	730
Transport into the Inner Mitochondrial Membrane Occurs Via	100
Several Routes	731
Bacteria and Mitochondria Use Similar Mechanisms to Insert	entitie
β Barrels into Their Outer Membrane	733
Two Signal Sequences Direct Proteins to the Thylakoid Membrane	
in Chloroplasts	733
Summary	735
THE TRANSPORT OF MOLECULES BETWEEN THE NUCLEUS	
AND THE CYTOSOL	735
Nuclear Pore Complexes Perforate the Nuclear Envelope	736
Nuclear Localization Signals Direct Proteins to the Nucleus	738
Nuclear Import Receptors Bind to Both Nuclear Localization	700
The Dep OTDeee Impegee Directionality of Number 1	739
The Han GTPase imposes Directionality on Nuclear Import	740
Nuclear Export Works Like Nuclear Import but in Deverse	740
Transport Through NPCs Can Be Regulated by Controlling Accord	141
to the Transport Machinery	742
The Nuclear Envelope Disassembles and Reassembles	
During Mitosis	743
	745

	The Assembly of a Clathrin Coat Drives Vesicle Formation	752
	Adaptor Proteins Select Cargo into Clathrin-coated Vesicles	753
	Membrane-bending Proteins Help Deform the Membrane	134
	During Vesicle Formation	755
	Cytoplasmic Proteins Regulate the Pinching off and Uncoating	
	of Coated Vesicles	756
	Monomeric GTPases Control Coat Assembly	750
	The Shape and Size of Transport Vesicles Are Diverse	750
	Rab Proteins Guide Transport Vesicles to Their	100
1	Target Membrane	760
	Rab Proteins Create and Change the Identity of an Organelle	761
	SNAREs Mediate Membrane Fusion	762
	Euleracting SNARES Need to be Pried Apart Before They Can	763
	Viruses Encode Specialized Membrane Fusion Proteins Needed	100
	for Cell Entry	764
	Summary	764
	TRANSPORT FROM THE ENDOPLASMIC RETICULUM	Char
	THROUGH THE GOLGI APPARATUS	765
	Proteins Leave the ER in COPII-coated Transport Vesicles	765
	Only Proteins That Are Properly Folded and Assembled Can	766
	Vesicular Tubular Clusters Mediate Transport from the ER to	100
	the Golgi Apparatus	766
	The Retrieval Pathway to the ER Uses Sorting Signals	768
	Many Proteins Are Selectively Retained in the Compartments	700
	The Coldi Apparatus Consists of an Ordered Series	768
	of Compartments	769
	Oligosaccharide Chains Are Processed in the Golgi Apparatus	771
	Proteoglycans Are Assembled in the Golgi Apparatus	772
	What Is the Purpose of Glycosylation?	773
	Iransport Through the Golgi Apparatus Occurs by Multiple	771
	Golgi Matrix Proteins Help Organize the Stack	775
	Summary	776
	TRANSPORT FROM THE TRANS GOLGI NETWORK	13000
	TO THE CELL EXTERIOR AND ENDOSOMES	776
	Many Proteins and Lipids Are Carried Automatically from	
	the Trans Golgi Network to the Cell Surface	777
	A Mannose 6-Phosphate Receptor Sorts Lysosomal Hydrolases	777
	Defects in the GlcNAc Phosphotransferase Cause a Lysosomal	
	Storage Disease in Humans	779
	Secretory Vesicles Bud from the Trans Golgi Network	780
	Precursors of Secretory Proteins Are Proteolytically Processed	701
	Secretory Vesicles Wait Near the Plasma Membrane Lintil	181
	Signaled to Release Their Contents	782
	For Rapid Exocytosis, Synaptic Vesicles Are Primed at the	
	Presynaptic Plasma Membrane	782
	Synaptic Vesicles Can Be Recycled Locally After Exocytosis	783
	from the Plasma Membrane	784
	Some Regulated Exocytosis Events Serve to Enlarge the Plasma	101
	Membrane	785
	Polarized Cells Direct Proteins from the Trans Golgi Network	BAQ
	to the Appropriate Domain of the Plasma Membrane	786
	Summary	101
	TRANSPORT INTO THE CELL FROM THE PLASMA	600
	Dipoputio Vacialas Form from Costad Dita in the Disama	788
	Membrane	789
		.00

Carriery Problems References

# Chapter 13 Intracellular Membrane Traffic MECHANISMS OF MEMBRANE TRANSPORT AND COMPARTMENT IDENTITY There Are Various Types of Coated Vesicles

Not All Membrane Invaginations and Pinocytic Vesicles 746 Are Clathrin Coated 748 Cells Use Receptor-mediated Endocytosis to Import Selected Extracellular Macromolecules Specific Proteins Are Retrieved from Early Endosomes 749 and Returned to the Plasma Membrane Recycling Endosomes Regulate Plasma Membrane Composition Plasma Membrane Signaling Receptors Are Down-regulated by 751 Degradation in Lysosomes

751

789

791

792

793

794

CONTENTS xxxiii

Early Endosomes Mature into Late Endosomes	795	
ESCRI Protein Complexes Mediate the Formation of Intralumental Vesicles in Multivesicular Bodies	796	
Summary	798	
THE DEGRADATION AND RECYCLING OF		
MACROMOLECULES IN LYSOSOMES	798	
Lysosomes Are the Principal Sites of Intracellular Digestion	798	
Lysosomes Are Heterogeneous	799	
Plant and Fungal Vacuoles Are Remarkably Versatile Lysosomes	800	
Multiple Pathways Deliver Materials to Lysosomes	801	
Cells Can Acquire Nutrients from the Extracellular Fluid by	Mus I	
Macropinocytosis	802	
Specialized Phagocytic Cells Can Ingest Large Particles	802	
Cargo Recognition by Cell-surface Receptors Initiates		
Phagocytosis	803	
Autophagy Degrades Unwanted Proteins and Organelles	804	
The Rate of Nonselective Autophagy Is Regulated by Nutrient		
Availability	805	
A Family of Cargo enacitic Recentors Madiatas Salactiva		

CHLOROPLASTS AND PHOTOSYNTHESIS Chloroplasts Resemble Mitochondria but Have a Separate	843
Chloroplasts Capture Energy from Sunlight and Use It	843
to Fix Carbon Carbon Fixation Uses ATP and NADPH to Convert CO <sub>2</sub>	844
into Sugars Carbon Fixation in Some Plants Is Compartmentalized	845
to Facilitate Growth at Low CO <sub>2</sub> Concentrations The Sugars Generated by Carbon Fixation Can Be Stored	846
as Starch or Consumed to Produce ATP	849
Complexes Required for Photosynthesis and ATP Generation Chlorophyll–Protein Complexes Can Transfer Either Excitation	849
Energy or Electrons A Photosystem Contains Chlorophylls in Antennae and	850
a Reaction Center	851
Working in Series	852
Photosystem II Uses a Manganese Cluster to Withdraw Electrons from Water	853
The Cytochrome b <sub>6</sub> -f Complex Connects Photosystem II to Photosystem I	854
Photosystem I Carries Out the Second Charge-Separation	OFF
The Chloroplast ATP Synthase Uses the Proton Gradient Generated by the Photosynthetic Light Reactions	000
to Produce ATP	855
and Chloroplasts Is Essentially the Same	856
Chemiosmotic Mechanisms Evolved in Stages By Providing an Inexhaustible Source of Reducing Power, Photosynthetic Rectoria Overcome a Major Evolutioner.	856
Obstacle	857
The Photosynthetic Electron-Transport Chains of Cyanobacteria Produced Atmospheric Oxygen and	
Permitted New Life-Forms	857
Summary	860
AND CHLOROPLASTS	861
The Genetic Systems of Mitochondria and Chloroplasts	061
Over Time, Mitochondria and Chloroplasts Have Exported	001
Most of Their Genes to the Nucleus by Gene Transfer Mitochondria Have a Relaxed Codon Usage and Can	862
Have a Variant Genetic Code Chloroplasts and Bacteria Share Many Striking Similarities	864 865
Organellar Genes Are Maternally Inherited in Animals and Plants Mutations in Mitochondrial DNA Can Cause Severe	866
Inherited Diseases Why Do Mitochondria and Chloroplasts Maintain a Costly	866
Separate System for DNA Transcription and Translation?	867
Summary Problems	868 869
References	871
Chapter 15 Cell Signaling	873
PRINCIPLES OF CELL SIGNALING	873
Extracellular Signals Can Act Over Short or Long Distances	874
Each Cell Is Programmed to Respond to Specific Combinations of	015
Extracellular Signals	876
Cell-Surface Receptors Relay Signals Via Intracellular Signaling	010
Molecules Intracellular Signals Must Re Specific and Robust in a Noisy	879

Autophagy	806
Some Lysosomes and Multivesicular Bodies Undergo Exocytosis	807
Summary	807
Problems	808
References	810

811

# Chapter 14 Energy Conversion and Metabolic Compartmentation: Mitochondria and Chloroplasts

THE MITOCHONDRION	813
Membrane	814
Fission, Fusion, Distribution, and Degradation of Mitochondria The Inner Membrane Cristae Contain the Machinery for Electron	815
Transport and ATP Synthesis	817
The Citric Acid Cycle in the Matrix Produces NADH	817
A Chemiosmotic Process Couples Oxidation Energy to ATP	818
The Energy Derived from Oxidation le Stored as an	821
Electrochemical Gradient	822
Summary	823
The Redox Potential Is a Measure of Electron Affinities Electron Transfers Release Large Amounts of Energy	823 823
Transition Metal lons and Quinones Accept and Release Electrons	024
Readily NADH Transfers Its Electrons to Oxygen Through Three Large	824
Enzyme Complexes Embedded in the Inner Membrane The NADH Dehvdrogenase Complex Contains Separate Modules	827
for Electron Transport and Proton Pumping	828
Cytochrome c Reductase Takes Up and Releases Protons on Opposite Sides of the Crista Membrane, Thereby	
Pumping Protons The Cytochrome c Oxidase Complex Pumps Protons	829
and Reduces O <sub>2</sub> Using a Catalytic Iron–Copper Center Succinate Dehydrogenase Acts in Both the Electron-Transport	831
Chain and the Citric Acid Cycle The Respiratory Chain Forms a Supercomplex in the	832
Crista Membrane	833
Protons Can Move Rapidly Through Proteins Along Predefined	
Summany	834
ATP PPODUCTION IN LATE SHOW TO	835
The Large Negative Value of $\triangle G$ for ATP Hydrolysis Makes ATP	835
Useful to the Cell	835

000 The ATP Synthase Is a Nanomachine That Produces ATP by Rotary Catalysis 837 Proton-driven Turbines Are Ancient and Critical for Energy Conversion 839 Mitochondrial Cristae Help to Make ATP Synthesis Efficient 840 Special Transport Proteins Move Solutes Through the Inner Membrane 841 Chemiosmotic Mechanisms First Arose in Bacteria 842 Summary 842 Cytoplasm881Intracellular Signaling Complexes Form at Activated Cell-Surface<br/>Receptors882Modular Interaction Domains Mediate Interactions Between<br/>Intracellular Signaling Proteins883The Relationship Between Signal and Response Varies in Different<br/>Signaling Pathways885The Speed of a Response Depends on the Turnover of Signaling<br/>Molecules886

Cells Can Respond Abruptly to a Gradually Increasing Signal Positive Feedback Can Generate an All-or-None Response Negative Feedback Is a Common Feature of Intracellular 887

888

890

890

892

892

893

895

896

898

899

900

911

911

913

913

915

916

918

919

920

921

923

923

924

926

927

928

928

930

932

934

935

937

938

939

940

940

941

941

943

944

945

946

948

Signaling Systems

Cells Can Adjust Their Sensitivity to a Signal Summary

#### SIGNALING THROUGH G-PROTEIN-COUPLED RECEPTORS

Heterotrimeric G Proteins Relay Signals from GPCRs Some G Proteins Regulate the Production of Cyclic AMP Cyclic-AMP-dependent Protein Kinase (PKA) Mediates Most

of the Effects of Cyclic AMP Some G Proteins Signal Via Phospholipids Ca<sup>2+</sup> Functions as a Ubiquitous Intracellular Mediator Feedback Generates Ca<sup>2+</sup> Waves and Oscillations Ca<sup>2+</sup>/Calmodulin-dependent Protein Kinases Mediate

Many Responses to Ca2+ Signals902Some G Proteins Directly Regulate Ion Channels904Smell and Vision Depend on GPCRs That Regulate Ion Channels905Nitric Oxide Gas Can Mediate Signaling Between Cells908Second Messengers and Enzymatic Cascades Amplify Signals909GPCR Desensitization Depends on Receptor Phosphorylation909910

	Chapter 16 The Cytoskeleton	949
	FUNCTION AND DYNAMICS OF THE CYTOSKELETON Cytoskeletal Filaments Are Dynamic, but Can Nevertheless	949
	Form Stable Structures The Cytoskeleton Determines Cellular Organization and Polarity Filaments Assemble from Protein Subunits That Impart	951 952
	Specific Physical and Dynamic Properties Accessory Proteins and Motors Act on Cytoskeletal Filaments Molecular Motors Operate in a Cellular Environment	953 955
1	Dominated by Brownian Motion Summary	956 957
	ACTIN	957
	Actin Subunits Assemble Head-to-Tail to Create Flexible, Polar Filaments	958
	Actin Filaments	958
	Actin Filaments Have Two Distinct Ends That Grow at Different Rates ATP Hydrolysis Within Actin Filaments Leads to Treadmilling	962
	at Steady State The Euroctions of Actin Filaments Are Inhibited by Both	962
	Polymer-stabilizing and Polymer-destabilizing Chemicals Actin-binding Proteins Influence Filament Dynamics	963
	Actin Nucleation Is Tightly Regulated and Generates Branched	964
	or Straight Filaments Actin Filament Elongation Is Regulated by Monomer-binding	964
	Proteins Actin Filement binding Dretaine Alter Filement Dynamics and	967
	Organization Severing Proteins Regulate Actin Filament Depolymerization	968 970
	Bacteria Can Hijack the Host Actin Cytoskeleton	971
	Actin at the Cell Cortex Determines Cell Shape	971
	Cells Migrating in Three Dimensions Can Navigate Around Barriers Summary	972 974 975
	MYOSIN AND ACTIN	976
	Actin-based Motor Proteins Are Members of the	070
	Myosin Superiamily Myosin Generates Force by Coupling ATP Hydrolysis	910
	to Conformational Changes Sliding of Myosin II Along Actin Filaments Causes Muscles	977
	to Contract A Suddon Rise in Outocolic Co2+ Concontration Initiator	977
	Muscle Contraction	981
	Heart Muscle Is a Precisely Engineered Machine	984
	Actin and Myosin Perform a Variety of Functions in Non-Muscle Cells Summary	984
	MICROTUBULES	987
	Microtubules Are Hollow Tubes Made of Protofilaments	988
	Microtubules Undergo a Process Called Dynamic Instability Microtubule Functions Are Inhibited by Both Polymer-stabilizing	988
	A Protein Complex Containing y-Tubulin Nucleates Microtubules	991
	The Centrosome Is a Prominent Microtubule Nucleation Site	991
	Microtubule Organization Varies Widely Among Cell Types Microtubule-binding Proteins Modulate Filament Dynamics and Organization	993
	Microtubule Plus End-binding Proteins Modulate Microtubule	000
	Dynamics and Attachments Tubulin-sequestering and Microtubule-severing Proteins Modulate	996
	Two Types of Motor Proteins Move Along Microtubules	999
	Microtubules and Motors Move Organelles and Vesicles	1002
	Motile Cilia and Flagella Are Built from Microtubules and Dyneins Primany Cilia Perform Important Signaling Eulertions in Animal Colla	1004
	Think on a chommonal ognaling functions in Amma dells	1000

#### SIGNALING THROUGH ENZYME-COUPLED RECEPTORS Activated Receptor Tyrosine Kinases (RTKs) Phosphorylate

Themselves

Phosphorylated Tyrosines on RTKs Serve as Docking Sites

for Intracellular Signaling Proteins

Proteins with SH2 Domains Bind to Phosphorylated Tyrosines The Monomeric GTPase Ras Mediates Signaling by Most RTKs Ras Activates a MAP Kinase Signaling Module Scaffold Proteins Reduce Cross-Talk Between Different MAP

Kinase Modules

Rho Family GTPases Functionally Couple Cell-Surface

Receptors to the Cytoskeleton

PI 3-Kinase Produces Lipid Docking Sites in the Plasma Membrane

The PI-3-Kinase-Akt Signaling Pathway Stimulates Animal

Cells to Survive and Grow

RTKs and GPCRs Activate Overlapping Signaling Pathways Some Enzyme-coupled Receptors Associate with Cytoplasmic

Tyrosine Kinases

Cytokine Receptors Activate the JAK-STAT Signaling Pathway

ogiorario riccoptoro rictivato tric	or a china orginaling rativay
Extracellular Signal Proteins of the	he TGFB Superfamily Act Through

Receptor Serine/Threonine Kinases and Smads

Summary

ALTERNATIVE SIGNALING ROUTES IN GENE REGULATION The Receptor Notch Is a Latent Transcription Regulator Wnt Proteins Activate Frizzled and Thereby Inhibit β-Catenin

Degradation

Hedgehog Proteins Initiate a Complex Signaling Pathway

in the Primary Cilium

Many Inflammatory and Stress Signals Act Through an

NFkB-dependent Signaling Pathway

Nuclear Receptors Are Ligand-modulated Transcription

Regulators

Circadian Clocks Use Negative Feedback Loops to

Control Gene Expression

Three Purified Proteins Can Reconstitute a Cyanobacterial

Circadian Clock in a Test Tube

Summary

#### SIGNALING IN PLANTS

Multicellularity and Cell Communicat	tion Evolved Independently
in Plants and Animals	ca Receptors Roley Signal

Receptor Serine/Threonine Kinases Are the Largest Class of

Cell-Surface Receptors in Plants

Ethylene Blocks the Degradation of Specific Transcription Regulatory Proteins in the Nucleus Regulated Positioning of Auxin Transporters Patterns Plant Growth Phytochromes Detect Red Light, and Cryptochromes Detect Blue Light Summary Problems References

# Summary1006INTERMEDIATE FILAMENTS AND OTHER CYTOSKELETAL<br/>POLYMERSIntermediate Filament Structure Depends on the Lateral Bundling<br/>and Twisting of Coiled-CoilsIntermediate Filaments Impart Mechanical Stability to<br/>Animal Cells1007Linker Proteins Connect Cytoskeletal Filaments and Bridge<br/>the Nuclear Envelope1011

CONTENTS XXXV

Sep	otins Form Filaments That Contribute to Subcellular Organization sterial Cell Shape and Division Depend on Homologs	1012
Dat	of Fukaryotic Cytoskeletal Proteins	1013
Sur	nmary	1016
CE	I POLARITY AND COORDINATION OF	
CE	THE CYTOSKELETON	1016
Cel	Polarity Is Governed by Small GTPases in Budding Yeast Proteins Generate Anterior–Posterior Polarity	1016
FAI	in Embryos	1018
Cor	nserved Complexes Polarize Epithelial Cells and Control	
00.	Their Growth	1019
Cel	Migration Requires Dynamic Cell Polarity	1020
Ext	ernal Signals Can Dictate the Direction of Cell Migration	1022
Cor	mmunication Among Cytoskeletal Elements Supports	
00.	Whole-Cell Polarity and Locomotion	1023
Sur	nmary	1023
Pro	blems	1024
Ref	erences	1025
1.000		

1027

Actin and Myosin II in the Contractile Ring Guide the Process of	1005
Cytokinesis	1065
of the Contractile Ring	1065
The Microtubules of the Mitotic Spindle Determine the Plane	1005
of Animal Cell Division	1066
The Phragmoplast Guides Cytokinesis in Higher Plants	1068
Membrane-enclosed Organelles Must Be Distributed to	28
Daughter Cells During Cytokinesis	1069
Some Cells Reposition Their Spindle to Divide Asymmetrically	1069
Mitosis Can Occur Without Cytokinesis	1070
Summary	1070
MEIOSIS	1071
Meiosis Includes Two Rounds of Chromosome Segregation	1071
Duplicated Homologs Pair During Meiotic Prophase	1073
Homolog Pairing Culminates in the Formation of a Synaptonemal	BO DEL
Complex	1073
Homolog Segregation Depends on Several Unique	19,259
Features of Meiosis I	1075
Crossing-Over is Hignly Regulated	1076
Summany	1077
CONTROL OF OFLI DIVIDION AND OFLI OFOUTIL	1077
CONTROL OF CELL DIVISION AND CELL GROWTH	1077
Iviltogens Stimulate Cell Division	1078
Mitogone Stimulate C. Cdk and C. /S. Cdk Activities	1078
DNA Damage Blocks Cell Division	1079
Many Human Cells Have a Built-In Limitation on the Number	1000
of Times They Can Divide	1082
Cell Proliferation Is Accompanied by Cell Growth	1083
Proliferating Cells Usually Coordinate Their Growth and Division	1084
Summary	1084
Problems	1085
References	1087
Chapter 18 Cell Death	1089
Apoptosis Eliminates Unwanted Cells	1090
Apoptosis Depends on an Intracellular Proteolytic Cascade	
Mediated by Caspases	1091
Activation of Cell-Surface Death Receptors Initiates the Extrinsic	
Pathway of Apoptosis	1093
The Intrinsic Pathway of Apoptosis Depends on Proteins	

# Chapter 17 The Cell Cycle

OVERVIEW OF THE CELL CYCLE The Eukaryotic Cell Cycle Usually Consists of Four Phases Cell-Cycle Control Is Similar in All Eukaryotes	<b>1027</b> 1028
Cell-Cycle Progression Can Be Studied in Various Ways Summary	1030 1031
THE CELL-CYCLE CONTROL SYSTEM The Cell-Cycle Control System Triggers the Major Events of	1031
the Cell Cycle The Cell-Cycle Control System Depends on Cyclically Activated	1032
Cyclin-dependent Protein Kinases Protein Phosphatases Reverse the Effects of Cdks	1033 1035
Hundreds of Cdk Substrates Are Phosphorylated in a Defined Order	1035
Positive Feedback Generates the Switchlike Behavior of Cell-Cycle Transitions	1036
The Anaphase-promoting Complex/Cyclosome (APC/C) Triggers the Metaphase-to-Anaphase Transition	1038
The G <sub>1</sub> Phase Is a Stable State of Cdk Inactivity The Cell-Cycle Control System Functions as a Linked Series	1040
of Biochemical Switches Summary	1041 1042

#### S PHASE 1042

S-Cdk Initiates DNA Replication Once Per Cell Cycle Chromosome Duplication Requires Duplication of

Chromatin Structure **Cohesins Hold Sister Chromatids Together** Summary

#### MITOSIS

M-Cdk and Other Protein Kinases Drive Entry into Mitosis Condensin Helps Configure Duplicated Chromosomes

for Separation

The Mitotic Spindle Is a Dynamic Microtubule-based Machine Microtubules Are Nucleated in Multiple Regions of the Spindle Microtubule Instability Increases Greatly in Mitosis Microtubule-based Motor Proteins Govern Spindle Assembly and Function

Bipolar Spindle Assembly in Most Animal Cells Begins

with Centrosome Duplication

Spindle Assembly in Animal Cells Requires Nuclear-Envelope Breakdown

Mitotic Chromosomes Promote Bipolar Spindle Assembly 1055 Kinetochores Attach Sister Chromatids to the Spindle 1056 Bi-orientation Is Achieved by Trial and Error 1057 Multiple Forces Act on Chromosomes in the Spindle 1059 The APC/C Triggers Sister-Chromatid Separation and the **Completion of Mitosis** 1060 Unattached Chromosomes Block Sister-Chromatid Separation: The Spindle Assembly Checkpoint 1062 Chromosomes Segregate in Anaphase A and B 1062 Segregated Chromosomes Are Packaged in Daughter Nuclei at Telophase 1063 Summary 1064 CYTOKINESIS 1064

1042 1042 1043 1043	The Intrinsic Pathway of Apoptosis Depends on Proteins Released from Mitochondria Bcl2 Proteins Are the Critical Controllers of the Intrinsic Pathway of Apoptosis An Inhibitor of Apoptosis (an IAP) and Two Anti-IAP Proteins	1094
1045 1046	Help Control Caspase Activation in the Cytosol of Some Mammalian Cells	1098
<b>1046</b> 1047	Extracellular Survival Factors Inhibit Apoptosis in Various Ways Healthy Neighbors Phagocytose and Digest Apoptotic Cells Either Excessive or Insufficient Apoptosis Can Contribute	1098 1100
1047	to Disease	1100
1050	Summary	1102
1051	Problems	1103
1052	References	1104
1052	Chapter 19 Cell Junctions and the	THE P
1053	Extracellular Matrix	1105
1054 1055 1056	CELL-CELL JUNCTIONS Cadherins Form a Diverse Family of Adhesion Molecules Cadherins Mediate Homophilic Adhesion Cadherin-dependent Cell-Cell Adhesion Guides the Organization	<b>1108</b> 1108 1108
1057	of Developing Tissues	1110

1110 Assembly of Strong Cell-Cell Adhesions Requires Changes in the Actin Cytoskeleton 1112 Catenins Link Classical Cadherins to the Actin Cytoskeleton 1113 Adherens Junctions Respond to Tension from Inside and Outside the Tissue 1113 Tissue Remodeling Depends on the Coordination of Actin-mediated Contraction with Cell-Cell Adhesion 1114 Desmosomes Give Epithelia Mechanical Strength 1116 Tight Junctions Form a Seal Between Cells and a Fence Between Plasma Membrane Domains 1116

# xxxvi CONTENTS

Tight Junctions Contain Strands of Transmembrane		Cancer Cells Contain Somatic Mutations	1166
Adhesion Proteins	1119	A Single Mutation Is Not Enough to Change a Normal Cell into a	
Scaffold Proteins Organize Junctional Protein Complexes	1120	Cancer Cell	1166
Gap Junctions Couple Cells Both Electrically and Metabolically	1121	Many Cancers Develop Gradually Through Successive Rounds of	
A Gap-Junction Connexon Is Made of Six Transmembrane		Random Inherited Change Followed by Natural Selection	1167
Connexin Subunits	1122	Cancers Can Evolve Abruptly Due to Genetic Instability	1168
In Plants Plasmodesmata Perform Many of the Same Functions		Some Cancers May Harbor a Small Population of Stem Cells	1170
as Gan Junctions	1123	A Common Set of Hallmarks Typically Characterizes Cancerous	
Selecting Mediate Transient Cell-Cell Adhesions in the		Growth	1171
Bloodetroom	1125	Cancer Cells Display an Altered Control of Growth and	
Members of the Immunoalobulin Superfamily Mediate Ca2+-	1120	Homeostasis	1172
independent Cell Cell Adhesion	1106	Human Cancor Colle Eccano a Ruilt in Limit to Coll Proliferation	1172
Independent Cell-Cell Adhesion	1120	Concor Collo Have on Abnormal Ability to Rynace Doath Signals	1170
Summary	1121	Cancer Cells Have Altered Sugar Matcheliem	1174
THE EXTRACELLULAR MATRIX OF ANIMALS	1127	Cancer Cells Have Allered Sugar Melabolism	1170
The Extracellular Matrix Is Made and Oriented by the		The Tumor Microenvironment Influences Cancer Development	11/5
Cells Within It	1128	Cancer Cells Must Survive and Proliferate in a Foreign	1170
Glycosaminoglycan (GAG) Chains Occupy Large Amounts		Environment	11/6
of Space and Form Hydrated Gels	1129	Summary	1178
Hyaluronan Acts as a Space Filler During Tissue Morphogenesis	Rock	CANCER-CRITICAL GENES: HOW THEY ARE FOUND	
and Renair	1129	AND WHAT THEY DO	1178
Proteoplycans Are Composed of GAG Chains Covalently Linked	1120	The Identification of Gain-of-Function and Loss-of-Function	Brie.
to a Core Protein	1130	Cancer Mutations Has Traditionally Required	
Collogono Aro the Major Protoine of the Extracollular Matrix	1120	Different Methode	1170
Collegen Chaine Underge & Series of Dest trapelational	1102	Different Methous Detrovirueee Lod to the Identification of Oneogenee	1180
Collagen Chains Undergo a Series of Post-translational	1100	Cance Mutated in Cancer Can De Made Overactive in Many Ways	1100
Modifications	1133	Genes mutated in Cancer Can be made Overactive in many ways	1101
Secreted Fibril-associated Collagens Help Organize the Fibrils	1135	Studies of Rare Hereditary Cancer Syndromes First Identified	1100
Elastin Gives Lissues Their Elasticity	1136	Tumor Suppressor Genes	1182
Cells Govern and Respond to the Mechanical Properties of	Visialul	Both Genetic and Epigenetic Mechanisms Can Inactivate Tumor	0.901
the Matrix	1137	Suppressor Genes	1183
Fibronectin and Other Multidomain Glycoproteins Help		Systematic Sequencing of Cancer Cell Genomes Has Transformed	k
Organize the Matrix	1138	Our Understanding of the Disease	1184
Fibronectin Binds to Integrins	1139	Many Cancers Have an Extraordinarily Disrupted Genome	1185
Tension Exerted by Cells Regulates the Assembly of Fibronectin		Epigenetic and Chromatin Changes Contribute to Most Cancers	1185
Fibrils	1140	Hundreds of Human Genes Contribute to Cancer	1186
The Basal Lamina Is a Specialized Form of Extracellular Matrix	1141	Disruptions in a Handful of Key Pathways Are Common to Many	
Laminin and Type IV Collagen Are Major Components of		Cancers	1187
the Basal Lamina	1141	Mutations in the PL3-kinase/Akt/mTOR Pathway Drive Cancer	
Rasal Laminae Have Diverse Functions	1143	Cells to Grow	1188
Colle Have to Re Able to Degrade Matrix as Well as	1110	Mutations in the n53 Pathway Enable Cancer Cells to Survive and	1100
Maka It	1111	Proliferate Despite Stress and DNA Damage	1180
Matrix Protocolycopo and Chycoprotoine Degulate the Activities	1144	Studios Lloing Mice Help to Define the Eurotions of Cancer critical	1103
of Socreted Droteine	1115	Conce	1100
Or Secreted Proteins	1140	Concern Deceme Mare and Mare Llateregeneous on They	1190
Summary	1140	Cancers Become More and More Heterogeneous as They	1100
CELL-MATRIX JUNCTIONS	1147	Progress	1192
Integrins Are Transmembrane Heterodimers That Link the		Colorectal Cancers Evolve Slowly Via a Succession of	1100
Extracellular Matrix to the Cytoskeleton	1147	Visible Changes	1192
Integrin Defects Are Responsible for Many Genetic Diseases	1148	A Few Key Genetic Lesions Are Common to a Large Fraction of	-
Integrins Can Switch Between an Active and an Inactive		Colorectal Cancers	1194
Conformation	1149	Some Colorectal Cancers Have Defects in DNA Mismatch	
Integrins Cluster to Form Strong Adhesions	1151	Repair	1195
Extracellular Matrix Attachments Act Through Integrins to	1101	The Steps of Tumor Progression Can Often Be Correlated	
Control Cell Proliferation and Sunvival	1151	with Specific Mutations	1196
Integrine Recruit Intracellular Signaling Proteine at Sites of	1101	The Changes in Tumor Cells That Lead to Metastasis Are	
Coll_Matrix Adhesion	1150	Still Largely a Mystery	1197
Coll Matrix Adhesions Respond to Mechanical Earces	1152	Summary	1197
Cell-Matrix Auriesions nespond to Mechanical Forces	1150	CANCED DEVENTION AND TREATMENT DRESENT	
Summary	1134	AND FUTURE	1100
THE PLANT CELL WALL	1154	AND FUTURE	1190
The Composition of the Cell Wall Depends on the Cell Type	1155	Epidemiology Reveals That Many Cases of Cancer Are	1100
The Tensile Strength of the Cell Wall Allows Plant Cells to	1100	Preventable	1198
Develop Turgor Pressure	1155	Sensitive Assays Can Detect Those Cancer-causing Agents That	1100
The Primary Cell Wall Is Built from Cellulose Microfibrile Interwover	1100	Damage DNA	1199
with a Network of Pectic Polysaccharides	1156	Fifty Percent of Cancers Could Be Prevented by Changes in	
Oriented Cell Wall Deposition Controls Plant Cell Growth	1157	Lifestyle	1200
Microtubulos Orient Coll Wall Deposition	1150	Viruses and Other Infections Contribute to a Significant	
Summon (	1150	Proportion of Human Cancers	1201
Droblomo	1160	Cancers of the Uterine Cervix Can Be Prevented by Vaccination	A stand

1100

1162

1163

Tight Junctions Contain Strands of Transmembrane		Cancer Cells Contain Somatic Mutations	1166
Adhesion Proteins	1119	A Single Mutation Is Not Enough to Change a Normal Cell into a	
Scaffold Proteins Organize Junctional Protein Complexes	1120	Cancer Cell	1166
Gap Junctions Couple Cells Both Electrically and Metabolically	1121	Many Cancers Develop Gradually Through Successive Rounds of	
A Gap-Junction Connexon Is Made of Six Transmembrane		Random Inherited Change Followed by Natural Selection	1167
Connexin Subunits	1122	Cancers Can Evolve Abruptly Due to Genetic Instability	1168
In Plants Plasmodesmata Perform Many of the Same Functions	q on T	Some Cancers May Harbor a Small Population of Stem Cells	1170
as Gan Junctions	1123	A Common Set of Hallmarks Typically Characterizes Cancerous	
Solocting Mediate Transient Cell_Cell Adhesions in the	1120	Growth	1171
Bloodetroom	1125	Cancer Cells Display an Altered Control of Growth and	
Mambara of the Immunoalobulin Superfamily Mediate Co2+	1120	Homoostasis	1172
Members of the infinituoglobulin Superiarily Mediate Ca	1106	Human Cancer Celle Econne a Ruilt in Limit to Cell Preliferation	1172
Independent Cell-Cell Adhesion	1120	Concer Celle Have on Abnormal Ability to Rynase Dooth Signale	1170
Summary	1121	Cancer Cells Have an Abnormal Ability to Bypass Death Signals	1174
THE EXTRACELLULAR MATRIX OF ANIMALS	1127	The Turser Mieree Altered Sugar Metabolism	1170
The Extracellular Matrix Is Made and Oriented by the		The Tumor Microenvironment Influences Cancer Development	11/5
Cells Within It	1128	Cancer Cells Must Survive and Proliferate in a Foreign	1170
Glycosaminoglycan (GAG) Chains Occupy Large Amounts		Environment	11/6
of Space and Form Hydrated Gels	1129	Summary	11/8
Hvaluronan Acts as a Space Filler During Tissue Morphogenesis		CANCER-CRITICAL GENES: HOW THEY ARE FOUND	
and Repair	1129	AND WHAT THEY DO	1178
Proteoplycans Are Composed of GAG Chains Covalently Linked	eminica	The Identification of Gain-of-Function and Loss-of-Function	
to a Core Protein	1130	Cancer Mutations Has Traditionally Required	
Collagens Are the Major Proteins of the Extracellular Matrix	1132	Different Methods	1179
Collagen Chaine I Indergo a Series of Post-translational	1102	Retroviruses Led to the Identification of Oncodenes	1180
Modificatione	1133	Gones Mutated in Cancer Can Re Made Overactive in Many Ways	1181
Secreted Eibril accoriated Collagona Hola Organiza the Eibrile	1125	Studios of Para Haraditany Cancer Syndromes First Identified	1101
Electin Cives Tissues Their Electicity	1100	Tumor Suppressor Conce	1182
Elastin Gives rissues meir Elasticity	1130	Reth Canatia and Enigenetic Mechaniama Can Inactivate Tumor	1102
Cells Govern and Respond to the Mechanical Properties of	1107	Both Genetic and Epigenetic Mechanisms Can mactivate rumor	1100
the Matrix	1137	Suppressor Genes	1183
Fibronectin and Other Multidomain Glycoproteins Help	1100	Systematic Sequencing of Cancer Cell Genomes Has Transformed	1
Organize the Matrix	1138	Our Understanding of the Disease	1184
Fibronectin Binds to Integrins	1139	Many Cancers Have an Extraordinarily Disrupted Genome	1185
Tension Exerted by Cells Regulates the Assembly of Fibronectin		Epigenetic and Chromatin Changes Contribute to Most Cancers	1185
Fibrils	1140	Hundreds of Human Genes Contribute to Cancer	1186
The Basal Lamina Is a Specialized Form of Extracellular Matrix	1141	Disruptions in a Handful of Key Pathways Are Common to Many	
Laminin and Type IV Collagen Are Major Components of		Cancers	1187
the Basal Lamina	1141	Mutations in the PI 3-kinase/Akt/mTOR Pathway Drive Cancer	
Basal Laminae Have Diverse Functions	1143	Cells to Grow	1188
Cells Have to Be Able to Degrade Matrix, as Well as		Mutations in the p53 Pathway Enable Cancer Cells to Survive and	
Make It	1144	Proliferate Despite Stress and DNA Damage	1189
Matrix Proteoglycans and Glycoproteins Regulate the Activities		Studies Using Mice Help to Define the Functions of Cancer-critical	
of Secreted Proteins	1145	Genes	1190
Summary	1146	Cancers Become More and More Heterogeneous as They	
OFUL MATDIX ILINICTIONIC	1117	Progress	1192
CELL-MATRIX JUNCTIONS	1147	Colorectal Cancers Evolve Slowly Via a Succession of	1905S-
Integrins Are Transmembrane Heterodimers That Link the	1117	Visible Changes	1192
Extracellular Matrix to the Cytoskeleton	1147	A Few Key Genetic Lesions Are Common to a Large Fraction of	1102
Integrin Defects Are Responsible for Many Genetic Diseases	1148	Colorectal Cancers	1194
Integrins Can Switch Between an Active and an Inactive		Some Colorectal Cancers Have Defects in DNA Mismatch	1101
Conformation	1149	Ropair	1105
Integrins Cluster to Form Strong Adhesions	1151	The Stope of Tumor Prograssion Can Often Re Correlated	1130
Extracellular Matrix Attachments Act Through Integrins to		The Steps of Tumor Progression Can Often be Conelated	1106
Control Cell Proliferation and Survival	1151	The Changes in Tymer Calls That Load to Matastasia Are	1190
Integrins Recruit Intracellular Signaling Proteins at Sites of		The Changes in Tumor Cells That Lead to Metastasis Are	1107
Cell–Matrix Adhesion	1152	Still Largely a Mystery	1107
Cell–Matrix Adhesions Respond to Mechanical Forces	1153	Summary	1197
Summary	1154	CANCER PREVENTION AND TREATMENT: PRESENT	
THE DLANT CELL MALL	1154	AND FUTURE	1198
THE PLANT CELL WALL	1154	Epidemiology Reveals That Many Cases of Cancer Are	
The Composition of the Cell Wall Depends on the Cell Type	1155	Preventable	1198
The Tensile Strength of the Cell Wall Allows Plant Cells to	4455	Sensitive Assays Can Detect Those Cancer-causing Agents That	
The Driver Or What he Duilt from Or What he did in the	1155	Damage DNA	1199
The Primary Cell Wall is Built from Cellulose Microfibrils Interwoven	4450	Fifty Percent of Cancers Could Be Prevented by Changes in	
with a Network of Pectic Polysaccharides	1156	Lifestyle	1200
Oriented Cell Wall Deposition Controls Plant Cell Growth	1157	Viruses and Other Infections Contribute to a Significant	
Microtubules Orient Cell Wall Deposition	1158	Proportion of Human Cancers	1201
Summary	1159	Cancers of the Uterine Cervix Can Be Prevented by Vaccination	
LIKODIOMO	1160		

LIODIEILIS References

Chapter 20 Cancer

CANCER AS A MICROEVOLUTIONARY PROCESS 1163 Cancer Cells Bypass Normal Proliferation Controls and Colonize 1164 Other Tissues Most Cancers Derive from a Single Abnormal Cell 1165

Against Human Papillomavirus 1202 Infectious Agents Can Cause Cancer in a Variety of Ways 1203 The Search for Cancer Cures Is Difficult but Not Hopeless 1204 Traditional Therapies Exploit the Genetic Instability and Loss of Cell-Cycle Checkpoint Responses in Cancer Cells 1204 New Drugs Can Kill Cancer Cells Selectively by Targeting **Specific Mutations** 1204 PARP Inhibitors Kill Cancer Cells That Have Defects in Brca1 or Brca2 Genes 1205

CONTENTS xxxvii

Small Molecules Can Be Designed to Inhibit Specific Oncogenic	
Proteins Occorro May Be Treatable by Enhancing Immune	1207
Many Cancers May De Treatable by Enflation of Mainer Many Cancers May De Treatable by Enflation of Mainer Hurdle for Cancer	1209
Immunosuppression is a major indicite for Gancer Immunotherapy	1210
Cancers Evolve Resistance to Therapies We Now Have the Tools to Devise Combination Therapies	1212
Tailored to the Individual Summary	1212
Problems	1214
References	1210
Chapter 21 Development of Multicellular	1217
Organisms	1211
OVERVIEW OF DEVELOPMENT	1218
The Developmental Potential of Cells Becomes Progressively	1210
Restricted	1219
Several Model Organisms Have Been Crucial for Understanding	1220
Development	1220
Regulatory DNA Seems Largely Responsible for the Differences Between Animal Species	1220
Small Numbers of Conserved Cell–Cell Signaling Pathways	1001
Coordinate Spatial Patterning Through Combinatorial Control and Cell Memory, Simple	1221
Signals Can Generate Complex Patterns	1221
Morphogens Are Diffusible Inductive Signals That Exert	1222
Lateral Inhibition Can Generate Patterns of Different Cell Types	1222
Asymmetric Cell Division Can Also Generate Diversity	1224
Initial Patterns Are Established in Small Fields of Cells and Refined by Sequential Induction as the Embryo Grows	1225
Developmental Biology Provides Insights into Disease and	
Tissue Maintenance Summary	1225
MECHANISMS OF PATTERN FORMATION	1226
Different Animals Use Different Mechanisms to Establish	
Their Primary Axes of Polarization Studies in Drosophila Have Revealed Many Genetic Control	1226
Mechanisms Underlying Development	1228
Gene Products Deposited in the Egg Organize the Axes of	1008
Three Groups of Genes Control Drosophila Segmentation	1220
A Hierarchy of Cono Regulatory Interactions Subdivides	1230
the Drosophila Embryo	1231
Egg-Polarity, Gap, and Pair-Rule Genes Create a Transient Pattern	1000
Hox Genes Permanently Pattern the A-P Axis	1233
Hox Proteins Give Each Segment Its Individuality	1234
the Hox Complex	1234
Trithorax and Polycomb Group Proteins Regulate Hox Expression	1201
The D-V Signaling Genes Create a Gradient of the Transcription	1235
A Hierarchy of Induction Induction On the Hierarchy of Induction	1236
Vertebrate Embryo	1238
A Competition Between Secreted Signaling Proteins Patterns the	
Hox Genes Control the Vertebrate A-P Axis	1239
Some Transcription Regulators Can Activate a Program	1240
Notch-mediated Lateral Life or Creates an Entire Organ	1241

	A Gene Expression Oscillator Acts as a Clock to Control	
	Vertebrate Segmentation	1249
	Cell-intrinsic Timing Mechanisms Can Lead to Different Cell Fates	1251
	Cells Rarely Count Cell Divisions to Time Their Development	1252
	MicroRNAs Can Regulate Developmental Transitions	1252
	Cell and Nuclear Size Relationships Schedule the Onset	
/	of Zygotic Gene Expression	1254
	Hormonal Signals Coordinate the Timing of Developmental	
	Iransitions	1255
	Environmental Cues Determine the Time of Flowering	1256
	Summary	1257
	MORPHOGENESIS	1257
	Imbalance in Physical Forces Acting on Cells Drives	
	Morphogenesis	1258
	Tension and Adhesion Determine Cell Packing Within	3
	Epithelial Sheets	1258
	Changing Patterns of Cell Adhesion Molecules Force	1050
	Cells into New Arrangements	1259
	Repuisive interactions Help Maintain Tissue Boundaries	1259
	Boorrangemente	1061
	Planar Cell Polarity Oriente Cell Rehaviore Within an Embryo	1201
	An Enithelium Can Rend During Development to Form a Tube	1263
	Interactions Between an Epithelium and Mesenchyme Generate	1200
	Branching Tubular Structures	1264
	The Extracellular Matrix Also Influences Tissue Shape	1265
	Cell Migration Is Guided by Environmental Signals	1266
	The Distribution of Migrant Cells Depends on Survival Factors	1267
	Cells Migrate in Groups to Achieve Large-Scale Morphogenetic	
	Movements	1268
	Summary	1269
	GROWTH	1269
	The Proliferation, Death, and Size of Cells Determine Organ	Relen
	and Organism Size	1270
	Changes in Cell Size Usually Result from Modified Cell Cycles	1271
	Animals and Organs Can Assess and Regulate Total Cell Mass	1272
	Various Extracellular Signals Stimulate or Inhibit Growth	1273
	The Hippo Pathway Relays Mechanical Signals Regulating	
	Growth	1273
	Hormones Coordinate Growth Throughout the Body	1274
	The Duration of Growth Influences Organism Size	1275
	Summary	1275
	Problems	1276

#### References

1	278	3

1279

# Chapter 22 Stem Cells in Tissue Homeostasis and Regeneration

Stem Cells Are Defined by Their Ability to Self-renew and	1279
Produce Differentiated Cells	1280
The Epithelial Lining of the Small Intestine Is Continually Renewed Through Cell Proliferation in Crypts	1281
Epidermal Stem Cells Maintain a Self-renewing, Waterproof,	1201
Epithelial Barrier on the Body Surface	1282
and Their Progeny	1284
Quiescent Stem Cells Are Difficult to Identify by Lineage	1201
Tracing	1285
Hematopoietic Stem Cells Can Be Identified by Transplantation Some Tissues Do Not Require Stem Cells for Their	1286
Maintenance	1289
n Response to Injury, Some Differentiated Cells Can Revert to Progenitor Cells and Some Progenitor Cells Can Revert	
to Stem Cells	1289
Some Tissues Lack Stem Cells and Are Not Renewable	1290

Patterns1242Cell-fate Determinants Can Be Asymmetrically Inherited1244Evolution of Regulatory DNA Explains Many Morphological1245Differences1245Summary1247DEVELOPMENTAL TIMING1248Molecular Lifetimes Play a Critical Part in Developmental1248Timing1248

. 200 1290 Summary CONTROL OF STEM-CELL FATE AND SELF-RENEWAL 1291 The Stem-Cell Niche Maintains Stem-Cell Self-Renewal 1291 The Size of the Niche Can Determine the Number of Stem Cells 1292 Asymmetric Stem-Cell Division Can Maintain Stem-Cell Number 1293 In Many Symmetric Stem-Cell Divisions, Daughter Cells Choose Their Fates Independently and Stochastically 1294 A Decline in Stem-Cell Function Contributes to Tissue Aging 1294

Summary	1296
REGENERATION AND REPAIR	1296
Planarian Flatworms Contain Stem Cells That Can Regenerat	e
a Whole New Body	1297
Some Vertebrates Can Regenerate Entire Limbs and Organs	1298
Stem Cells Can Be Used Clinically to Replace Lost Hematopo	oietic
or Skin Cells	1299
Neural Stem Cells Can Be Manipulated in Culture and Used t	0
Repopulate a Diseased Central Nervous System	1299
Summary	1300
CELL REPROGRAMMING AND PLURIPOTENT STEM CEL	LS 1300
Nuclei Can Be Reprogrammed by Transplantation into Foreig	n
Cytoplasm	1301
Reprogramming of a Transplanted Nucleus Involves Drastic	1001
Changes in Chromatin Embryopia Stom (ES) Colla Con Conorata Any Part of the Roy	1301
A Coro Sot of Transcription Regulators Defines and Maintains	uy 1502
the ES-Cell State	1303
Fibroblasts Can Be Reprogrammed to Create Induced Pluring	otent
Stem (iPS) Cells	1303
Reprogramming Involves a Massive Upheaval of the Gene Co	ontrol
System	1304
An Experimental Manipulation of Factors That Modify Chroma	atin
Can Increase Reprogramming Efficiencies	1305
ES and iPS Cells Can Be Guided to Generate Specific Adult (	Cell
Types and Even Organoids	1306
Cells of One Specialized Type Can Be Forced to Transdifferer	ntiate
Directly into Another	1306
ES and iPS Cells Are Also Useful for Drug Discovery and Ana	lysis
of Disease	1308
Summary	1309
Problems	1310
neierences	1012
Chapter 23 Pathogons and Infection	1212
Chapter 23 Pathogens and Infection	1313
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS	<b>1313</b> 1313
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS Pathogens Can Be Viruses, Bacteria, or Eukaryotes	<b>1313</b> 1313 1314
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS Pathogens Can Be Viruses, Bacteria, or Eukaryotes Pathogens Interact with Their Hosts in Different Ways	<b>1313</b> 1313 1314 1314
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS Pathogens Can Be Viruses, Bacteria, or Eukaryotes Pathogens Interact with Their Hosts in Different Ways Bacteria Are Diverse and Occupy a Remarkable Variety	<b>1313</b> 1314 1314
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS Pathogens Can Be Viruses, Bacteria, or Eukaryotes Pathogens Interact with Their Hosts in Different Ways Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches	<b>1313</b> 1314 1314 1315
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS Pathogens Can Be Viruses, Bacteria, or Eukaryotes Pathogens Interact with Their Hosts in Different Ways Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches Bacterial Pathogens Carry Specialized Virulence Genes	1313 1313 1314 1314 1315 1317
Chapter 23 Pathogens and Infection INTRODUCTION TO PATHOGENS Pathogens Can Be Viruses, Bacteria, or Eukaryotes Pathogens Interact with Their Hosts in Different Ways Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches Bacterial Pathogens Carry Specialized Virulence Genes Bacterial Virulence Genes Encode Toxins and Secretion Syste	1313 1313 1314 1314 1315 1317 ems
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System</li> <li>That Deliver Effector Proteins to Host Cells</li> </ul>	1313 1313 1314 1315 1317 ems 1319
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 ery 1322 1325
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 ery 1322 1325
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>Al Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 1325 1325
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion Syste That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize on Epithelium Must Overseme</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 1325 1325 1325 1326
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>Al Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 1325 1325 1325 1326
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1321 1325 1325 1325 1326
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 1325 1325 1326
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>INTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion Syste That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 1325 1325 1326 1326
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> </ul>	1313 1313 1314 1314 1315 1317 ers 1321 1325 1325 1326 1326
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machine Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> </ul>	1313 1313 1314 1314 1315 1317 ems 1319 1321 1325 1325 1325 1326 1328
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> </ul>	1313 1313 1314 1314 1314 1315 1317 ems 1319 1321 1325 1325 1326 1326 1328 1328
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Viruses Enter Host Cells by Membrane Fusion, Pore Formation</li> </ul>	1313 1313 1314 1314 1314 1315 1317 ers 1321 1325 1325 1325 1326 1326 1328 1328
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Viruses Enter Host Cells by Membrane Fusion, Pore Formatio or Membrane Disruption</li> </ul>	1313 1313 1314 1314 1314 1315 1317 ems 1319 1321 1325 1325 1325 1326 1326 1328 1328
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion Syster That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Viruses Enter Host Cells by Membrane Fusion, Pore Formatio or Membrane Disruption</li> <li>Bacteria Enter Host Cells by Phagocytosis</li> </ul>	1313 1314 1314 1314 1314 1315 1317 ems 1319 1321 1325 1325 1325 1326 1326 1328 1328
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Viruses Enter Host Cells by Membrane Fusion, Pore Formatio or Membrane Disruption</li> <li>Bacteria Enter Host Cells by Phagocytosis</li> <li>Intracellular Eukaryotic Parasites Actively Invade Host Cells</li> </ul>	1313 1313 1314 1314 1314 1315 1317 ems 1329 1328 1328 1328 1329 1329 1329 1329 1329 1329 1329
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion Syste That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Viruses Enter Host Cells by Membrane Fusion, Pore Formation or Membrane Disruption</li> <li>Bacteria Enter Host Cells by Phagocytosis</li> <li>Intracellular Eukaryotic Parasites Actively Invade Host Cells</li> <li>Some Intracellular Pathogens Escape from the Phagosome</li> </ul>	1313 1314 1314 1314 1314 1315 1317 ems 1319 1321 1325 1325 1326 1326 1328 1328 1329 1329 1329 n, 1330
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion Syste That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Viruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Viruses Enter Host Cells by Membrane Fusion, Pore Formation or Membrane Disruption</li> <li>Bacteria Enter Host Cells by Phagocytosis</li> <li>Intracellular Eukaryotic Parasites Actively Invade Host Cells</li> <li>Some Intracellular Pathogens Escape from the Phagosome into the Cytosol</li> </ul>	1313 1313 1314 1314 1314 1315 1317 ems 1321 1325 1325 1325 1326 1326 1328 1328 1329 1323 1329 1331 1330 1331 1333
<ul> <li>Chapter 23 Pathogens and Infection</li> <li>NTRODUCTION TO PATHOGENS</li> <li>Pathogens Can Be Viruses, Bacteria, or Eukaryotes</li> <li>Pathogens Interact with Their Hosts in Different Ways</li> <li>Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches</li> <li>Bacterial Pathogens Carry Specialized Virulence Genes</li> <li>Bacterial Virulence Genes Encode Toxins and Secretion System That Deliver Effector Proteins to Host Cells</li> <li>Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms</li> <li>All Aspects of Viral Propagation Depend on Host-Cell Machin Summary</li> <li>CELL BIOLOGY OF PATHOGEN INFECTION</li> <li>Pathogens Breach Epithelial Barriers to Infect the Host Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms</li> <li>Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them</li> <li>Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells</li> <li>Wiruses Bind to Virus Receptors at the Host-Cell Surface</li> <li>Wiruses Enter Host Cells by Membrane Fusion, Pore Formation or Membrane Disruption</li> <li>Bacteria Enter Host Cells by Phagocytosis</li> <li>Intracellular Eukaryotic Parasites Actively Invade Host Cells</li> <li>Some Intracellular Pathogens Escape from the Phagosome into the Cytosol</li> <li>Many Pathogens Alter Membrane Traffic in the Host Cell</li> </ul>	1313 1313 1314 1314 1314 1315 1317 1319 1321 1325 1325 1326 1326 1328 1328 1328 1329 n, 1330 1331 1331 1333

THE HUMAN MICROBIOTA	1347
The Human Microbiota Is a Complex Ecological System	1347
The Microbiota Influences Our Development and Health	1348
Summary	1349
Problems	1350
References	1351
Have the Toble to Devise Combination Therabids while Toble 1.	
Chapter 24 The Innate and Adaptive	
Immune Systems	1353
THE ININIATE MANALINE OVOTEM	1054
THE INNATE INNOUNE SYSTEM	1354
Epithelial Surfaces Serve as Barriers to Infection	1354
Pattern Recognition Receptors (PRRs) Recognize Conserved	1051
Features of Pathogens	1354
There Are Multiple Families of PRRs	1355
Activated PRRs Trigger an Inflammatory Response at Sites	
of Infection	1356
Phagocytic Cells Seek, Engulf, and Destroy Pathogens	1358

Phagocytic Cells Seek, Engulf, and Destroy Pathogens Complement Activation Targets Pathogens for Phagocytosis

or Lysis	1358
Virus-infected Cells Take Drastic Measures to Prevent	
Viral Replication	1360
Natural Killer Cells Induce Virus-infected Cells to Kill Themselves Dendritic Cells Provide the Link Between the Innate	1361
and Adaptive Immune Systems	1362
Summary	1362
OVERVIEW OF THE ADAPTIVE IMMUNE SYSTEM	1364
B Cells Develop in the Bone Marrow, T Cells in the Thymus	1365
and Lymphocyte Differentiation	1366
Nost B and T Cells Continually Recirculate Through Peripheral	1000
Immunological Solf toloronoo Enguroo That R and T Collo	1300
Do Not Attack Normal Host Colls and Molecules	1370
Summany	1372
	1072
B CELLS AND IMMUNOGLOBULINS	1372
B Cells Make Immunoglobulins (Igs) as Both Cell-Surface	1070
Antigen Receptors and Secreted Antibodies	13/3
In Light and Lloover Chains of Antihadian Consist of Constant	13/3
and Variable Regions	1375
la Gones Are Assembled from Senarate Gene Segments	1070
During R Cell Development	1377
Antigen-driven Somatic Hypermutation Fine-Tunes	1011
Antibody Responses	1379
B Cells Can Switch the Class of Ig They Make	1379
Summary	1381
T CELLS AND MHC PROTEINS	1382
T Cell Recentors (TCRs) Are la-like Heterodimers	1382
Activated Dendritic Cells Activate Naïve T Cells	1383
T Cells Recognize Foreign Peptides Bound to MHC Proteins	1384
MHC Proteins Are the Most Polymorphic Human	1001
Proteins Known	1388
CD4 and CD8 Co-receptors on T Cells Bind to Invariant	
Parts of MHC Proteins	1389
Developing Thymocytes Undergo Positive and Negative Selection	1389
Cytotoxic T Cells Induce Infected Target Cells to Undergo Apoptosis	1391
Effector Helper T Cells Help Activate Other Cells of the	
Innate and Adaptive Immune Systems	1392
Naïve Helper T Cells Can Differentiate into Different Types	
of Effector T Cells	1393
Both T and B Cells Require Multiple Extracellular Signals	1001
for Activation	1394
Many Cell-Surface Proteins Belong to the Ig Superfamily	1396
Vaccination Against Pathogens Has Been Immunology's	1000
Greatest Contribution to Human Health	1090

1400

1402

1404

G:1

1:1

Bacteria and Viruses Use the Host-Cell Cytoskeleton for Intracellular Movement Many Microbes Manipulate Autophagy Viruses Can Take Over the Metabolism of the Host Cell Pathogens Can Evolve Rapidly by Antigenic Variation Error-prone Replication Dominates Viral Evolution Drug-resistant Pathogens Are a Growing Problem Summary

Summary Problems References

1338

1340

1340

1341

1343

1344

1346

Glossary

Index