

# Contents

<i>Preface</i>	<i>xvii</i>		
<i>Acknowledgments</i>	<i>xix</i>		
<i>Author</i>	<i>xxi</i>		
<b>1 THE FUNDAMENTALS OF MOLECULAR AND CELLULAR VIROLOGY</b>	<b>1</b>		
1.1 Molecular and cellular virology focuses on the molecular interactions that occur when a virus infects a host cell	2	2.4 The host surface is especially important for attachment, penetration, and uncoating	23
1.2 The discipline of virology can be traced historically to agricultural and medical science	3	2.5 Viral gene expression and genome replication take advantage of host transcription, translation, and replication features	26
1.3 Basic research in virology is critical for molecular biology, both historically and today	6	2.6 The host cytoskeleton and membranes are typically crucial during virus assembly	27
1.4 Viruses, whether understood as living or not, are the most abundant evolving entities known	8	2.7 Host-cell surfaces influence the mechanism of virus release	27
1.5 Viruses can be defined unambiguously by four traits	8	2.8 Viruses can also cause long-term infections	27
1.6 Virions are infectious particles minimally made up of nucleic acids and proteins	10	2.9 Herpesvirus is a model for latent infections	29
1.7 Viruses can be classified according to the ways they synthesize and use mRNA	11	2.10 Research in molecular and cellular virology often focuses on the molecular details of each stage of the replication cycle	29
1.8 Viruses are propagated in the laboratory by mixing them with host cells	12	Essential concepts	30
1.9 Viral sequences are ubiquitous in animal genomes, including the human genome	14	Questions	30
Essential concepts	17	Further reading	31
Questions	17		
Further reading	18		
<b>2 THE VIRUS REPLICATION CYCLE</b>	<b>19</b>	<b>3 ATTACHMENT, PENETRATION, AND UNCOATING</b>	<b>33</b>
2.1 Viruses reproduce through a lytic virus replication cycle	20	3.1 Viruses enter the human body through one of six routes	33
2.2 Molecular events during each stage of the virus replication cycle	22	3.2 The likelihood of becoming HIV+ depends on the route of transmission and the amount of virus in the infected tissue	34
2.3 The influenza virus is a model for replication of an animal virus	23	3.3 Viruses are selective in their host range and tissue tropism	35
		3.4 The virion is a genome delivery device	36
		3.5 The genomic contents of a virion are irrelevant for attachment, penetration, and uncoating	37
		3.6 Animal viruses attach to specific cells and can spread to multiple tissues	40
		3.7 Noncovalent intermolecular forces are responsible for attaching to host cells	41
		3.8 Most animal virus receptors are glycoproteins	42

3.9	Animal virus receptors can be identified through genetic, biochemical, and immunological approaches	43	3.28	Vesicle fusion in neuroscience is a model for viral membrane fusion	61
3.10	Animal virus receptors can be identified through molecular cloning	43	3.29	HIV provides a model of membrane fusion triggered by a cascade of protein–protein interactions	63
3.11	Animal virus receptors can be identified through affinity chromatography	44	3.30	Influenza provides a model for viral envelope fusion triggered by acidification of an endocytic vesicle	64
3.12	Antibodies can be used to identify animal virus receptors	45	3.31	The destination for the virus genome may be the cytoplasm or the nucleus	65
3.13	Rhinovirus serves as a model for attachment by animal viruses lacking spikes	47	3.32	Subversion of the cellular cytoskeleton is critical for uncoating	65
3.14	Several independent lines of evidence indicate that ICAM-1 is the rhinovirus receptor	50	3.33	Viruses that enter an intact nucleus must manipulate gated nuclear pores	66
3.15	Experiments using molecular genetics support the conclusion that ICAM-1 is the rhinovirus receptor	50	3.34	Viruses introduce their genomes into the nucleus in a variety of ways	67
3.16	Structural biology experiments support the conclusion that ICAM-1 is the rhinovirus receptor	51	3.35	Adenovirus provides a model for uncoating that delivers the viral genome into the nucleus	68
3.17	Bioinformatics comparisons support the conclusion that ICAM-1 is the rhinovirus receptor	51	3.36	The unusual uncoating stages of reoviruses and poxviruses leave the virions partially intact in the cytoplasm	69
3.18	Influenza serves as a model for attachment by enveloped viruses	52	3.37	Viruses that penetrate plant cells face plant-specific barriers to infection	71
3.19	The influenza HA spike protein binds to sialic acids	53	3.38	Plant viruses are often transmitted by biting arthropod vectors	72
3.20	The second stage of the virus replication cycle includes both penetration and uncoating and, if necessary, transport to the nucleus	55		Essential concepts	73
3.21	Viruses subvert the two major eukaryotic mechanisms for internalizing particles	56		Questions	74
3.22	Many viruses subvert receptor-mediated endocytosis for penetration	56		Further reading	74
3.23	Herpesvirus penetrates the cell through phagocytosis	57	<b>4</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN MODEL BACTERIOPHAGES</b>	<b>77</b>
3.24	Common methods for determining the mode of viral penetration include use of drugs and RNA interference	58	4.1	Bacterial host cell transcription is catalyzed by a multisubunit machine that catalyzes initiation, elongation, and termination	78
3.25	The virion is a metastable particle primed for uncoating once irreversible attachment and penetration have occurred	59	4.2	Bacterial host cell and bacteriophage mRNA are typically polycistronic	80
3.26	Picornaviruses are naked viruses that release their genomic contents through pore formation	60	4.3	Transcription and translation in bacterial host cells and bacteriophages are nearly simultaneous because of the proximity of ribosomes and chromosomes	81
3.27	Some enveloped viruses use membrane fusion with the outside surface of the cell for penetration	60	4.4	Bacterial translation initiation, elongation, and termination are controlled by translation factors	81
			4.5	Bacteriophages, like all viruses, encode structural and nonstructural proteins	83

4.6	The T7 bacteriophage has naked, complex virions and a large double-stranded DNA genome	84	4.24	The abundance of host DnaA protein relative to the amount of phage DNA controls the switch to rolling-circle replication	102
4.7	Bacteriophage T7 encodes 55 proteins in genes that are physically grouped together by function	85	4.25	There are billions of other bacteriophages that regulate gene expression in various ways	103
4.8	Bacteriophage T7 proteins are expressed in three major waves	85	4.26	Some bacteriophages have ssDNA, dsDNA, or (+) ssRNA genomes	104
4.9	The functions of bacteriophage proteins often correlate with the timing of their expression	86	4.27	The replication cycles of ssDNA bacteriophages always include formation of a double-stranded replicative form	104
4.10	Bacteriophage T7 gene expression is highly regulated at the level of transcription initiation	87	4.28	Bacteriophage $\phi\chi 174$ is of historical importance	105
4.11	Bacterial host chromosome replication is regulated by the DnaA protein and occurs via a $\theta$ intermediate	88	4.29	Bacteriophage $\phi\chi 174$ has extremely overlapping protein-coding sequences	105
4.12	Many bacterial proteins are needed to catalyze chromosome replication	90	4.30	Bacteriophage $\phi\chi 174$ proteins are expressed in different amounts	106
4.13	Although many bacteriophages have linear dsDNA genomes, bacterial hosts cannot replicate the ends of linear DNA	92	4.31	A combination of mRNA levels and differential translation accounts for levels of bacteriophage $\phi\chi 174$ protein expression	107
4.14	T7 bacteriophage genome replication is catalyzed by one of the simplest known replication machines	93	4.32	Bacteriophage M13 genome replication is catalyzed by host proteins and occurs via a replicative form	108
4.15	The $\lambda$ bacteriophage has naked, complex virions and a large double-stranded DNA genome	96	4.33	Bacteriophage MS2 is a (+) ssRNA virus that encodes four proteins	110
4.16	Bacteriophage $\lambda$ can cause lytic or long-term infections	96	4.34	Bacteriophage MS2 protein abundance is controlled by secondary structure in the genome	111
4.17	There are three waves of gene expression during lytic $\lambda$ replication	98	4.35	Bacteriophage RdRp enzymes subvert abundant host proteins to create an efficient replicase complex	114
4.18	The $\lambda$ control region is responsible for early gene expression because of its promoters and the Cro and N proteins it encodes	99	4.36	Bacteriophage proteins are common laboratory tools	115
4.19	The $\lambda$ N antitermination protein controls the onset of delayed-early gene expression	99		Essential concepts	121
4.20	The $\lambda$ Q antitermination protein and Cro repressor protein control the switch to late gene expression	100		Questions	122
4.21	Bacteriophages T7 and $\lambda$ both have three waves of gene expression but the molecular mechanisms controlling them differ	100		Further reading	123
4.22	Bacteriophage $\lambda$ genome replication occurs in two stages, through two different intermediates	101	<b>5</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN THE POSITIVE-STRAND RNA VIRUSES</b>	<b>125</b>
4.23	Lambda genome replication requires phage proteins O and P and many subverted host proteins	102	5.1	Class IV virus replication cycles have common gene expression and genome replication strategies	126
			5.2	Terminal features of eukaryotic mRNA are essential for translation	127

5.3	Monopartite Class IV (+) strand RNA viruses express multiple proteins from a single genome	128	5.23	Coronaviruses have long (+) strand RNA genomes and novel mechanisms of gene expression and genome replication	152
5.4	Picornaviruses are models for the simplest (+) strand RNA viruses	128	5.24	Coronaviruses have enveloped spherical virions and encode conserved and species-specific accessory proteins	152
5.5	Class IV viruses such as poliovirus encode one or more polyproteins	130	5.25	Coronaviruses express a nested set of sgRNAs with leader and TRS sequences	153
5.6	Class IV viruses such as poliovirus use proteolysis to release small proteins from viral polyproteins	132	5.26	Coronaviruses use a discontinuous mechanism for synthesis of replicative forms	155
5.7	Translation of Class IV virus genomes occurs despite the lack of a 5' cap	134	5.27	Most coronavirus sgRNA is translated into a single protein	156
5.8	Class IV virus genome replication occurs inside a virus replication compartment	136	5.28	Coronaviruses use a leaky scanning mechanism to synthesize proteins from overlapping sequences	156
5.9	The picornavirus 3D <sup>pol</sup> is an RdRp and synthesizes a protein-based primer	137	5.29	Coronaviruses may proofread RNA during synthesis	157
5.10	Structural features of the viral genome are essential for replication of Class IV viral genomes	137	5.30	Plants can also be infected by Class IV RNA viruses	159
5.11	Picornavirus genome replication occurs in four phases	138	5.31	Comparing Class IV viruses reveals common themes with variations	160
5.12	Flaviviruses are models for simple enveloped (+) strand RNA viruses	141		Essential concepts	161
5.13	The linear (+) strand RNA flavivirus genomes have unusual termini	141		Questions	161
5.14	Enveloped HCV encodes 10 proteins including several with transmembrane segments	142		Further reading	162
5.15	Togaviruses are small enveloped viruses with replication cycles more complex than those of the flaviviruses	143	<b>6</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN THE NEGATIVE-STRAND RNA VIRUSES</b>	<b>163</b>
5.16	Four different togavirus polyproteins are found inside infected cells	145	6.1	Study of two historically infamous Class V viruses, rabies and influenza, were instrumental in the development of molecular and cellular virology	163
5.17	Different molecular events predominate early and late during togavirus infection	146	6.2	The mononegavirus replication cycle includes primary and secondary transcription catalyzed by the viral RdRp	164
5.18	Translation of togavirus sgRNA requires use of the downstream hairpin loop	147	6.3	Rhabdoviruses have linear (–) RNA genomes and encode five proteins	166
5.19	Suppression of translation termination is necessary for production of the nonstructural p1234 Sindbis virus polyprotein	148	6.4	Rhabdoviruses produce five mRNAs with 5' caps and polyadenylated 3' tails through a start–stop mechanism	167
5.20	Sindbis virus uses an unusual mechanism to encode the TF protein	149	6.5	Rhabdovirus genome replication occurs through the use of a complete antigenome cRNP as a template	169
5.21	A programmed –1 ribosome frameshift is needed to produce the togavirus TF protein	150	6.6	The paramyxoviruses are mononegaviruses that use RNA editing for gene expression	170
5.22	The picornaviruses, flaviviruses, and togaviruses illustrate many common properties among (+) strand RNA viruses	151			

6.7	Filoviruses are filamentous mononegaviruses that encode seven to nine proteins	173	<b>8</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN THE DOUBLE-STRANDED DNA VIRUSES</b>	<b>193</b>
6.8	The filovirus VP30 protein, not found in other mononegaviruses, is required for transcription	175	8.1	DNA viruses can cause productive lytic infections, cellular transformation, or latent infections	194
6.9	Influenza is an example of an orthomyxovirus	175	8.2	Most Class I animal viruses rely on host transcription machinery for gene expression	194
6.10	Of the 17 influenza A proteins, 9 are found in the virion	176	8.3	Eukaryotic transcription is affected by the state of the chromatin	195
6.11	Orthomyxovirus nucleic acid synthesis occurs in the host cell nucleus, not in the cytoplasm	177	8.4	Eukaryotic capping, splicing, and polyadenylation occur co-transcriptionally	196
6.12	The first step of transcription by influenza virus is cap snatching	178	8.5	Polyomaviruses are small DNA viruses with early and late gene expression	199
6.13	An influenza cRNP intermediate is used as the template for genome replication	179	8.6	The SV40 polyomavirus encodes seven proteins in only 5,243 bp of DNA	200
6.14	Arenavirus RNA genomes are ambisense	181	8.7	The synthesis of mRNA in SV40 is controlled by the noncoding control region	201
6.15	Expression of the four arenavirus proteins reflects the ambisense nature of the genome	182	8.8	Late SV40 transcription is regulated by both host and viral proteins	202
Essential concepts		183	8.9	Most Baltimore Class I viruses including polyomaviruses manipulate the eukaryotic cell cycle	204
Questions		184	8.10	Most Class I viruses prevent or delay cellular apoptosis	206
Further reading		184	8.11	SV40 forces the host cell to express S phase genes and uses large T antigen and host proteins for genome replication	207
<b>7</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN THE DOUBLE-STRANDED RNA VIRUSES</b>	<b>185</b>	8.12	SV40 genome replication requires viral and host proteins to form active DNA replication forks	208
7.1	The rotavirus replication cycle includes primary transcription, genome replication, and secondary transcription inside partially intact capsids in the host cytoplasm	186	8.13	The papillomavirus replication cycle is tied closely to the differentiation status of its host cell	209
7.2	Rotavirus A has a naked capsid with three protein layers enclosing 11 segments of dsRNA	186	8.14	Human papillomaviruses encode about 13 proteins that are translated from polycistronic mRNA	211
7.3	Rotavirus A encodes 13 proteins	188	8.15	The long control region of HPV regulates papillomavirus transcription in which pre-mRNA is subjected to alternative splicing	213
7.4	Synthesis of rotavirus nucleic acids occurs in a fenestrated double-layered particle	188	8.16	Leaky scanning, internal ribosome entry sites, and translation re-initiation lead to the expression of papillomavirus proteins from polycistronic mRNA	213
7.5	Translation of rotavirus mRNA requires NSP3 and occurs in viroplasm formed by NSP2 and NSP5	189	8.17	DNA replication in papillomaviruses is linked to host cell differentiation status	215
7.6	Rotavirus genome replication precedes secondary transcription	191			
Essential concepts		191			
Questions		191			
Further reading		192			

8.18	Papillomaviruses use early proteins to manipulate the host cell cycle and apoptosis	216	8.34	Poxviruses are extremely large dsDNA viruses that replicate in the host cytoplasm	231
8.19	Comparing the small DNA viruses reveals similar economy in coding capacity but different mechanisms for gene expression, manipulating the host cell cycle, and DNA replication	216	8.35	Many vaccinia virus proteins are associated with the virion itself	233
8.20	Adenoviruses are large dsDNA viruses with three waves of gene expression	217	8.36	Vaccinia RNA polymerase transcribes genes in three waves using different transcription activators	233
8.21	Adenoviruses have large naked spherical capsids with prominent spikes and large linear dsDNA genomes	217	8.37	Vaccinia genome replication requires the unusual ends of the genome sequence	236
8.22	Adenoviruses encode early, delayed-early, and late proteins	218	8.38	The synthetic demands on the host cell make vaccinia a possible anticancer treatment	238
8.23	The large E1A protein is important for regulating the adenovirus cascade of gene expression	220		Essential concepts	238
8.24	Splicing of pre-mRNA was first discovered through studying adenovirus gene expression	220		Questions	239
8.25	Both host cells and adenovirus rely on alternative splicing to encode multiple proteins using the same DNA sequence	221		Further reading	240
8.26	Regulated alternative splicing of a late adenovirus transcript relies on <i>cis</i> -acting regulatory sequences, on the E4-ORF4 viral protein, and on host splicing machinery	222	<b>9</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN THE SINGLE-STRANDED DNA VIRUSES</b>	<b>241</b>
8.27	Adenovirus shuts off translation of host mRNA, while ensuring translation of its own late mRNAs through a ribosome-shunting mechanism	224	9.1	The ssDNA viruses express their genes and replicate their genomes in the nucleus	242
8.28	DNA replication in adenovirus requires three viral proteins even though the genome is replicated in the host cell nucleus	225	9.2	Circoviruses are tiny ssDNA viruses with circular genomes	242
8.29	Herpesviruses have very large enveloped virions and large linear dsDNA genomes	228	9.3	Although their genomes are shorter than an average human gene, circoviruses encode at least four proteins	243
8.30	Lytic herpesvirus replication involves a cascade with several waves of gene expression	228	9.4	Both host and viral proteins are needed for circovirus genome replication	244
8.31	Groups of herpes simplex virus 1 proteins have functions relating to the timing of their expression	229	9.5	Parvoviruses are tiny ssDNA viruses with linear genomes having hairpins at both ends	245
8.32	Waves of gene expression in herpesviruses are controlled by transcription activation and chromatin remodeling	230	9.6	The model parvovirus MVM encodes six proteins using alternative splicing	245
8.33	Herpesvirus genome replication results in concatamers	231	9.7	The model parvovirus MVM uses a rolling-hairpin mechanism for genome replication	246
				Essential concepts	248
				Questions	248
				Further reading	249
			<b>10</b>	<b>GENE EXPRESSION AND GENOME REPLICATION IN THE RETROVIRUSES AND HEPADNAVIRUSES</b>	<b>251</b>
			10.1	Viral reverse transcriptases have polymerase and RNase H activity	254

10.2	Retroviruses are enveloped and have RNA genomes yet express their proteins from dsDNA	254	11	ASSEMBLY, RELEASE, AND MATURATION	277
10.3	Reverse transcription occurs during transport of the retroviral nucleic acid to the nucleus, through a discontinuous mechanism	255	11.1	The last stages of the virus replication cycle are assembly, release, and maturation	278
10.4	Retroviral integrase inserts the viral cDNA into a chromosome, forming proviral DNA that can be transcribed by host Pol II	256	11.2	Unlike cells, viruses assemble from their constituent parts	278
10.5	All retroviruses express eight essential proteins, whereas some such as HIV encode species-specific accessory proteins	259	11.3	Virions more structurally complex than TMV also reproduce by assembly, not by division	280
10.6	The retroviral LTR sequences interact with host proteins to regulate transcription	259	11.4	Typical sites of assembly in eukaryotic viruses include the cytoplasm, plasma membrane, and nucleus	281
10.7	The compact retroviral genome is used economically to encode many proteins through the use of polyproteins, alternative splicing, and translation of polycistronic mRNA	260	11.5	Eukaryotic virus assembly must take cellular protein localization into account	282
10.8	The HIV-1 accessory protein TAT is essential for viral gene expression	264	11.6	Capsids and nucleocapsids associate with genomes using one of two general strategies	283
10.9	The HIV-1 accessory protein Rev is essential for exporting some viral mRNA from the nucleus	265	11.7	Assembly of some viruses depends on DNA replication to provide the energy to fill the icosahedral heads	283
10.10	Retrovirus genome replication is accomplished by host Pol II	265	11.8	Assembly of some viruses depends on a packaging motor to fill the icosahedral heads	284
10.11	HIV-1 is a candidate gene therapy vector for diseases that involve the immune cells normally targeted by HIV	266	11.9	Negative RNA viruses provide a model for concerted nucleocapsid assembly	286
10.12	Hepadnaviruses are enveloped and have genomes containing both DNA and RNA in an unusual arrangement	267	11.10	To assemble, some viruses require assistance from proteins not found in the virion	287
10.13	Hepadnaviruses use reverse transcription to amplify their genomes	268	11.11	Viruses acquire envelopes through one of two pathways	287
10.14	The cccDNA of HBV is not perfectly identical to the DNA in the infecting virion	269	11.12	The helical vRNPs of influenza virus assemble first, followed by envelope acquisition at the plasma membrane	288
10.15	The tiny HBV genome encodes eight proteins through alternative splicing, overlapping coding sequences, and alternative start codons	269	11.13	Some viruses require maturation reactions during release in order to form infectious virions	290
10.16	HBV genome replication relies upon an elaborate reverse transcriptase mechanism	270	11.14	Assembly of HIV occurs at the plasma membrane	290
Essential concepts		274	11.15	Inhibition of HIV-1 maturation provides a classic example of structure–function research in medicine	291
Questions		275	11.16	Release from bacterial cells usually occurs by lysis	293
Further reading		275	11.17	Release from animal cells can occur by lysis	295
			11.18	Release from animal cells can occur by budding	296

11.19 Release from plant cells often occurs through biting arthropods	298	13.6 Some lysogens provide their bacterial hosts with virulence genes	323
Essential concepts	298	13.7 Prophages affect the survival of their bacterial hosts	324
Questions	299	13.8 Persistent infections in humans include those with ongoing lytic replication and latent infections	326
Further reading	299	13.9 Human immunodeficiency virus causes persistent infections	326
<b>12 VIRUS–HOST INTERACTIONS DURING LYTIC GROWTH</b>	<b>301</b>	13.10 Human herpesvirus 1 is a model for latent infections	327
12.1 All viruses subvert translation	302	13.11 Oncogenic viruses cause cancer through persistent infections	329
12.2 Bacteriophages subvert translation indirectly	302	13.12 DNA viruses transform cells with oncoproteins that affect the cell cycle and apoptosis	330
12.3 Animal viruses have many strategies to block translation of host mRNA	304	13.13 HPV oncoproteins E6 and E7 cause transformation	331
12.4 Animal viruses cause structural changes in host cells referred to as cytopathic effects	306	13.14 HPV E6 and E7 overexpression occurs when the virus genome recombines with a host chromosome	332
12.5 Viruses affect host cell apoptosis	306	13.15 Merkel cell polyomavirus is also associated with human cancers	332
12.6 Some viruses delay apoptosis in order to complete their replication cycles before the host cell dies	308	13.16 Epstein–Barr virus is an oncogenic herpesvirus	332
12.7 Some viruses subvert apoptosis in order to complete their replication cycles	309	13.17 Latency-associated viral proteins are responsible for Epstein–Barr virus-induced oncogenesis	334
12.8 Viruses use the ubiquitin system to their advantage	309	13.18 The Kaposi's sarcoma herpesvirus also causes persistent oncogenic infections	335
12.9 Viruses can block or subvert the cellular autophagy system	311	13.19 Hepatocellular carcinoma is caused by persistent lytic viral infections	336
12.10 Viruses subvert or co-opt the misfolded protein response triggered in the endoplasmic reticulum	312	13.20 Retroviruses have two mechanisms by which they can cause cancer	337
12.11 Viruses modify internal membranes in order to create virus replication compartments	312	13.21 Viral oncoproteins can be used to immortalize primary cell cultures	339
Essential concepts	315	13.22 The human virome is largely uncharacterized but likely has effects on human physiology	340
Questions	315	Essential concepts	341
Further reading	316	Questions	341
<b>13 PERSISTENT VIRAL INFECTIONS</b>	<b>317</b>	Further reading	342
13.1 Some bacteriophages are temperate and can persist as genomes integrated into their hosts' chromosomes	318	<b>14 VIRAL EVASION OF INNATE HOST DEFENSES</b>	<b>345</b>
13.2 Bacteriophage $\lambda$ serves as a model for latency	318	14.1 Restriction enzymes are a component of innate immunity to bacteriophages	346
13.3 The amount of stable CII protein in the cell determines whether the phage genome becomes a prophage	320	14.2 Bacteriophages have counterdefenses against restriction-modification systems	349
13.4 Activation of $P_{RE}$ , $P_L$ , and $P_{antiQ}$ by CII results in lysogeny	320		
13.5 Stress triggers an exit from lysogeny	322		



<b>14.3</b>	Human innate immune defenses operate on many levels	349	<b>15.5</b>	Professional antigen-presenting cells degrade exogenous antigens and display epitopes in MHC-II molecules	372
<b>14.4</b>	The human innate immune system is triggered by pattern recognition	349	<b>15.6</b>	Some viruses evade MHC-II presentation	373
<b>14.5</b>	Innate immune responses include cytokine secretion	351	<b>15.7</b>	Lymphocytes that control viral infections have many properties in common	375
<b>14.6</b>	Interferon causes the antiviral state	351	<b>15.8</b>	CD4 <sup>+</sup> helper T lymphocytes interact with viral epitopes displayed in MHC-II molecules	375
<b>14.7</b>	Some viruses can evade the interferon response	353	<b>15.9</b>	Antibodies are soluble B-cell receptors that bind to extracellular antigens such as virions	377
<b>14.8</b>	Neutrophils are active during an innate immune response against viruses	357	<b>15.10</b>	During an antiviral response, B cells differentiate to produce higher-affinity antibodies	378
<b>14.9</b>	Viruses manipulate immune system communication to evade the net response	357	<b>15.11</b>	Viruses have strategies to evade or subvert the antibody response	379
<b>14.10</b>	Inflammation is the hallmark of an innate immune response	358	<b>15.12</b>	CD8 <sup>+</sup> cytotoxic T lymphocytes are crucial for controlling viral infections	380
<b>14.11</b>	In order to be recognized as healthy, all cells present endogenous antigens in MHC-I molecules	358	<b>15.13</b>	Some viruses can evade the CTL response	381
<b>14.12</b>	Cells infected by viruses produce and display viral antigens in MHC-I	359	<b>15.14</b>	Viruses that cause persistent infections evade immune clearance for a long period of time	382
<b>14.13</b>	Viruses have strategies to evade MHC-I presentation of viral antigens	360	<b>15.15</b>	The immune response to influenza serves is a comprehensive model for antiviral immune responses in general	383
<b>14.14</b>	Natural killer cells attack cells with reduced MHC-I display	360	<b>15.16</b>	Influenza provides a model for how a lytic virus evades both innate and adaptive immunity long enough to replicate	386
<b>14.15</b>	The complement system targets enveloped viruses and cells infected by them	361		Essential concepts	387
<b>14.16</b>	Some viruses can evade the complement system	362		Questions	388
<b>14.17</b>	Viral evasion strategies depend on the coding capacity of the virus	362		Further reading	388
<b>14.18</b>	In vertebrates, if an innate immune reaction does not clear an infection, adaptive immunity comes into play	362			
	Essential concepts	363			
	Questions	364			
	Further reading	364			
<b>15</b>	<b>VIRAL EVASION OF ADAPTIVE HOST DEFENSES</b>	<b>365</b>	<b>16</b>	<b>MEDICAL APPLICATIONS OF MOLECULAR AND CELLULAR VIROLOGY</b>	<b>389</b>
<b>15.1</b>	CRISPR-Cas is an adaptive immune response found in bacteria	366	<b>16.1</b>	Vaccines are critical components of an effective public health system	390
<b>15.2</b>	Some bacteriophages can evade or subvert the CRISPR-Cas system	370	<b>16.2</b>	Attenuated vaccines are highly immunogenic because they can still replicate	391
<b>15.3</b>	The human adaptive immune response includes cell-mediated and humoral immunity	371	<b>16.3</b>	Inactivated vaccines are composed of nonreplicating virions	392
<b>15.4</b>	The human adaptive immune response has specificity because it responds to epitopes	371	<b>16.4</b>	Subunit vaccines are composed of selected antigenic proteins	393
			<b>16.5</b>	Although seasonal influenza vaccines are useful, a universal flu vaccine is highly sought after	394

16.6	Preventative HIV vaccines are in development	396	17.4	Transposons and introns are subviral entities	423
16.7	Extreme antigenic variation is a problem for developing an HIV vaccine	398	17.5	Viruses have ancient origins	425
16.8	An effective HIV vaccine may require stimulating a strong CTL response	398	17.6	Viral hallmark proteins can be used to trace evolutionary history	425
16.9	Antiviral drugs target proteins unique to viruses and essential for their replication cycle	399	17.7	Metagenomics will revolutionize evolutionary understanding of viruses	427
16.10	Many antiviral drugs are nucleoside or nucleotide structural analogs that target the active site of viral polymerases	401	17.8	Viral genetic diversity arises through mutation and recombination	429
16.11	Drugs to treat influenza target the uncoating and release stages of viral replication	402	17.9	Genetic diversity among influenza A viruses arises through mutation and recombination	430
16.12	Drugs to treat hepatitis C virus target the viral polymerase	403	17.10	Influenza A spike proteins are particularly diverse	431
16.13	Drugs to treat HIV target many stages of the virus replication cycle	404	17.11	Variations among influenza A viruses reflects genetic drift and natural selection	432
16.14	Viral evolution occurs in response to selective pressure from antiviral drugs	406	17.12	Pandemic influenza A strains have arisen through recombination	433
16.15	It might be possible to develop bacteriophage therapy to treat people with antibiotic-resistant bacterial infections	407	17.13	New pandemic influenza A strains may be able to arise through mutation	435
16.16	Engineered viruses could in principle be used for gene therapy to treat cancer and other conditions	408	17.14	Selective pressures and constraints influence viral evolution	436
16.17	Gene therapy and oncolytic virus treatments currently in use	410	17.15	Some viruses and hosts coevolve	438
16.18	Therapeutic applications of CRISPR-Cas technology	415	17.16	Medically dangerous emerging viruses are zoonotic	440
Essential concepts		416	17.17	HIV exhibits high levels of genetic diversity and transferred from apes to humans on four occasions	442
Questions		417	17.18	HIV-1 has molecular features that reflect adaptation to humans	443
Further reading		418	17.19	Viruses and subviral entities are common in the human genome	444
<b>17 VIRAL DIVERSITY, ORIGINS, AND EVOLUTION</b>	<b>419</b>		17.20	Viruses and subviral entities have strongly affected the evolution of organisms including humans	445
17.1	The viral world is extremely diverse	420	17.21	Virology unites the biosphere	446
17.2	Satellite viruses and nucleic acids require co-infection with a virus to spread	421	Essential concepts		446
17.3	Viroids are infectious RNA molecules found in plants	423	Questions		447
			Further reading		447
			<b>GLOSSARY</b>	<b>449</b>	
			<b>ANSWERS</b>	<b>473</b>	
			<b>INDEX</b>	<b>487</b>	