

Contents

<i>Preface</i>	<i>xix</i>		
<i>Acknowledgments</i>	<i>xxi</i>		
<i>Author</i>	<i>xxiii</i>		
<i>Instructor and Student Resources</i>	<i>xxiv</i>		
1 THE FUNDAMENTALS OF MOLECULAR AND CELLULAR VIROLOGY	1		
1.1 Molecular and cellular virology focuses on the molecular interactions that occur when a virus infects a host cell	2		
1.2 The discipline of virology can be traced historically to agricultural and medical science	3		
1.3 Basic research in virology is critical for molecular biology, both historically and today	6		
1.4 Viruses, whether understood as living or not, are the most abundant evolving entities known	8		
1.5 Viruses can be defined unambiguously by four traits	9		
1.6 Virions are infectious particles minimally made up of nucleic acids and proteins	10		
1.7 Viruses can be classified according to the ways they synthesize and use mRNA	11		
1.8 Viruses are propagated in the laboratory by mixing them with host cells	13		
1.9 Viral sequences are ubiquitous in animal genomes, including the human genome	16		
Essential concepts	17		
Questions	18		
Further reading	18		
2 THE VIRUS REPLICATION CYCLE	21		
2.1 Viruses reproduce through a lytic virus replication cycle	23		
2.2 Molecular events during each stage of the virus replication cycle	24		
2.3 The influenza virus is a model for replication of an animal virus	25		
2.4 The host surface is especially important for attachment, penetration, and uncoating	27		
2.5 Viral gene expression and genome replication take advantage of host transcription, translation, and replication features	28		
2.6 The host cytoskeleton and membranes are typically crucial during virus assembly	29		
2.7 Host-cell surfaces influence the mechanism of virus release	30		
2.8 Viruses can also cause long-term infections	30		
2.9 Herpesvirus is a model for latent infections	32		
2.10 Research in molecular and cellular virology often focuses on the molecular details of each stage of the replication cycle	32		
Essential concepts	32		
Questions	33		
Further reading	33		
3 ATTACHMENT, PENETRATION, AND UNCOATING	35		
3.1 Viruses enter the human body through one of six routes	35		
3.2 The likelihood of becoming HIV+ depends on the route of transmission and the amount of virus in the infected tissue	36		
3.3 Viruses are selective in their host range and tissue tropism	37		
3.4 The virion is a genome delivery device	38		
3.5 The genomic contents of a virion are irrelevant for attachment, penetration, and uncoating	39		
3.6 Animal viruses attach to specific cells and can spread to multiple tissues	42		

3.7	Noncovalent intermolecular forces are responsible for attaching to host cells	43	3.26	Picornaviruses are naked viruses that release their genomic contents through pore formation	62
3.8	Most animal virus receptors are glycoproteins	44	3.27	Some enveloped viruses use membrane fusion with the outside surface of the cell for penetration	63
3.9	Animal virus receptors can be identified through genetic, biochemical, and immunological approaches	45	3.28	Vesicle fusion in neuroscience is a model for viral membrane fusion	63
3.10	Animal virus receptors can be identified through molecular cloning	46	3.29	HIV provides a model of membrane fusion triggered by a cascade of protein–protein interactions	65
3.11	Animal virus receptors can be identified through affinity chromatography	47	3.30	Influenza provides a model for viral envelope fusion triggered by acidification of an endocytic vesicle	67
3.12	Antibodies can be used to identify animal virus receptors	49	3.31	The destination for the virus genome may be the cytoplasm or the nucleus	67
3.13	Rhinovirus serves as a model for attachment by animal viruses lacking spikes	50	3.32	Subversion of the cellular cytoskeleton is critical for uncoating	67
3.14	Several independent lines of evidence indicate that ICAM-1 is the rhinovirus receptor	53	3.33	Viruses that enter an intact nucleus must manipulate gated nuclear pores	69
3.15	Experiments using molecular genetics support the conclusion that ICAM-1 is the rhinovirus receptor	53	3.34	Viruses introduce their genomes into the nucleus in a variety of ways	69
3.16	Structural biology experiments support the conclusion that ICAM-1 is the rhinovirus receptor	54	3.35	Adenovirus provides a model for uncoating that delivers the viral genome into the nucleus	71
3.17	Bioinformatics comparisons support the conclusion that ICAM-1 is the rhinovirus receptor	54	3.36	The unusual uncoating stages of reoviruses and poxviruses leave the virions partially intact in the cytoplasm	72
3.18	Influenza serves as a model for attachment by enveloped viruses	55	3.37	Viruses that penetrate plant cells face plant-specific barriers to infection	73
3.19	The influenza HA spike protein binds to sialic acids	56	3.38	Plant viruses are often transmitted by biting arthropod vectors	74
3.20	The second stage of the virus replication cycle includes both penetration and uncoating and, if necessary, transport to the nucleus	57		Essential concepts	76
3.21	Viruses subvert the two major eukaryotic mechanisms for internalizing particles	59		Questions	76
3.22	Many viruses subvert receptor-mediated endocytosis for penetration	59		Further reading	77
3.23	Herpesvirus penetrates the cell through phagocytosis	60			
3.24	Common methods for determining the mode of viral penetration include use of drugs and RNA interference	60			
3.25	The virion is a metastable particle primed for uncoating once irreversible attachment and penetration have occurred	61			
			4	GENE EXPRESSION AND GENOME REPLICATION IN MODEL BACTERIOPHAGES	79
			4.1	Bacterial host cell transcription is catalyzed by a multisubunit machine that catalyzes initiation, elongation, and termination	80
			4.2	Bacterial host cell and bacteriophage mRNA are typically polycistronic	82
			4.3	Transcription and translation in bacterial host cells and bacteriophages are nearly simultaneous because of the proximity of ribosomes and chromosomes	83

4.4	Bacterial translation initiation, elongation, and termination are controlled by translation factors	83	4.21	Bacteriophages T7 and λ both have three waves of gene expression but the molecular mechanisms controlling them differ	103
4.5	Bacteriophages, like all viruses, encode structural and nonstructural proteins	85	4.22	Bacteriophage λ genome replication occurs in two stages, through two different intermediates	104
4.6	The T7 bacteriophage has naked, complex virions and a large double-stranded DNA genome	86	4.23	Lambda genome replication requires phage proteins O and P and many subverted host proteins	105
4.7	Bacteriophage T7 encodes 55 proteins in genes that are physically grouped together by function	87	4.24	The abundance of host DnaA protein relative to the amount of phage DNA controls the switch to rolling-circle replication	105
4.8	Bacteriophage T7 proteins are expressed in three major waves	87	4.25	There are billions of other bacteriophages that regulate gene expression in various ways	106
4.9	The functions of bacteriophage proteins often correlate with the timing of their expression	88	4.26	Some bacteriophages have ssDNA, dsDNA, or (+) ssRNA genomes	107
4.10	Bacteriophage T7 gene expression is highly regulated at the level of transcription initiation	89	4.27	The replication cycles of ssDNA bacteriophages always include formation of a double-stranded replicative form	107
4.11	Bacterial host chromosome replication is regulated by the DnaA protein and occurs via a θ intermediate	91	4.28	Bacteriophage Φ X174 is of historical importance	108
4.12	Many bacterial proteins are needed to catalyze chromosome replication	93	4.29	Bacteriophage Φ X174 has extremely overlapping protein-coding sequences	108
4.13	Although many bacteriophages have linear dsDNA genomes, bacterial hosts cannot replicate the ends of linear DNA	94	4.30	Bacteriophage Φ X174 proteins are expressed in different amounts	109
4.14	T7 bacteriophage genome replication is catalyzed by one of the simplest known replication machines	95	4.31	A combination of mRNA levels and differential translation accounts for levels of bacteriophage Φ X174 protein expression	110
4.15	The λ bacteriophage has naked, complex virions and a large double-stranded DNA genome	98	4.32	Bacteriophage M13 genome replication is catalyzed by host proteins and occurs via a replicative form	111
4.16	Bacteriophage λ can cause lytic or long-term infections	99	4.33	Bacteriophage MS2 is a (+) ssRNA virus that encodes four proteins	113
4.17	There are three waves of gene expression during lytic λ replication	100	4.34	Bacteriophage MS2 protein abundance is controlled by secondary structure in the genome	114
4.18	The λ control region is responsible for early gene expression because of its promoters and the Cro and N proteins it encodes	101	4.35	Bacteriophage RdRp enzymes subvert abundant host proteins to create an efficient replicase complex	117
4.19	The λ N antitermination protein controls the onset of delayed-early gene expression	102	4.36	Bacteriophage proteins are common laboratory tools	118
4.20	The λ Q antitermination protein and Cro repressor protein control the switch to late gene expression	102	Essential concepts		125
			Questions		125
			Further reading		126

5	GENE EXPRESSION AND GENOME REPLICATION IN THE POSITIVE-STRAND RNA VIRUSES	129	5.19	Suppression of translation termination is necessary for production of the nonstructural P1234 Sindbis virus polyprotein	150
5.1	Class IV virus replication cycles have common gene expression and genome replication strategies	130	5.20	Sindbis virus uses an unusual mechanism to encode the TF protein	151
5.2	Terminal features of eukaryotic mRNA are essential for translation	131	5.21	A programmed -1 ribosome frameshift is needed to produce the togavirus TF protein	152
5.3	Monopartite Class IV (+) strand RNA viruses express multiple proteins from a single genome	132	5.22	The picornaviruses, flaviviruses, and togaviruses illustrate many common properties among (+) strand RNA viruses	153
5.4	Picornaviruses are models for the simplest (+) strand RNA viruses	132	5.23	Coronaviruses have long (+) strand RNA genomes and novel mechanisms of gene expression and genome replication	154
5.5	Class IV viruses such as poliovirus encode one or more polyproteins	134	5.24	Coronaviruses have enveloped spherical virions and encode conserved and species-specific accessory proteins	154
5.6	Class IV viruses such as poliovirus use proteolysis to release small proteins from viral polyproteins	137	5.25	Coronaviruses express a nested set of sgRNAs with leader and transcription regulating sequences	156
5.7	Translation of Class IV virus genomes occurs despite the lack of a 5' cap	138	5.26	Coronaviruses use a discontinuous mechanism for synthesis of replicative forms	157
5.8	Class IV virus genome replication occurs inside a virus replication compartment	139	5.27	Most coronavirus sgRNA is translated into a single protein	158
5.9	The picornavirus 3D ^{pol} is an RdRp and synthesizes a protein-based primer	140	5.28	Coronaviruses use a leaky scanning mechanism to synthesize proteins from overlapping sequences	158
5.10	Structural features of the viral genome are essential for replication of Class IV viral genomes	140	5.29	Coronaviruses proofread RNA during synthesis	159
5.11	Picornavirus genome replication occurs in four phases	141	5.30	Plants can also be infected by Class IV RNA viruses	161
5.12	Flaviviruses are models for simple enveloped (+) strand RNA viruses	143	5.31	Comparing Class IV viruses reveals common themes with variations	162
5.13	The linear (+) strand RNA flavivirus genomes have unusual termini	144		Essential concepts	163
5.14	Enveloped HCV encodes 10 proteins including several with transmembrane segments	144		Questions	164
5.15	Togaviruses are small enveloped viruses with replication cycles more complex than those of the flaviviruses	146		Further reading	165
5.16	Four different togavirus polyproteins are found inside infected cells	147	6	GENE EXPRESSION AND GENOME REPLICATION IN THE NEGATIVE-STRAND RNA VIRUSES	167
5.17	Different molecular events predominate early and late during togavirus infection	148	6.1	Study of two historically infamous Class V viruses, rabies and influenza, were instrumental in the development of molecular and cellular virology	167
5.18	Translation of togavirus sgRNA requires use of the downstream hairpin loop	148			

6.2	The mononegavirus replication cycle includes primary and secondary transcription catalyzed by the viral RdRp	168	7.2	Rotavirus A has a naked capsid with 3 protein layers enclosing 11 segments of dsRNA	192
6.3	Rhabdoviruses have linear (–) RNA genomes and encode five proteins	170	7.3	Rotavirus A encodes 13 proteins	194
6.4	Rhabdoviruses produce five mRNAs with 5' caps and polyadenylated 3' tails through a start–stop mechanism	171	7.4	Synthesis of rotavirus nucleic acids occurs in a fenestrated double-layered particle	194
6.5	Rhabdovirus genome replication occurs through the use of a complete antigenome cRNP as a template	173	7.5	Translation of rotavirus mRNA requires NSP3 and occurs in viroplasm formed by NSP2 and NSP5	195
6.6	The paramyxoviruses are mononegaviruses that use RNA editing for gene expression	175	7.6	Rotavirus genome replication precedes secondary transcription	197
6.7	Filoviruses are filamentous mononegaviruses that encode seven to nine proteins	177	Essential concepts		197
6.8	The filovirus VP30 protein, not found in other mononegaviruses, is required for transcription	179	Questions		198
6.9	Influenza is an example of an orthomyxovirus	179	Further reading		198
6.10	Of the 17 influenza A proteins, 9 are found in the virion	180			
6.11	Orthomyxovirus nucleic acid synthesis occurs in the host cell nucleus, not in the cytoplasm	181	8	GENE EXPRESSION AND GENOME REPLICATION IN THE DOUBLE-STRANDED DNA VIRUSES	199
6.12	The first step of transcription by influenza virus is cap snatching	181	8.1	DNA viruses can cause productive lytic infections, cellular transformation, or latent infections	200
6.13	An influenza cRNP intermediate is used as the template for genome replication	183	8.2	Most Class I animal viruses rely on host transcription machinery for gene expression	200
6.14	Arenavirus RNA genomes are ambisense	185	8.3	Eukaryotic transcription is affected by the state of the chromatin	201
6.15	Expression of the four arenavirus proteins reflects the ambisense nature of the genome	186	8.4	Eukaryotic capping, splicing, and polyadenylation occur co-transcriptionally	202
Essential concepts		187	8.5	Polyomaviruses are small DNA viruses with early and late gene expression	205
Questions		188	8.6	The SV40 polyomavirus encodes seven proteins in only 5,243 bp of DNA	206
Further reading		188	8.7	The synthesis of mRNA in SV40 is controlled by the noncoding control region	207
7	GENE EXPRESSION AND GENOME REPLICATION IN THE DOUBLE-STRANDED RNA VIRUSES	191	8.8	Late SV40 transcription is regulated by both host and viral proteins	208
7.1	The rotavirus replication cycle includes primary transcription, genome replication, and secondary transcription inside partially intact capsids in the host cytoplasm	192	8.9	Most Baltimore Class I viruses including polyomaviruses manipulate the eukaryotic cell cycle	210
			8.10	Most Class I viruses prevent or delay cellular apoptosis	212
			8.11	SV40 forces the host cell to express S-phase genes and uses large T antigen and host proteins for genome replication	212

8.12	SV40 genome replication requires viral and host proteins to form active DNA replication forks	213	8.27	Adenovirus shuts off translation of host mRNA, while ensuring translation of its own late mRNAs through a ribosome-shunting mechanism	230
8.13	The papillomavirus replication cycle is tied closely to the differentiation status of its host cell	214	8.28	DNA replication in adenovirus requires three viral proteins even though the genome is replicated in the host cell nucleus	231
8.14	Human papillomaviruses encode about 13 proteins that are translated from polycistronic mRNA	217	8.29	Herpesviruses have very large enveloped virions and large linear dsDNA genomes	233
8.15	The long control region of HPV regulates papillomavirus transcription in which pre-mRNA is subjected to alternative splicing	218	8.30	Lytic herpesvirus replication involves a cascade with several waves of gene expression	234
8.16	Leaky scanning, internal ribosome entry sites, and translation reinitiation lead to the expression of papillomavirus proteins from polycistronic mRNA	219	8.31	Groups of herpes simplex virus 1 proteins have functions relating to the timing of their expression	235
8.17	DNA replication in papillomaviruses is linked to host cell differentiation status	220	8.32	Waves of gene expression in herpesviruses are controlled by transcription activation and chromatin remodeling	236
8.18	Papillomaviruses use early proteins to manipulate the host cell cycle and apoptosis	221	8.33	Herpesvirus genome replication results in concatamers	236
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	222	8.34	Poxviruses are extremely large dsDNA viruses that replicate in the host cytoplasm	237
8.20	Adenoviruses are large dsDNA viruses with three waves of gene expression	223	8.35	Many vaccinia virus proteins are associated with the virion itself	238
8.21	Adenoviruses have large naked spherical capsids with prominent spikes and large linear dsDNA genomes	224	8.36	Vaccinia RNA polymerase transcribes genes in three waves using different transcription activators	239
8.22	Adenoviruses encode early, delayed-early, and late proteins	225	8.37	Vaccinia genome replication requires the unusual ends of the genome sequence	242
8.23	The large E1A protein is important for regulating the adenovirus cascade of gene expression	226	8.38	The synthetic demands on the host cell make vaccinia a possible anticancer treatment	244
8.24	Splicing of pre-mRNA was first discovered through studying adenovirus gene expression	226		Essential concepts	244
8.25	Both host cells and adenovirus rely on alternative splicing to encode multiple proteins using the same DNA sequence	227		Questions	245
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	228		Further reading	246
			9	GENE EXPRESSION AND GENOME REPLICATION IN THE SINGLE-STRANDED DNA VIRUSES	249
			9.1	The ssDNA viruses express their genes and replicate their genomes in the nucleus	250
			9.2	Circoviruses are tiny ssDNA viruses with circular genomes	250

9.3	Although their genomes are shorter than an average human gene, circoviruses encode at least four proteins	251	10.9	The HIV-1 accessory protein Rev is essential for exporting some viral mRNA from the nucleus	274
9.4	Both host and viral proteins are needed for circovirus genome replication	252	10.10	Retrovirus genome replication is accomplished by host Pol II	274
9.5	Parvoviruses are tiny ssDNA viruses with linear genomes having hairpins at both ends	253	10.11	HIV-1 is a candidate gene therapy vector for diseases that involve the immune cells normally targeted by HIV	274
9.6	The model parvovirus MVM encodes six proteins using alternative splicing	253	10.12	Hepadnaviruses are enveloped and have genomes containing both DNA and RNA in an unusual arrangement	276
9.7	The model parvovirus MVM uses a rolling-hairpin mechanism for genome replication	254	10.13	Hepadnaviruses use reverse transcription to amplify their genomes	276
Essential concepts		256	10.14	The cccDNA of HBV is not perfectly identical to the DNA in the infecting virion	277
Questions		256	10.15	The tiny HBV genome encodes eight proteins through alternative splicing, overlapping coding sequences, and alternative start codons	278
Further reading		257	10.16	HBV genome replication relies upon an elaborate reverse transcriptase mechanism	279
10	GENE EXPRESSION AND GENOME REPLICATION IN THE RETROVIRUSES AND HEPADNAVIRUSES	259	Essential concepts		283
10.1	Viral reverse transcriptases have polymerase and RNase H activity	262	Questions		284
10.2	Retroviruses are enveloped and have RNA genomes yet express their proteins from dsDNA	262	Further reading		284
10.3	Reverse transcription occurs during transport of the retroviral nucleic acid to the nucleus, through a discontinuous mechanism	264	11	ASSEMBLY, RELEASE, AND MATURATION	287
10.4	Retroviral integrase inserts the viral cDNA into a chromosome, forming proviral DNA that can be transcribed by host Pol II	266	11.1	The last stages of the virus replication cycle are assembly, release, and maturation	288
10.5	All retroviruses express eight essential proteins, whereas some such as HIV encode species-specific accessory proteins	266	11.2	Unlike cells, viruses assemble from their constituent parts	288
10.6	The retroviral LTR sequences interact with host proteins to regulate transcription	268	11.3	Virions more structurally complex than TMV also reproduce by assembly, not by division	290
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	269	11.4	Typical sites of assembly in eukaryotic viruses include the cytoplasm, plasma membrane, and nucleus	291
10.8	The HIV-1 accessory protein Tat is essential for viral gene expression	272	11.5	Eukaryotic virus assembly must take cellular protein localization into account	291
			11.6	Capsids and nucleocapsids associate with genomes using one of two general strategies	292
			11.7	Assembly of some viruses depends on DNA replication to provide the energy to fill the icosahedral heads	293

11.8	Assembly of some viruses depends on a packaging motor to fill the icosahedral heads	294	12.6	Some viruses delay apoptosis in order to complete their replication cycles before the host cell dies	318
11.9	Negative RNA viruses provide a model for concerted nucleocapsid assembly	295	12.7	Some viruses subvert apoptosis in order to complete their replication cycles	319
11.10	To assemble, some viruses require assistance from proteins not found in the virion	297	12.8	Viruses use the ubiquitin system to their advantage	319
11.11	Viruses acquire envelopes through one of two pathways	297	12.9	Viruses can block or subvert the cellular autophagy system	321
11.12	The helical vRNPs of influenza virus assemble first, followed by envelope acquisition at the plasma membrane	298	12.10	Viruses subvert or co-opt the misfolded protein response triggered in the endoplasmic reticulum	322
11.13	Coronaviruses assemble in the ER–Golgi intermediate compartment	299	12.11	Viruses modify internal membranes in order to create virus replication compartments	322
11.14	Some viruses require maturation reactions during release in order to form infectious virions	300	Essential concepts		325
11.15	Assembly of HIV occurs at the plasma membrane	300	Questions		325
11.16	Inhibition of HIV-1 maturation provides a classic example of structure–function research in pharmaceutical research	301	Further reading		326
11.17	Release from bacterial cells usually occurs by lysis	303	13 PERSISTENT VIRAL INFECTIONS	329	
11.18	Release from animal cells can occur by lysis	305	13.1	Some bacteriophages are temperate and can persist as genomes integrated into their hosts' chromosomes	330
11.19	Release from animal cells can occur by budding	305	13.2	Bacteriophage λ serves as a model for latency	330
11.20	Release from animal cells can occur by exocytosis	307	13.3	The amount of stable CII protein in the cell determines whether the phage genome becomes a prophage	332
11.21	Release from plant cells often occurs through biting arthropods	308	13.4	Activation of P_{RE} , P_L , and P_{antiQ} by CII results in lysogeny	332
Essential concepts		308	13.5	Stress triggers an exit from lysogeny	335
Questions		309	13.6	Some lysogens provide their bacterial hosts with virulence genes	336
Further reading		309	13.7	Prophages affect the survival of their bacterial hosts	336
12 VIRUS–HOST INTERACTIONS DURING LYTIC GROWTH	311		13.8	Persistent infections in humans include those with ongoing lytic replication and latent infections	338
12.1	All viruses subvert translation	312	13.9	Human immunodeficiency virus causes persistent infections	338
12.2	Bacteriophages subvert translation indirectly	312	13.10	Human herpesvirus 1 is a model for latent infections	339
12.3	Animal viruses have many strategies to block translation of host mRNA	314	13.11	Oncogenic viruses cause cancer through persistent infections	341
12.4	Animal viruses cause structural changes in host cells referred to as cytopathic effects	316	13.12	DNA viruses transform cells with oncoproteins that affect the cell cycle and apoptosis	343
12.5	Viruses affect host cell apoptosis	316	13.13	HPV oncoproteins E6 and E7 cause transformation	343

13.14	HPV E6 and E7 overexpression occurs when the virus genome recombines with a host chromosome	344
13.15	Merkel cell polyomavirus is also associated with human cancers	345
13.16	Epstein–Barr virus is an oncogenic herpesvirus	345
13.17	Latency-associated viral proteins are responsible for Epstein–Barr virus-induced oncogenesis	346
13.18	The Kaposi’s sarcoma herpesvirus also causes persistent oncogenic infections	347
13.19	Hepatocellular carcinoma is caused by persistent lytic viral infections	348
13.20	Retroviruses have two mechanisms by which they can cause cancer	349
13.21	Viral oncoproteins can be used to immortalize primary cell cultures	352
13.22	The human virome is largely uncharacterized but likely has effects on human physiology	352
	Essential concepts	353
	Questions	354
	Further reading	355

14 VIRAL EVASION OF INNATE HOST DEFENSES 357

14.1	Restriction enzymes are a component of innate immunity to bacteriophages	358
14.2	Bacteriophages have counterdefenses against restriction–modification systems	361
14.3	Human innate immune defenses operate on many levels	361
14.4	The human innate immune system is triggered by pattern recognition	361
14.5	Viruses have counterdefenses against pattern recognition	362
14.6	Innate immune responses include cytokine secretion	363
14.7	Interferon causes the antiviral state	363
14.8	Some viruses can evade the interferon response	366
14.9	Neutrophils are active during an innate immune response against viruses	369
14.10	Viruses manipulate immune system communication to evade the NET response	370
14.11	Inflammation is the hallmark of an innate immune response	370

14.12	In order to be recognized as healthy, all cells present endogenous antigens in MHC-I molecules	371
14.13	Cells infected by viruses produce and display viral antigens in MHC-I	372
14.14	Viruses have strategies to evade MHC-I presentation of viral antigens	372
14.15	Natural killer cells attack cells with reduced MHC-I display	373
14.16	The complement system targets enveloped viruses and cells infected by them	374
14.17	Some viruses can evade the complement system	374
14.18	Viral evasion strategies depend on the coding capacity of the virus	374
14.19	In vertebrates, if an innate immune reaction does not clear an infection, adaptive immunity comes into play	375
	Essential concepts	375
	Questions	376
	Further reading	377

15 VIRAL EVASION OF ADAPTIVE HOST DEFENSES 379

15.1	CRISPR-Cas is an adaptive immune response found in bacteria	380
15.2	Some bacteriophages can evade or subvert the CRISPR-Cas system	384
15.3	The human adaptive immune response includes cell-mediated and humoral immunity	385
15.4	The human adaptive immune response has specificity because it responds to epitopes	386
15.5	Professional antigen-presenting cells degrade exogenous antigens and display epitopes in MHC-II molecules	387
15.6	Some viruses evade MHC-II presentation	388
15.7	Lymphocytes that control viral infections have many properties in common	389
15.8	CD4+ T helper lymphocytes interact with viral epitopes displayed in MHC-II molecules	389
15.9	Antibodies are soluble B-cell receptors that bind to extracellular antigens such as virions	392

15.10	During an antiviral response, B cells differentiate to produce higher-affinity antibodies	393	16.10	Many antiviral drugs are nucleoside or nucleotide structural analogs that target the active site of viral polymerases	418
15.11	Viruses have strategies to evade or subvert the antibody response	394	16.11	Drugs to treat influenza target the uncoating and release stages of viral replication	419
15.12	CD8+ cytotoxic T lymphocytes are crucial for controlling viral infections	395	16.12	Drugs to treat COVID-19 target the viral polymerase or one of the viral proteases	420
15.13	Some viruses can evade the CTL response	396	16.13	Drugs to treat hepatitis C virus target the viral polymerase	420
15.14	Viruses that cause persistent infections evade immune clearance for a long period of time	396	16.14	Drugs to treat HIV target many stages of the virus replication cycle	421
15.15	The immune response to influenza serves as a comprehensive model for antiviral immune responses in general	398	16.15	Viral evolution occurs in response to selective pressure from antiviral drugs	423
15.16	Influenza provides a model for how a lytic virus evades both innate and adaptive immunity long enough to replicate	400	16.16	It might be possible to develop bacteriophage therapy to treat people with antibiotic-resistant bacterial infections	424
Essential concepts		402	16.17	Engineered viruses could in principle be used for gene therapy to treat cancer and other conditions	425
Questions		402	16.18	Gene therapy and oncolytic virus treatments currently in use	428
Further reading		403	16.19	Therapeutic applications of CRISPR-Cas technology	432
 16 MEDICAL APPLICATIONS OF MOLECULAR AND CELLULAR VIROLOGY		 405	16.20	Antibodies to treat viral infections	433
16.1	Vaccines are critical components of an effective public health system	406	Essential concepts		433
16.2	Attenuated vaccines are highly immunogenic because they can still replicate	407	Questions		434
16.3	Inactivated vaccines are composed of nonreplicating virions	408	Further reading		435
16.4	Subunit vaccines are composed of selected antigenic proteins	409	 17 VIRAL DIVERSITY, ORIGINS, AND EVOLUTION		 437
16.5	Although seasonal influenza vaccines are useful, a universal flu vaccine is highly sought after	410	17.1	The viral world is extremely diverse	438
16.6	Preventative HIV vaccines are in development	412	17.2	Satellite viruses and nucleic acids require co-infection with a virus to spread	439
16.7	Extreme antigenic variation is a problem for developing an HIV vaccine	414	17.3	Viroids are infectious RNA molecules found in plants	441
16.8	An effective HIV vaccine may require stimulating a strong CTL response	415	17.4	Transposons and introns are subviral entities	441
16.9	Antiviral drugs target proteins unique to viruses and essential for their replication cycle	415	17.5	Viruses have ancient origins	443
			17.6	Viral hallmark proteins can be used to trace evolutionary history	444
			17.7	Metagenomics is revolutionizing evolutionary understanding of viruses	446
			17.8	Viral genetic diversity arises through mutation and recombination	447

17.9	Genetic diversity among influenza A viruses arises through mutation and recombination	448	17.19	Viruses and subviral entities are common in the human genome	464
17.10	Influenza A spike proteins are particularly diverse	450	17.20	Viruses and subviral entities have strongly affected the evolution of organisms including humans	465
17.11	Variations among influenza A viruses reflect genetic drift and natural selection	450	17.21	Virology unites the biosphere	466
17.12	Pandemic influenza A strains have arisen through recombination	451	Essential concepts	466	
17.13	New pandemic influenza A strains may be able to arise through mutation	453	Questions	467	
17.14	Selective pressures and constraints influence viral evolution	454	Further reading	467	
17.15	Some viruses and hosts coevolve	456			
17.16	Medically dangerous emerging viruses are zoonotic	458	18	VIRUSES AND PUBLIC HEALTH (available online at www.routledge.com/cw/lostroh)	
17.17	HIV exhibits high levels of genetic diversity and transferred from apes to humans on four occasions	462	GLOSSARY	471	
17.18	HIV-1 has molecular features that reflect adaptation to humans	463	ANSWERS	495	
			INDEX	511	