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Pathogenic mechanisms of foodborne viral disease

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15.1 Introduction

Infection of a host with a virus unleashes various defense mechanisms based on the induction and secretion of cytokines, necessary to activate both innate (interferons, other cytokines) and adaptive immune responses to control and eliminate the virus. Our understanding of the dynamics of host–virus interaction has been greatly augmented by the ability to culture animal cells outside the organism,[59,269] and the ability to infect such cultured cells with viruses, first demonstrated with poliovirus.[326] The outcome of a virus infection is predicated upon the nature of these defense mechanisms and the ability of the infecting virus to block or evade such antiviral mechanisms. Depending on these factors, predicted outcomes of a virus infection can be the death of the cell or organism due to unrestricted viral replication; effective inhibition of virus replication resulting in the survival of the cell or organism; or the establishment of a persistent or latent infection with a limited amount of viral replication or viral gene expression, until some event disturbs the balance in favor of the virus.

Pathogenicity of a virus is frequently not the result of the toxic effect of a particular viral function on host cell. Programmed cell death (also know as apoptosis) is often induced by the host to eliminate the infected cells, whereas the virus may trigger apoptosis to facilitate virus spread and to circumvent the host immune response.[17,268] Certain cells of the immune system, such as cytotoxic T cells and natural killer (NK) cells, also mobilize to recognize and bind virus infected cells, and induce apoptosis. These virus and cell mediated mechanisms result in damage to infected organs, although the host organism may survive.

15.2 Factors contributing to the pathogenicity of viral foodborne diseases

The pathogenicity of foodborne viruses depend on both the stability of the virus in the environment, as well as virus–host interactions at several different levels. The route of entry into the organism, mechanism of virus spread, site of replication, effects of virus infection on cells, and the adaptive and innate antiviral responses all play roles in determining the pathogenicity of the virus. Recent studies show that the nutritional status of the host also contributes to the ultimate pathogenesis of the virus.[22,23,96] The presence of virus receptors at the cell surface determines virus susceptibility, and is genetically controlled.[181,234,323] A genetic component for susceptibility to human norovirus (NoV) infection is also suggested by the recent finding of cell surface receptors for this virus.[157,199] The role of the JAK-STAT pathway of interferon signaling during the replication of rotavirus, hepatitis A virus (HAV) and mouse norovirus (MNV) also point to the critical role played by the genetic background of the host in foodborne virus infections.[126,187,263,337]

15.2.1 Nature of the pathogens

Most foodborne viruses belong to the picornavirus, calicivirus, and reovirus families (Table 15.1). The total number of illnesses caused by these viruses has been estimated to be upwards of 30 million cases per year in the United States. However, most estimates indicate foods as a primary source of infection in only 5–6% of the incidences.[75,186,221] For reasons to be discussed in Section 15.6, direct demonstration of the presence of viruses in foods implicated in foodborne outbreaks have been achieved only in a few instances.[125,182,195] In terms of sheer numbers, Norwalk virus (NV) within the genus norovirus (NoV) is responsible for the vast majority of foodborne illnesses in the United States, followed by astro- and rotaviruses.[221] Hepatitis A virus comes in at a distant fourth, and the numbers have dropped somewhat following the development of an effective vaccine.[12] However, like many enteric viruses, the number of asymptomatic infections is high, and the reported cases may not reflect the actual number of infections. Asymptomatic individuals excrete the virus in the feces and are capable of spreading the virus via person-to-person contact, as well as through contaminated foods.[186] Poliovirus (PV) infections have been eradicated in most industrialized countries but remain endemic in some developing countries.[66] Circulating vaccine-derived poliovirus (cVDPV), however, may be of concern to non-immunized populations.[43,180] Hepatitis E virus (HEV), was once thought to be mainly a waterborne disease in the third world; however, many industrialized countries including the United States, Japan, and countries in the European Union have recently reported sporadic HEV infections from farm and game animals.[100] Particularly intriguing are reports from Japan that people who consumed undercooked meat from wild boars and deer have contracted the disease.[300]

These reports raise the question whether other viruses, such as avian influenza or hantaviruses not normally associated with foodborne outbreaks,

Table 15.1 Viruses transmitted by food or water

Virus species	Classification	Disease
Norovirus	Calicivirus	Gastoenteritis
Poliovirus	Picornavirus	Paralytic poliomyelitis
Coxsackievirus (Human enterovirus A–C)	Picornavirus	Gastroenteritis Respiratory infections Juvenile diabetes Meningitis Myocarditis, pericarditis
Echovirus (Human enterovirus B)	Picornavirus	Gastroenteritis Respiratory and skin infections
Hepatitis A virus	Picornavirus	Hepatitis
Hepatitis E virus	Unclassified	Hepatitis
Astrovirus	Astrovirus	Gastroenteritis
Rotavirus	Reovirus	Gastroenteritis
Adenovirus 40,41	Adenovirus	Gastroenteritis

Additional details regarding taxonomic classification can be obtained at www.ncbi.nlm.nih.gov/ICTVdb/Ictv/index.htm.

also could spread by contaminated foods. Mortality due to foodborne illnesses remains low in the healthy immunocompetent population, but increased mortality due to HAV infection is observed in immunocompromised people,[186] and for unknown reasons, among pregnant women infected with HEV.[218] Rotavirus remains a leading cause of infantile gastroenteritis and infant mortality in the third world.[57] At present, there are no effective vaccines for HEV, rotavirus, and norovirus. Foodborne infections due to coxsackievirus (CV) or echovirus (EV) are less frequent.

15.2.2 Viral genomes

The genomes of representative members of all categories of foodborne viruses have been cloned and sequenced.[13,78,164,169,184,189,232,302,311] With the exception of rotavirus (family Reoviridae), which is a double-stranded RNA (dsRNA) virus with a segmented genome, the genomes of major foodborne viruses are single-stranded RNAs of positive polarity (i.e. viral genome is mRNA). The replication of RNA viral genomes are error-prone owing to the lack of the proof-reading ability of RNA viral replicases; thus RNA viral genomes are present in infected cells as quasispecies.[72,129] A quasispecies is defined as a collection of multiple sequences of a single strain, each sequence differing from the other by a few nucleotides. As shown in Fig. 15.1, the structural organization, gene expression, and replication strategies of the two major groups of foodborne viruses, namely picorna- and caliciviruses are similar but not identical.[24,55,193,291]

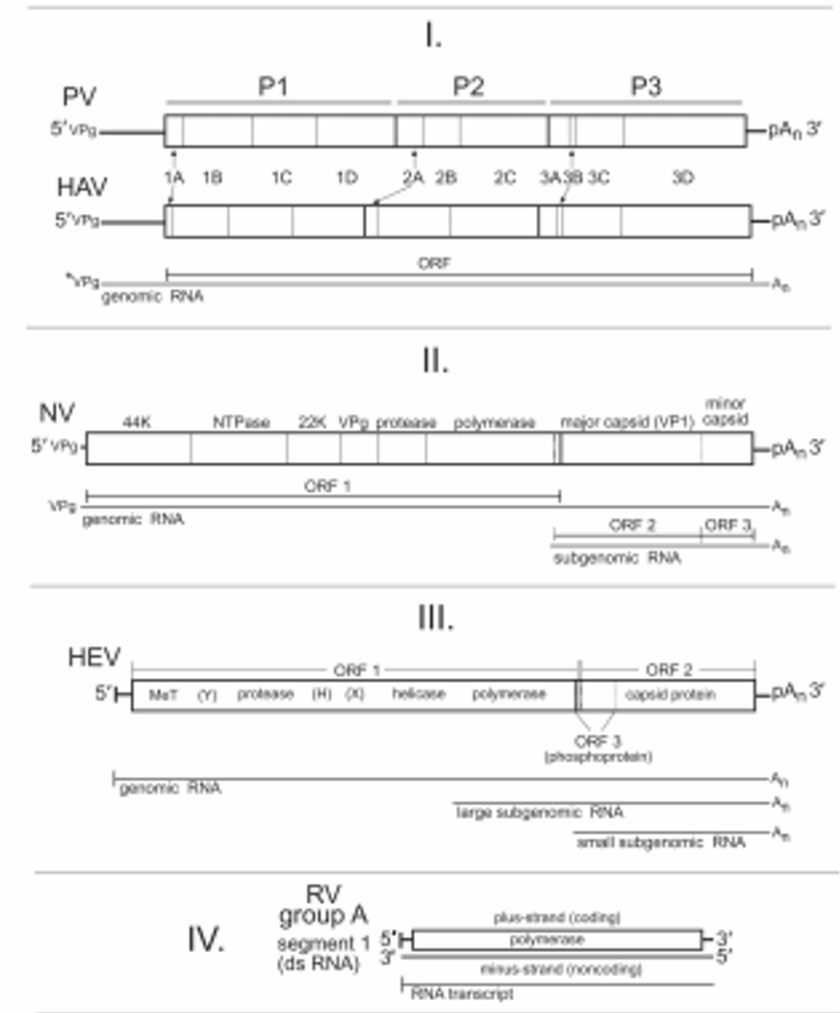

Fig. 15.1 Diagrammatic comparison of selected genomes of major foodborne viruses. Comparison of representative picornavirus species (panel I), poliovirus (PV) and hepatitis A virus (HAV); norovirus species, Norwalk virus (NV) (panel II); hepatitis E virus (HEV) (panel III) and rotavirus (RV), group A (panel IV) are illustrated.

Information derived from published materials was used to generate Fig. 15.1 and the references cited herein may be referred to as a guide for obtaining further details regarding genome organization and expression of the various encoded proteins.[9,86,104,131,150,164,184,238] The open boxed regions represent the coding regions for the respective genomes. Vertical demarcations within the boxed regions indicate the amino- and carboxy-terminal boundaries of fully processed viral proteins. The relative locations of the proline-rich hinge region (H), X and Y domains (X and Y in parentheses) encoded by HEV ORF1 are also

indicated. The significance of stippled versus solid demarcations is discussed further below. The 5′ and 3′ untranslated regions (UTRs) are shown as solid lines and the relative differences in nucleotide length of the UTRs among the various genomes is schematically illustrated by the differences in length of the line. Beneath each genome, horizontal lines define the genomic and subgenomic RNAs and delineate the respectively encoded open reading frames (ORFs), in order to highlight the differences that exist among the virus groups regarding the number, size, and genomic location of the viral genome/transcripts utilized by these viruses to produce their respective viral proteins. Panel I–III viruses have polyadenylated genomes. Their genome is the primary viral transcript used for initial viral protein translation upon host cell infection. Group I viruses encode a single polyprotein identified by one ORF, whereby capsid (i.e. structural) proteins are derived from the P1 region and nonstructural proteins (e.g. protease, RNA polymerase) are derived from the P2 and P3 regions. Group II and III viruses produced nonstructural proteins (ORF1) from their primary transcript and also produce subgenomic RNAs during infection for translation of their structural proteins, and putative accessory phosphoprotein for HEV (ORFs 2 and 3). ORF1 is differentiated from ORFs 2 and 3 by solid versus stippled vertical lines, respectively, within the open boxes. Viruses in group I and II are not capped but rather have a covalently attached VPg (viral protein g) moiety at the 5′ end of the genome. For PV, this moiety is removed (*) by a cellular enzyme following infection. Viruses in group III and IV have a 7 mG cap moiety at the 5′ end of their genomes. Unlike the single-stranded, positive polarity of the viruses in groups I–III, the rotaviruses (group IV) genomes are double-stranded and segmented. Rotaviruses contain 11 dsRNA segments which encode 12 proteins, whereby the 11th segment encodes two proteins. Shown as a representative segment in this figure, segment 1 encodes for the viral RNA polymerase. Each rotavirus genome segment is transcribed (from the negative strand) into an RNA transcript which is 7 mG capped prior to the translation of its ORF. It is important to note that actual nucleotide lengths and distances are not drawn to scale.

The common structural features include a genome linked protein VPg, a 5′ untranslated region (UTR), and a 3′ terminal poly(A) sequence. The 5′ UTR of picornaviruses is larger than the 5′ UTR in caliciviruses, and houses the internal ribosomal entry segment or IRES (Fig. 15.2). As depicted and discussed in Fig. 15.2, viral RNA translation occurs in a cap-independent manner as opposed to the translation of host cellular mRNAs.[54,78,184,194,253,311] The major difference is that picornaviral genomes are translated as a single polyprotein (Fig. 15.1), which are then cleaved by viral coded proteases 2A and 3C (only 3C in the case of HAV) to produce mature viral proteins. Calicivirus genomes, on the other hand, are organized into three different ORFs, and are translated into three different proteins, with the lone viral protease 3C performing all maturation cleavages (Fig. 15.1). Recent studies indicate that the 5′ terminal IRES also plays a significant role in pathogenesis of picornaviruses (see Section 15.2.5). For a full discussion of the various aspects of viral RNA synthesis, protein

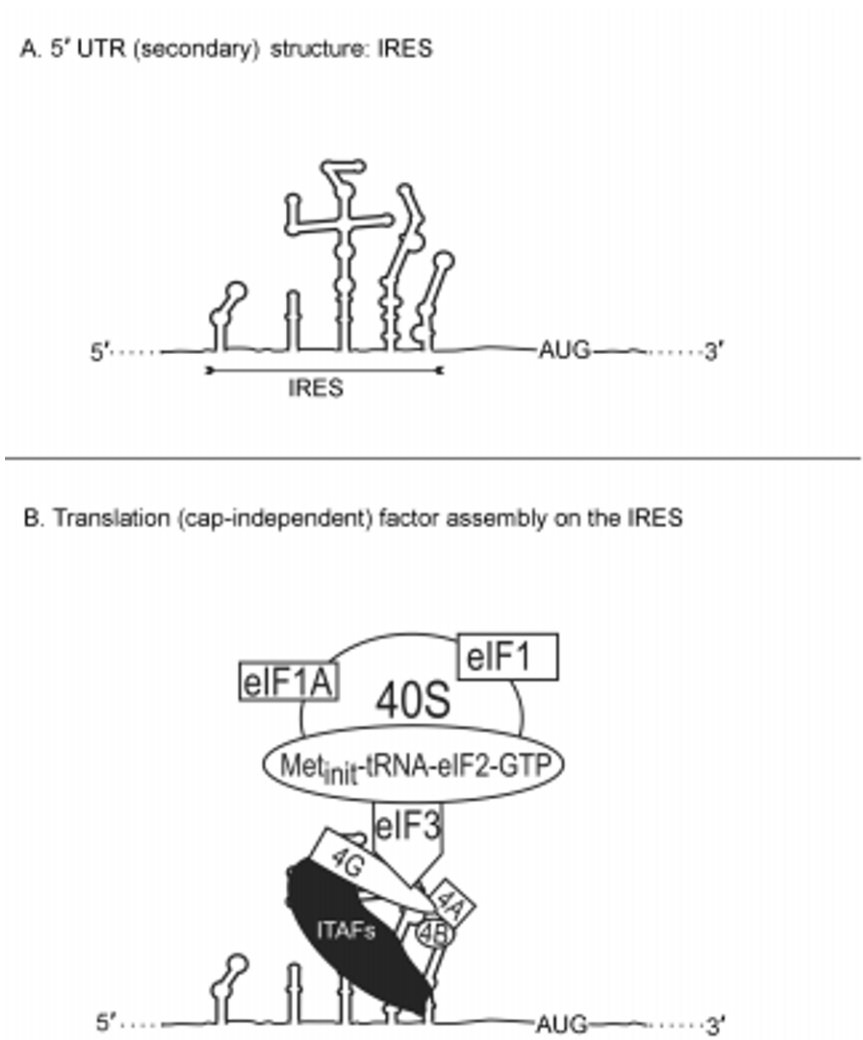

Fig. 15.2 Picornavirus internal ribosome entry sequence (IRES): structure and cap-independent translation factor assembly.

translation, and processing, the reader is referred to several recent reviews.[131,135,150,216,291] Unlike picorna- and calicivirus genomes, a 7-methyl guanosine cap structure[284] is present in the genomes of HEV,[172,208,251] and rotaviruses.[116] The double-stranded RNA genome of rotavirus is not active as mRNA.[104,116,164,240] Instead, the minus strand of each segment of the genome is first transcribed to yield the plus (coding) strand and then capped by virus coded capping enzymes, which is then translated to produce viral proteins. Unlike other foodborne viruses, neither the genomic nor the newly synthesized rotaviral RNAs are polyadenylated at the 3′ end.[229]

15.2.3 Viral capsid

The basic virion structure of all viruses, including foodborne viruses, is a nucleic acid core surrounded by a protein shell.[135,239,266,291] Rotavirus is unique in having two concentric protein shells forming the capsid, each having a different set of structural proteins. The rotavirus capsid also contains the viral RNA polymerase and capping enzymes.[229] The purpose of the protein shell or capsid is to protect the nucleic acid genome from damage by physical and chemical agents. Foodborne viruses lack a lipid envelope/membrane that is a feature of many of the larger DNA and RNA viruses which may explain their resistance to bile salts *in vivo* and detergents and organic solvents *in vitro*.[135,266] However, the enveloped avian influenza virus is stable at the low pH of the gut in birds and is excreted in bird feces at very high concentrations.[301] Thus, the absence of an envelope is not the only determinant of resistance to bile. The proteins of the capsid bind to specific receptors on cell surfaces in order to gain viral entry into the cell, and are important determinants of the host range and pathogenicity of the virus (see Section 15.3.1). The primary and higher-order structures of the capsid proteins also play critical roles in determining heat and acid stability, as well as resistance to stomach and intestinal proteases. Recent studies[230,231] showed that even digestion with proteinase K failed to expose the HAV genome to RNase activity as measured by reverse-transcription polymerase chain reaction (RT-PCR) unless the virions were also treated with heat or other chemical agents. The stability of enteric viruses to physical and chemical agents has been the subject of much experimentation and controversy owing to the lack of a standardized set of conditions to be followed for such studies.[83,84,159,207,220,236,273] Constituents of food matrices (such as sucrose in strawberry mash) also affect the heat stability of HAV.[35,87] NoV has not been grown in cell culture; thus the heat and acid stability is inferred from either experiments with a surrogate virus, such as the feline calicivirus,[97,230,288] or by the resistance of the viral genome to various treatments as detected by RT-PCR.[207,231] However, feline calicivirus infects via the respiratory route, and therefore cannot be considered truly representative of enteric human caliciviruses. The RT-PCR approach (Fig. 15.3) suffers from the small target size of the amplicon, which may not detect damage to the genome over its entire length.[34] The RT-PCR approach also suffers from the disadvantage that inactivated virus often produce positive RT-PCR signal, particularly when a small region of the viral genome is targeted for amplification.[34,230,231] The apparent lack of correlation between infectivity and nucleic acid detection by molecular methods is of great concern to food virologists and regulatory agencies concerned with food safety (see Section 15.6).

15.2.4 Routes of entry

Foodborne viruses gain entry to the host organism via the alimentary tract, and replicate initially in the small intestine before gaining access to the body via the lymph nodes.[10,53,73,104,131,225,339] Thus, the survival of the incoming infectious virus in the hostile environment of stomach acids, bile, and proteolytic enzymes

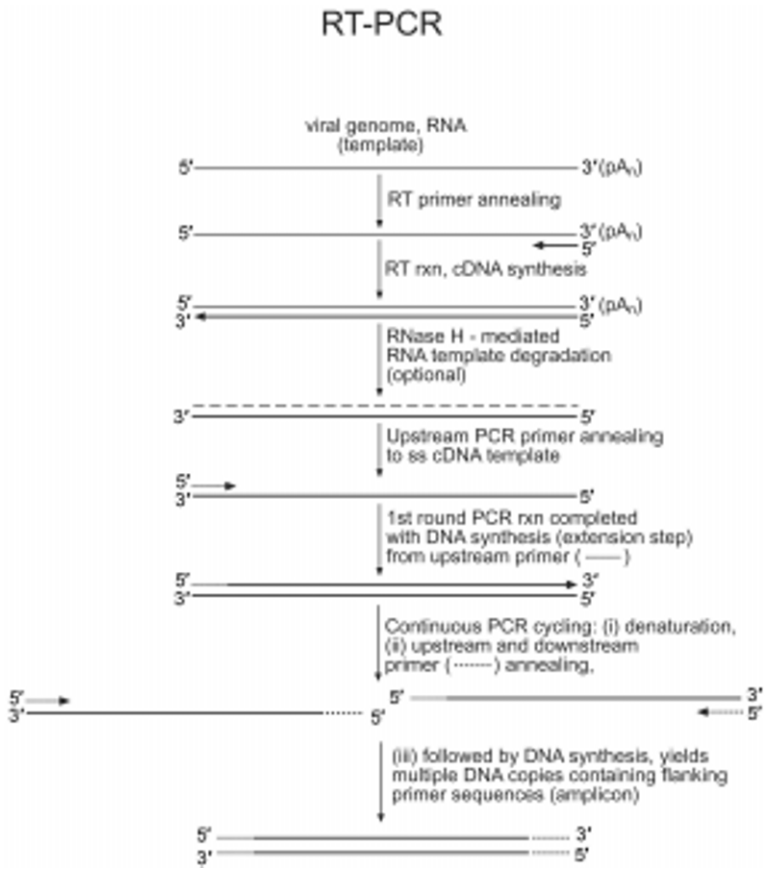

Fig. 15.3 Overview of essential steps and reactions involved in the targeted amplification of a specific RNA sequence or genomic region by the application of reverse transcription-polymerase chain reaction (RT-PCR). Viral RNA is annealed to a primer and copied into the complementary strand (cDNA) by the enzyme reverse transcriptase (RT). The primer may be complementary to sequences within the genome, the polyA region (if present) or be designed to target a broader range of sequences through the application of degenerate primer design. Degradation of the RNA strand may be accomplished through the use of an RT having endogenous RNaseH activity or by including the enzyme into the procedure (an optional step). A thermostable DNA polymerase, in combination with PCR primers which are designed as complementary sequences to the cDNA, is used to complete the PCR amplification. The typical PCR has a number of steps/cycles which usually include template denaturation, primer annealing, and primer extension. The final product of PCR is double-stranded DNA, termed an amplicon. The conditions (such as time and temperature) for each of the steps, as well as the total number of cycles, in the PCR are in part determined by the length and primary sequence of the primers, predicted length of amplicon, and target concentration. Since the target for PCR is single-stranded cDNA, the first round of PCR begins from the upstream, annealed primer. Following extension and denaturation, two complementary target DNA strands become available for both upstream and downstream primer annealing and extension. PCR cycling yields multiple copies of a sequence flanked by primer sequences. The length of the amplicon is determined by the relative position of the upstream and downstream primers on the target.

in the gastrointestinal tract all contribute to its pathogenicity. Proteases such as trypsin, elastase, pancreatin, and chymotrypsin convert non-infectious rotavirus to infectious subvirion particles (ISVPs) through the cleavage of the capsid protein VP4 to two polypeptides.[7,42,106] One of these, VP5, is responsible for the binding to the cell membrane and internalization of the virus.[42,106,226] Stomach and intestinal proteases, low pH and/or a combination of these processes result in the cleavage of capsid protein VPI and enhanced infectivity and antigenicity of HAV,[38,196] PV,[114,261] and astrovirus.[20] Virus-like particles (VLPs) assembled in insect cells infected with a recombinant baculovirus expressing the NoV capsid protein undergo proteolytic cleavage of the 58 kDa capsid protein when treated with the intestinal protease trypsin.[137] The model of infection that emerges from these studies is one in which stomach acids and intestinal proteases expose receptor binding sites in the capsid proteins enhancing infectivity and pathogenicity of the enteric viruses.

15.2.5 Viral genes and pathogenicity

Many recent insights into the pathogenic mechanisms of enteroviruses have come from the development of transgenic mouse models expressing the human poliovirus receptor.[234] Mouse is a natural host of coxsackievirus (CV) and mouse models for the investigation of CV pathology have been extensively utilized.[23,154] In addition, primate models for PV and HAV have been the source of much of the information currently available. *In vitro* studies with mammalian cells in culture, as well as in cell-free systems, have been invaluable in elucidating many of the molecular mechanisms of virus replication, and host defenses such as apoptosis.[80,121,323] These studies indicate that the viral encoded proteases 2A and 3C, as well as the 5′ UTR encompassing the IRES, play key roles in the pathogenicity of picornaviruses.

The viral IRES

As shown in Fig. 15.1, the 5′ end of all picornavirus and calicivirus genomes contain an untranslated region or UTR. The relatively long UTR of picornaviruses houses the IRES (Fig. 15.2), and is responsible for the internal initiation of protein synthesis from viral mRNA in a cap-independent manner.[24,55,193,271,291] Panel A of Fig. 15.2 shows the IRESs identified for picornaviruses are located in their 5′ UTR. Based on their conserved RNA sequences and secondary structures, most picornavirus IRESs can be divided into two groups, Type I and Type II. Type I IRESs are present in enteroviruses and human rhinovirus while Type II IRESs are present in other picornaviruses such as cardioviruses and aphthoviruses. A possible third Type III IRES has been identified in hepatitis A virus. A representative IRES structure is shown in panel A to illustrate the highly ordered secondary structures present in IRESs.[24,216,271] Panel B shows the mechanism of cap-independent translation of picornaviral genomic RNA (via the IRES structure). It is believed that 40S ribosomal subunit recognition of an IRES and subsequent translation factor assembly is facilitated in part by RNA–protein

interactions; translation efficiency is further augmented though interaction with other cellular factors termed IRES-trans-acting factors (ITAFs). The illustration depicts a general representation of translation factor assembly at an IRES (refer to Fig. 15.4 for a description of the various translation factors depicted in this figure). eIF4G (4G) has been reported to participate in cap-independent translation either as an intact protein (e.g. HAV IRES)[45] or in the truncated form (illustrated in Fig. 15.2) generated following enterovirus protease cleavage (see Fig. 15.4). ITAFs that are reported to be involved in interaction with picornavirus (e.g. enterovirus and hepatitis A virus) IRESs include pyrimidine tract binding protein, poly(rC) binding proteins and La autoantigen.[24,120,149,216]

There is general agreement that the IRES of different picornaviruses differ in their ability to initiate protein synthesis in cultured cells and cell-free systems that correlates with their ability to induce a cytopathic effect (cpe) in tissue culture cells.[44,49,52,128,241,260,276,341] The IRES may even be responsible for determining the tissue or species specificity,[49] pathogenesis and attenuation phenotype,[181,209,297,298] and efficiency of translation of the viral genome.[52,209,244] In particular, nucleotides at positions 472, 480, and 481 of the PV IRES have been reported as critical determinants of neurovirulence, although nucleotide changes elsewhere in the genome also contribute to the virulence phenotype.[177] Replacement of the PV IRES with the IRES from rhinovirus abolished the virulence phenotype.[133,134] In contrast, the IRES of cell-culture adapted HAV are more efficient in initiating protein synthesis *in vitro* and *in vivo*.[276,330,331,340]

The IRES of cytopathic strains of HAV (e.g. HM 175/18f) have a higher efficiency of translation initiation than the non-cytopathic strains, apparently because of decreased binding of the IRES to GAPDH,[275,276,340,341] a protein known to bind and destabilize RNA secondary structure. The significance of the low efficiency of translation initiation *in vitro* of HAV IRES to virulence is questionable, since chimeric HAV viruses with an EMCV IRES, although more efficient in translation, nevertheless showed no effect on the replication phenotype,[165] and the culture adapted rapidly replicating P16 strain is attenuated for virulence in animal models.[175,223,287,305] Attenuated strains of PV, on the other hand, are less efficient than their virulent parent strains in protein synthesis and host shut-off,[297,298] although such differences may be cell-line specific.[190] Clearly, IRES efficiency *in vitro* is not the sole determinant of pathogenicity in susceptible animals. The importance of other mechanisms is emphasized by the isolation of a recombinant vaccine derived poliovirus (VDPV) from a child with paralytic poliomyelitis that had the Sabin type-3 capsid antigenic site replaced by a Type II site due to recombination.[215] Remarkably, a six amino acid change in the antigenic site 1 of PV-1 (Mahoney) by the sequence of PV-2 (Lansing) rendered the non-pathogenic Mahoney strain to neurovirulence in mice.[214]

The 2A protease

The pathogenicity of foodborne viruses is dependent on their ability to kill the infected cells by either necrosis or apoptosis. Enteroviruses such as PV and CV that are highly cytolytic to cultured cells use a virally coded protease 2A-

mediated cleavage of eIF4G and other cellular proteins such as PABP (polyA binding protein) involved in translation to inhibit cellular protein synthesis (host shut-off).[4,5,107,170,178,191,255] As shown in Fig. 15.4, the host shut-off occurs because cellular mRNAs having a 5′ 7-methyl guanosine cap require functional interaction between eIF4G and eIF4E (cap binding protein) for translation, whereas the viral RNA translation initiated by an IRES remains unaffected by such cleavage events (Fig. 15.2).[24,55,247,278]

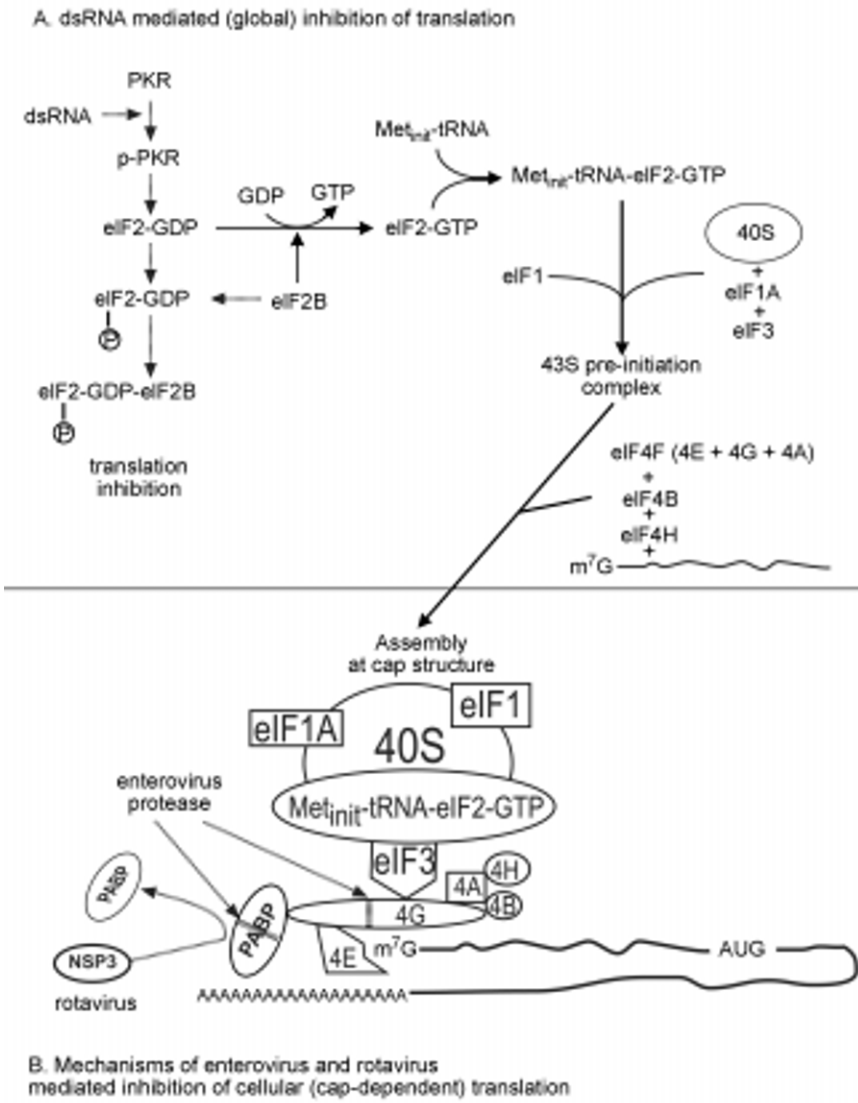

Fig. 15.4 Illustration of dsRNA and virus mediated inhibition of cellular protein synthesis.

The cap-dependent translation of cellular mRNAs shown in Fig. 15.4 is a cyclical process involving recruitment, dissociation, and recycling of various components and can be essentially divided into three phases: initiation, elongation, and termination. The study of cellular factors and mechanisms involved in this highly coordinated, regulated and complex process is the subject of numerous reviews.[24,55,74,120,149] The following discussion is limited to the events regarding translation initiation and the modes by which enteric viruses may affect this process. As shown in panel A, the recruitment of the cap binding protein complex (eIF4F) to the mRNA 5′ cap moiety m7G may be considered the beginning of translation initiation. The eIF4F complex contains the cap binding protein [eIF4E (4E)], and RNA helicase [eIF4A (4A)] and a scaffold protein [eIF4G (4G)]. The factors eIF4B (4B) and eIF4H (4H) promote RNA helicase activity through association with eIF4F. The 40S ribosome-eIF3-eIF1A complex is converted to the 43S pre-initiation complex following interaction with a ternary complex consisting of eIF2, methionyl-initiator tRNA and (eIF2-bound) GTP and the addition of eIF1.

In panel B of Fig. 15.4, the 43S pre-initiation complex subsequently associates with eIF4F through a bridging interaction between eIF3 and the eIF4G subunit to form the core of the 48S initiation complex. The tethering of eIF4F to the 43S complex is important for cap-dependent recognition and translation initiation. The scaffolding function of eIF4G is provided by its binding domains for eIF4E, eIF3, eIF4A, an eIF4A associated kinase (Mnk1), and a translation enhancing factor, poly(A) binding protein (PABP).

Not shown in Fig. 15.4 is the 5′ to 3′ mRNA scanning of the initiation complex to the start codon AUG (methionine), thus beginning the elongation phase of translation, where eIF5 facilitates the release of eIFs from the complex (factors are recycled). Following the hydrolysis of eIF2-bound GTP to GDP (panel A) which is facilitated by eIF2B, the cycle of factor assembly and translation initiation begins again. The enterovirus 2A and 3C proteases can inhibit cap-dependent translation via cleavage of factors such as eIF4G and PABP which disrupt the critical scaffolding function of these factors. The rotavirus nonstructural protein 3 (NSP3) interacts with the 3′ end of its viral mRNAs and can substitute for PABP, thereby displacing PABP from interaction with the initiation complex and negatively affecting translation. Translation initiation can be further regulated not only by the level and availability of the various factors described above, but also ‘globally’ by the modification state (e.g. phosphorylation) of particular subunits. As illustrated in panel A of Fig. 15.4, phosphorylation of the alpha subunit of eIF2 prevents eIF2B-mediated exchange of GDP for GTP and can occur (e.g. via dsRNA mediated activation of PKR, also see Fig. 17.5) following induction of an antiviral response, thus leading to a reduction in protein synthesis. It is of interest to note that at least three other kinases can also mediate this phosphorylation event, HRI (heme-regulated inhibitor), GCN2 (general control non-depressable 2) and PERK (PKR-like endiplasmic reticulum kinase). The latter is notable because of its connection to ER-stress induced apoptosis.[51,224]

HAV infection of permissive cells does not induce host shut-off. HAV lacks detectable 2A protease activity,[187,201,274] and HAV IRES driven translation requires a functional eIF4G moiety.[45] However, there may be other as yet unidentified functions of HAV 2A, since *in vitro* translation of capped mRNA was inhibited by HAV 2A,[91,210] and the 2A gene was required for maximum virulence.[21,101,139] Rotavirus uses a different mechanism. The viral NSP3 protein binds specifically to the conserved viral 3′ end sequences, and effectively out-competes PABP for interaction with eIF4G, thereby disrupting the interaction between PABP and eIF4G on cellular mRNAs.[237,245] The two consequences of NSP3 expression, therefore, are reduced efficiency of host mRNA translation and circularization-mediated translational enhancement of rotavirus mRNAs (Fig. 15.4).

The 3C protease

All picornaviruses, including HAV, as well as caliciviruses encode a second protease called 3C. The 3C protease of picorna- and caliciviruses is responsible for almost all the maturation cleavages of the viral polyprotein.[239,247,274,278] There is, however, some evidence to suggest that protein processing intermediates from entero-, hepato-, and calicivirus, such as the 3CD (protease-polymerase) are multifunctional in their precursor form and may interact with other viral proteins and viral RNA, thus affecting viral RNA replication.[27,137,138,338] In addition, the enterovirus 3C protease cleaves a variety of cellular proteins involved in transcriptional and translational regulation, including PABP, TATA binding protein, TFIIIC, CREB, and OCT-1,[247,325] and is directly involved in virus induced cell-killing by apoptosis.[18] No information is currently available on the effect of HAV or NoV 3C proteases on cellular proteins.

15.3 Mechanisms of host cell invasion

The primary mode for natural infection by enteric viruses is by ingestion, although a respiratory route of transmission may also be important for some enteroviruses[252] and norovirus.[213] In general, the age, gender, and socio-economic status of an infected individual or population can be factors that influence the probability of infection, severity of illness and sequellae, and prognosis for recovery from enteric virus infection.

Enteric virus infection may result in clinically defined illness or in asymtopmatic infection.[343] Norovirus and rotavirus infections typically give rise to localized disease due to primary replication that is generally limited to the small intestinal epithelium, although the rare development of systemic sequellae have been attributed to rotavirus infection possibly a consequence of viremia.[71,157,254] Enteroviruses initially produce a localized infection in intestinal cells or in mucosal tissue (Peyer's patches, tonsils), followed by replication in cervical and mesenteric lymphoid tissue. A systemic (viremia) phase may follow, leading to

infection/replication of other tissues/organs resulting in non-enteric illnesses such as aseptic meningitis, mild paralytic disease, acute hemorrhagic conjunctivitis or poliomyelitis (poliovirus).[238] This is in contrast to the primarily systemic infection and illness (e.g. hepatitis) observed following hepatic infection with hepatitis A virus.[150] As with non-enteric viral diseases, illnesses caused by an enteric viral infection may be due to a direct and/or immunolopathologic consequence of virus replication in the infected tissue/organ.

15.3.1 Virus binding and cell surface receptors

Once within the host, viruses gain entry into the target cell population by the interaction between the viral capsid and receptors and co-receptors on the cell surface.[90,318] Receptors and co-receptors involved in virus binding are listed for selected enteric viruses in Table 15.2. Many of these cell receptors participate in cell-specific functions such as signal transduction (e.g. DAF/CD55, integrins), cell-to-cell interactions (e.g. HBGAs, JAM), receptor-mediated uptake of nutrients/metabolic factors, cell matrix attachment (e.g. integrins) and immunologic recognition (e.g. ICAM-1, HBGAs). The cellular functions of some receptors such as the poliovirus receptor (PVR) (CD155) and HAV cellular receptor (havcr-1) remain unknown.[11,111,222,267,285] Some viruses interact with secondary receptors (or co-receptors) after the initial binding to and interaction with its primary receptor.

Table 15.2 Examples of cell receptors known or implicated in virus binding

Virus/species/serotype	Receptor/co-receptor[a]	Reference
Poliovirus	PVR(CD155)	222
Coxsackievirus B3	CAR/CD55*	31, 32, 282, 309
Coxsackievirus B1, 3, 5	CD55/αvβ6	1, 30, 282
Coxsackie A9	Integrin αvβ3, αvβ6/GRP78, MHC-1	262, 312–314, 335
Coxsackievirus A21	CD55/ICAM-1	281
Echovirus 22	Integrin αvβ3, αvβ1	250
Echovirus 11	CD55/α2β1, αvβ1	211, 312
Echovirus 1, 8	Integrin α2β1	29, 235, 314
Echovirus 3, 6, 7, 12, 13, 20, 21, 24, 29, 33	CD55	30, 185, 238, 249
Rotavirus	SA (oligosaccharides), Gangliosides, Integrin α2β1/ Integrin α2β1, α4β1, JAM	19, 113, 146, 203, 264, 296
Norovirus	HBGAs, Lewis antigen	156, 199
Hepatitis A virus	havcr-1	111

[a] PVR means poliovirus receptor. CAR means coxsackievirus-adenovirus receptor. CD means cluster of differentiation. GRP means glucose response protein. MHC-1 means major histocompatibility complex-1. ICAM means intercellular adhesion molecule. SA means sialic acid containing receptors. JAM is junction adhesion molecule. HBGAs mean histo-blood group antigens. Havcr-1 means hepatitis A virus receptor.
* CD55 is also reported as DAF (decay accelerating factor).

Picornaviruses
Picornavirus capsids are composed of four proteins (VP1–4) arranged in an icosahedral symmetry. Their surface architecture and receptor binding specificity differ due primarily to amino acid differences, and the tissue distribution/expression of receptors contributes to viral tropism and pathogenesis.[215,234,238,252] Some virus serotypes within the same species (e.g. coxsackieviruses) have been reported to use different cell receptors depending upon the target cell (Table 15.2).

Norovirus
In the absence of a suitable cell-culture model for NoV, recombinant virus-like particles (rVLP)[167,168] produced in insect cells have been used for the study of virus-cell interactions.[136,152,332] These studies have identified the human histo-blood group antigens (HBGAs), present on red blood and mucosal epithelial cells, saliva and intestinal fluid as the putative NoV receptor.[157,212,332] HBGAs were subsequently implicated in resistance or susceptibility to NoV infection, as well as the binding of the major capsid protein VP1 of NoV genogroups.[151,156,199,303,304]

Rotavirus
Human infections by rotavirus are attributed to serogroups A, B, and C. They primarily infect mature enterocytes of the small intestinal villi. However, some evidence indicates a possibly broader host tissue range based on reports of extra-intestinal spread following initial infection.[57,206,225,258] Both sialic-acid containing receptors[93,174,203] and members of the integrin family of receptors $\alpha 2\beta 1$ and $\alpha 4\beta 1$[82,146] can serve as the primary receptors for capsid proteins VP4, VP7, or VP5, the protease cleavage product of VP4.

15.3.2 Different (multiple) virus species may use the same cell receptor
As identified in Table 15.2, different virus species appear to use similar receptor types, or the same receptor, for cell binding. For example, the CAR receptor is used by both coxsackie B virus and adenoviruses.[242] PVR(CD155) is the primary receptor for poliovirus and has been reported to function as a secondary receptor for alphaherpesviruses.[118] ICAM-1 (intracellular cell adhesion molecule-1) has been identified as a primary or secondary receptor for coxsackievirus A, and also functions as the primary receptor for major group members of genus Rhinoviruses.[238,252,281]

15.3.3 Role of circulating Ab-Ag virus complexes in cell attachment
A host has many defense mechanisms which can be utilized to respond to a virus infection. These molecular and cellular defenses may be considered as part of two broad categories: innate and adaptive immunity. A detailed discussion of innate versus adaptive immunity is beyond the scope of this review and the reader is referred to examples of articles in this subject area.[3,6,25,36,50,64,310,333,343] Innate immunity includes those responses such as phagocytosis (e.g. macrophages),

cytokine release (e.g. interferon, interleukins), cell/tissue surface defenses, and cell-mediated killing of virus infected cells (e.g. NK cells) that do not require specific viral antigen recognition in order to initiate and mediate the response. The development of antiviral antibodies and cell-mediated immunity are part of the more slowly developing and longer-lived antiviral response categorized as adaptive immunity. Cellular components of an adaptive immune response (e.g. B cells, T cells) can recognize viral proteins as foreign (antigens) and develop specifically targeted responses (e.g. antiviral antibodies, antigen-dependent cell-mediated killing) against domains (epitopes) of the viral antigen. Antibodies produced (humoral immunity) in response to virus infection can include members of the immunoglobulin (Ig) classes IgM, IgG, and IgA. An initial humoral response typically involves IgM production followed by a switch to IgG production later in the infection/antibody response. The highest levels of IgG are typically observed in the serum while those of IgA are typically observed at the mucosal tissue or fluids (e.g. intestine, saliva), and in these locations is sometimes referred to as secretory IgA.

Interestingly, antiviral antibodies can provide an alternative mechanism by which a virus may gain entry into cells such as through receptor-mediated binding and entry of virus particles into a cell as antibody–virus complexes. These complexes are formed when sub- or non-neutralizing quantities of anti-virus antibodies are bound to the virus particle,[8,299,333] allowing the exposed Fc-region ('tail') of the antibody to attach to cells via Fc receptors expressed on the cell surface, thus facilitating entry into that cell. This facilitated uptake of antibody bound virus complexes has been reported for a variety of both RNA and DNA viruses in cell culture and *in vivo*.[299] The existence and utilization of this alternative pathway suggest that a mechanism exists for expanding viral tropism *in vivo* under conditions whereby a host immune response generates sub-neutralizing titers of anti-viral antibodies.[217,257,322] Similar antibody-dependent enhancement or ADE has been reported for CV[148,183] and HAV.[94,95,110] In coxsackievirus B4 infection, ADE has been implicated in increased infectivity of the virus, implicating this mechanism in the development of myocarditis, at least in a mouse model.[148,183] Dotzauer *et al.*[94] demonstrated infection of both mouse and human hepatocytes using antibody–HAV complexes, and suggested that the formation of these complexes may play a role in relapsing HAV infections through its function as a possible liver-directed carrier mechanism. It is also important to note that the expression of Fcγ receptor on phagocytic cells (viz. macrophages, neutrophils) is part of the viral clearance mechanism used by the immune system to remove virus–antibody complexes from circulation, but ironically may contribute to the risk factors associated with disease[322] as suggested by Rekand *et al.*[257] regarding allelic polymorphisms in the FcγIIIA receptor and risk factor development for acute illness (poliomyelitis).

15.4 Host cell defenses

15.4.1 Protective immunity

There are numerous physiologic hurdles that a virus must overcome to establish an infection within the host (Section 15.2), but enteric viruses are capable of surviving many of these assaults primarily because of the structure and composition of their capsids. The host, however, has mechanisms such as antiviral and immunological responses to combat a potential enteric virus infection.[333] For example, both serum and secretory antibodies play major roles in protective immunity against enterovirus infections. For HAV infection, circulating anti-HAV IgG is protective against viral disease, but it is unclear what role immunity at the intestinal surface (such as secretory Ig) may play in protection from infection.

Human volunteer feeding studies using either infectious inoculums or NoV rVLPs, and epidemiologic and serologic studies have indicated the absence of any long-term immunity to NoV infection.[105] The relatively rapid rate of recovery from NoV infection and illness suggests both an antiviral and immunological response play a role in the overall host response to infection.[39,130]

Rotavirus nonstructural protein NSP4 has been found to have a toxin-like activity that effects diarrheagenic changes without direct destruction of villus enterocytes.[254] The major outer capsid proteins VP4 and VP7 are involved in virus attachment and cell entry and induction of neutralizing and protective antibodies.[219,233,345] VP6, an intermediate layer virus structural protein, has also been implicated as part of an IgA-specific non-neutralizing, but protective immune response.[109] Primate and mouse model studies also indicate that transcytosis of serum IgG to the intestinal lumen may be important in blocking virus attachment or endocytosis.[277,329]

15.4.2 The interferon (IFN) response

To survive a virus infection the host relies on both innate and adaptive defense mechanisms which the invading virus must overcome to replicate and assure its own survival.[79,112,143,158] Since there is usually a time lag of several days before the adaptive immune response becomes functional, the cytokine response (IFN) is crucial for the survival of the organism.[3,36,173,227] There are two major IFN-controlled cellular defense mechanisms that are important in the context of foodborne viruses: the 2-5A dependent RNase L pathway and the PKR (protein kinase RNA activated) pathway (Fig. 15.5).[17,158,280,286,292]

Apoptosis is referred to as programmed cell death.[17,51,256] This process is often argued as the means by which a cell may limit virus replication and spread through initiation of this cellular 'self-destruct' mechanism. Some viruses have evolved mechanisms to either induce or suppress apoptosis. The former may function as a means to facilitate release of progeny virus from the infected host while the latter may aid in delaying cell destruction in order to provide additional time for virus replication and progeny production. The induction of apoptosis in virus infected cells may occur as a consequence of protein synthesis

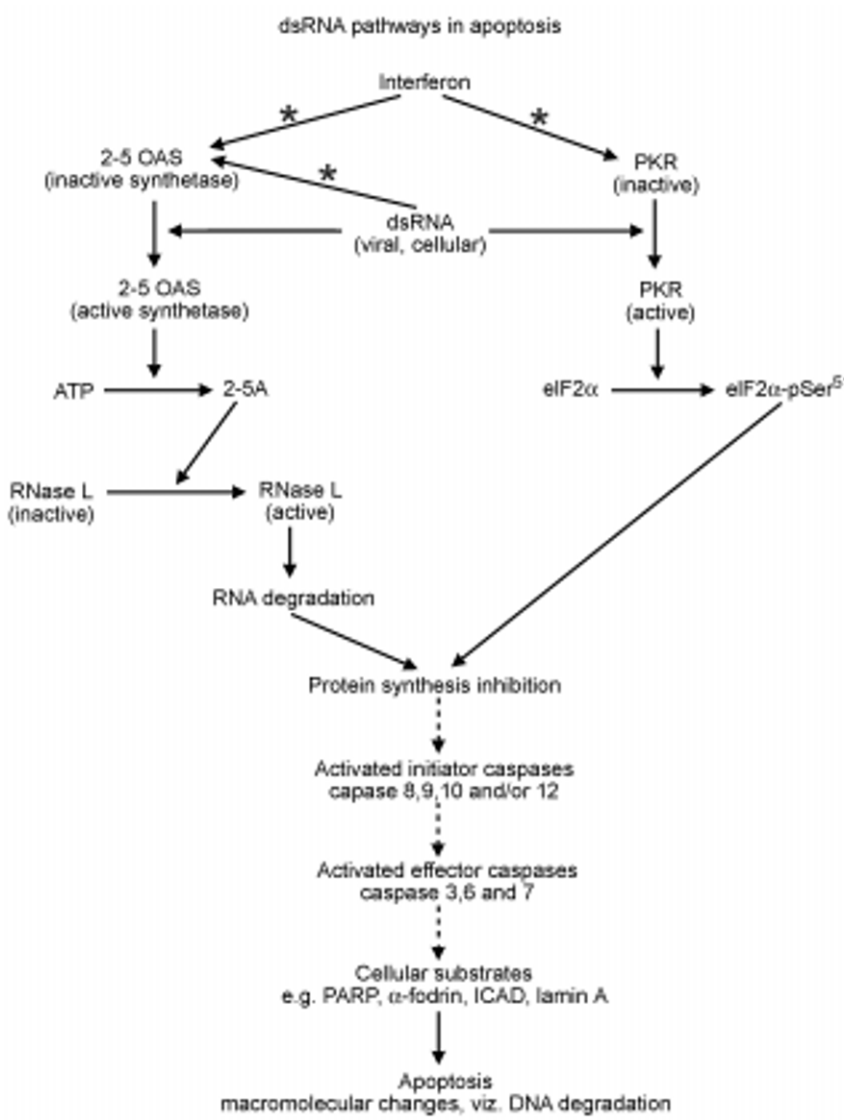

Fig. 15.5 Diagrammatic representation of the relationship between activation of the dsRNA pathways and induction of apoptosis.

inhibition resulting from, for example, modification of protein kinase signaling factors or cellular metabolic pathways leading to endoplasmic reticulum (ER) stress induction (e.g. amino acid depletion, unfolded protein response); cleavage of critical translation factors (see Fig. 15.4); and/or antiviral (dsRNA and interferon) pathway activation. As shown in Fig. 15.5, one of the cellular responses to interaction with interferon can be the induction (increased expression) (*) of 2–5 OAS (oligoadenylate synthetase) and/or PKR, whose

latent enzymatic activites are activated by viral dsRNA. dsRNA alone may function to induce expression of 2–5 OAS. Activated 2–5 OAS produces 2′–5′ adenylate oligomers which in turn activate latent, endogenous RNase L to ultimately affect protein synthesis by degrading RNA. Activated PKR phosphorylates serine 51 of eIF2 subunit α resulting in inhibition of protein synthesis (see Fig. 15.4), The link between protein synthesis inhibition and activation of initiator caspases (----→) is not fully understood and appears to be in part virus and cell/tissue dependent. Central to apoptosis is the activation of members of a family of intracellular cysteine aspartyl-specific proteases known as caspases.[77,88,103] Fourteen caspases have been identified with some reported to have a tissue-restricted specificity for activation. With few reported exceptions, capases require cleavage through an auto- or trans-catalytic process for their activation. The activation of initiator caspases (e.g. caspase 2, 8, 9, 10, 12) can occur through receptor (extrinsic) or intracellular initiated (intrinsic) mechanisms. This triggers activation of an enzymatic (caspase) cascade leading to downstream activation of effector caspases (e.g. caspase 3, 6, 7), resulting in targeted cleavage of various cellular proteins that ultimately mediate the observed physical and biochemical changes ascribed to apoptosis.

Ironically, the viral genome itself (or its replication strategy) is the Achilles heel of the foodborne viruses. This is because one or both of these two major IFN stimulated antiviral systems are triggered when the cell encounters a virus. With few exceptions, the trigger is dsRNA either in the form of viral transcript (e.g. reovirus s1) secondary structure, or in the dsRNA replicative intermediates of ssRNA viruses, although a direct role of dsRNA viral genomes has not been completely ruled out.[17,37,144,161,270] Synthesis of dsRNA is unavoidable even in dsDNA virus infected cells owing to convergent transcription from both DNA strands.[89,127] Moreover, both dsRNA triggered antiviral mechanisms are apoptotic.[17,69,280] Picornaviral 2A and 3C proteases (Section 15.2) can also induce apoptosis in infected cells by mechanisms that share some features of the apoptosis triggered by dsRNA, namely the caspase pathway.[18,56,61,123] The difference is in the timing of the onset of apoptosis. Viral proteases induce apoptosis late in infection when the viral replication cycle is complete.[4,41,47,60,61,80,121,124,255,265] With few exceptions, the dsRNA activated apoptotic pathways require prior exposure to IFN either as pre-treatment of tissue culture cells prior to virus infection, or virus-induced synthesis of IFN, which sensitizes surrounding uninfected cells to an incoming virus, and therefore induces apoptosis in these cells before virus replication can take place.[17,280,292]

15.4.3 Inhibition of virus replication by protein kinase RNA activated pathway

Activation of PKR requires dsRNA mediated autophosphorylation and dimerization (Fig. 15.5). Activated PKR phosphorylates a number of cellular proteins such as eIF2α, and I$\kappa\kappa\beta$. Phosphorylation of eIF2α renders it inactive in protein synthesis (Fig. 15.4), both cellular and viral, resulting in the inhibition of virus

replication, and in apoptotic death of virus-infected cells,[74,149] contributing to viral pathogenicity.[272] Phosphorylation of I$\kappa\kappa\beta$, on the other hand, induces the synthesis of the transcription factor NF-$\kappa\beta$, resulting in the induction of several cellular genes (including IFN) with both pro- and anti-apoptotic functions.[161]

15.4.4 Inhibition of PKR by viruses

PKR activation must be suppressed for virus specific protein synthesis and virus replication to occur.[15,37,76,293] The reovirus outer capsid protein σ3 binds to and inhibits PKR activity.[119,160,202] However, the σ3 protein is also responsible for inhibition of host cell protein synthesis.[283] A second reovirus protein μ1 may bind to σ3 and prevent its dsRNA binding function.[279,342] The NSP3 protein of reovirus, specifically an 8 kDa cleavage product, has been shown to bind and antagonize the antiviral effects of dsRNA.[192] In some cell lines of tumor origin, PKR expression is down-regulated, resulting in high-level replication of these viruses and efficient cell killing.[98,140,294] The virus induced cell-killing of certain tumor cell lines may be an interesting therapeutic application of these viruses.

Regarding other important foodborne pathogens, PV causes reduction in PKR levels by an unknown mechanism possibly involving a cellular protease and poliovirus dsRNA.[40] Evidence suggests that a reduction in cellular RNA synthesis via the degradation of a variety of RNA polymerase transcription factors[247] coupled with an inhibition of cellular protein synthesis, results in a significant reduction in PKR levels. Other enteroviruses probably employ similar mechanisms. It is not known how HAV, NoV, or HEV evade the consequences of PKR activation. Infection with apoptotic as well as non-apoptotic strains of HAV did not result in PKR activation (Fig. 15.6). Figure 15.6 shows the results of dsRNA treatment and HAV infection on 2–5 OAS levels and PKR phosphorylation in FrhK4 cells. FrhK4 cells were either mock or HAV 18f infected [48 hpi (hours post-infection)], or mock or polyI:C (i.e. dsRNA) transfected (48 h) prior to protein extraction and denaturing gel electrophoresis/immunoblot analysis (see Goswami *et al.*[126] and Kulka *et al.*[187] for experimental details) for detection of 2–5 OAS (panel A), phosphorylated PKR (panel B), or nonphosphorylated PKR (panel C). Persistently HAV clone 1 infected (>300 days pi) FrhK4 cells were mock or dsRNA treated (48 h) prior to protein extraction and immunoblot analysis. The positions of the 100 kDa and 69/71 kDa isoforms of 2–5 OAS are identified with arrows. 2–5 OAS was detected only in dsRNA-treated FrhK4 cells. Nonphosphorylated PKR (67 kDa) was present at equivalent levels in all samples, while phosphorylated PKR was not detected in any of the samples. Thus PKR phosphorylation may be defective in these cells, allowing HAV to establish a latent infection as suggested by Gale and Katze.[117] dsRNA induced synthesis of OAS, while neither the apoptotic HAV strain (18f), nor the tissue culture adapted parent strain (clone 1) caused induction of OAS. Moreover, the clone 1 virus inhibited dsRNA induction of OAS. HAV is thus equipped with an as-yet unidentified function that can

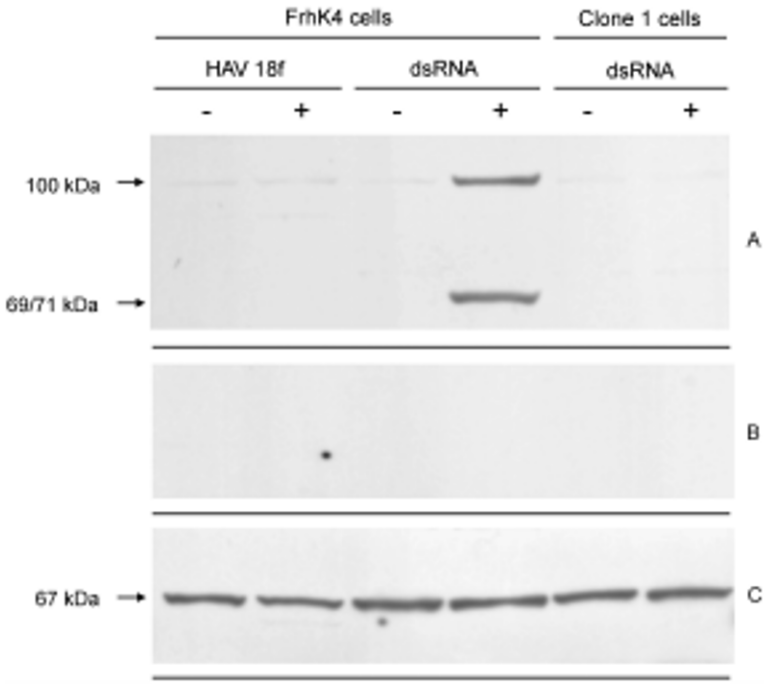

Fig. 15.6 Induction of 2-5OAS expression in response to dsRNA treatment of FrhK4 (fetal rhesus monkey kidney) cells.

interfere with dsRNA activated antiviral mechanisms. The role of cellular protein modulators of PKR activation, which work by either binding to PKR or to dsRNA,[158] are currently unknown. It has been suggested that lack of PKR activation may be the reason why some viruses are able to establish persistent or latent infection.[117]

15.4.5 Inhibition of virus replication by RNase L

A second IFN-induced antiviral pathway involved in apoptosis of virus infected cells is activation of a latent endoribonuclease RNase L (Fig. 15.5).[62,163] This ribonuclease is present in inactive form in many cell lines and is apparently involved in many physiological processes.[286] The enzyme is activated when 5′ phosphorylated trimers or higher oligomers of 2′–5′linked oligoadenylic acids (collectively referred to as 2–5A) bind to the inactive form of RNase L.[179] Synthesis of 2–5A is a function of the enzyme 2′–5′ OAS, which is induced by IFN and activated by dsRNA. Several isoforms of OAS have been described, while only a single molecular form of RNase L in a given cell type is known. The activated RNase L degrades cellular as well as viral RNAs after UpNp dinucleotides. In interferon-treated cells, degradation of both viral and ribosomal RNA (rRNA) molecules are observed following infection with several RNA and DNA viruses, or treatment with dsRNA.[62,286]

15.4.6 Viral evasion of the RNase L pathway

Little is known about how ssRNA or dsRNA viruses escape the RNase L pathway. Since cells that have not been treated with IFN contain little or no OAS, viral infection of such cells does not trigger the RNase L-mediated RNA degradation owing to the lack of the activator 2–5A. The only exceptions known to date for the requirement of IFN for RNA degradation in virus infected cells are the apoptotic strains of HAV,[125,187] and mouse coronavirus.[16] Degradation of rRNA occurred following HAV infection in the absence of prior IFN treatment of the cells, and in the absence of detectable OAS mRNA or protein (Figs 15.6 and 15.7). In contrast, treatment of the same cell line with dsRNA resulted in rRNA degradation and also induction of the 69/71 kDa form of 2–5 OAS mRNA and protein (Figs 15.6 and 15.7); degradation of viral genomic RNA in virus infected cells did not occur,[187] and virus replication was not inhibited. Along with the previous reports that HAV inhibits dsRNA-induced

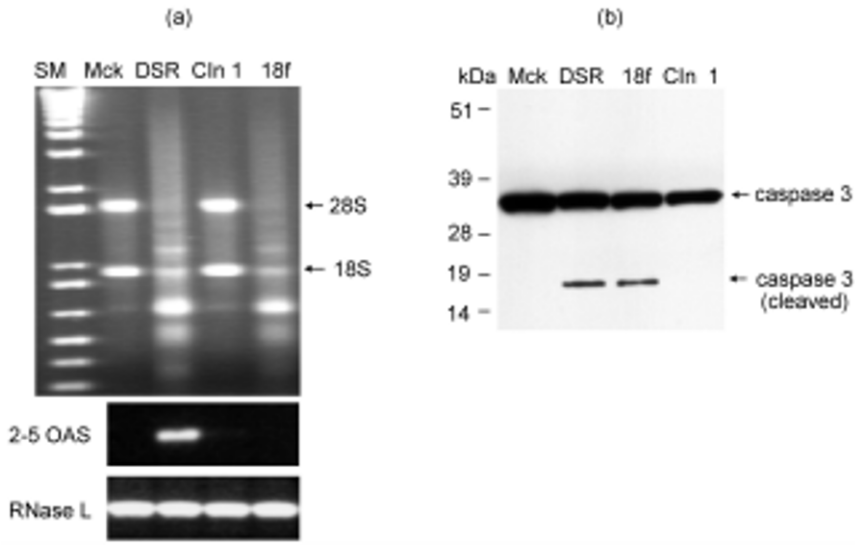

Fig. 15.7 Activation of apoptotic pathways (RNase L and caspase) following HAV infection or dsRNA treatment of FrhK4 cells. Replicate samples of FrhK4 cells either mock (Mck) treated, HAV 18f infected (18f), HAV clone 1 infected (Cln 1) or polyI:C transfected (DSR) for 48 h were subjected to either total RNA extraction/isolation for RNA analysis and RT-PCR (A, upper and lower panels, respectively), or protein extraction followed by denaturing gel electrophoresis/immunoblot analysis for caspase-3 activation (panel B) (see Goswami *et al.*[126] and Kulka *et al.*[187] for experimental details). The positions of the 28S and 18S rRNAs are indicated with arrows. Degraded rRNA appears as stained bands located both between the 28S and 18S, and below the 18S positions (A, top panel). While RT-PCR generated a 2-5OAS amplicon from dsRNA-treated FrhK4 cells, the remaining samples were negative, indicating the lack of induction of 2-5OAS gene expression in these samples. RNase L was activated in 18f infected as well as dsRNA-treated cells, suggesting 2-5A-independent activation in 18f infected cells. Activation of caspase-3 in dsRNA-treated and 18f infected cells is indicated by detection of the (cleaved) large fragment of caspase-3 (panel B).

synthesis of IFNβ[48] and the absence of activation of the JAK-STAT pathway in HAV infected cells,[125,187] it is likely that activation of RNase L in the FrhK4 cells following HAV infection is an example of the usurping of this activity by the virus to its advantage, analogous to the usurping of the PKR pathway by reovirus.[76,294]

15.4.7 Interferon, apoptosis and pathogenesis

In the context of virus infection, apoptosis is a two-edged sword. As a host defense mechanism, induction of apoptosis early in infection inhibits viral replication and formation of progeny virus. A late induction after the completion of the viral replication cycle favors the virus by circumventing the immune and inflammatory responses.[17,268] For enteroviruses, the usual outcome of a productive infection is cell lysis and release of progeny virus.[41,58,69,205] However, even with these highly cytolytic viruses, recent results indicate a significant role of apoptosis in viral-induced pathogenesis.[4,46,56,60,61,67,68,80,141,197,198,255] In general, signals for apoptotic induction converge on the enzyme cascade called caspases (Fig. 15.5), which include initiator caspases (8, 9, 10, and 12) and effector caspases (3, 6, and 7). Caspases are present in cells in inactive forms and require activation by proteolytic cleavage.[77,103,307] In this scheme, caspase 3 plays a central role, in being both activated by initiator caspases, and activating the other two effector caspases. Caspase 3 activation and caspase-mediated cleavage of cellular proteins involved in apoptosis have been observed in enteric virus infected cells.[18,26,60,67,123,126,187,265] Although it is generally thought that changes in mitochondrial membrane permeability resulting in cytochrome *c* release and activation of caspase 9 leads to activation of caspase 3 in some enterovirus infected cells, activation of upstream caspases has not been observed in HAV-induced apoptosis (Goswami and Kulka, unpublished). Similarly, the role of RNase L-mediated rRNA degradation in caspase activation remains to be established.

JAK-STAT

Central to the antiviral and proapoptotic effects of the IFN induced systems, PKR and RNase L, is the JAK-STAT pathway which controls IFN stimulated gene expression. Phosphorylation of the transcription factor STAT1 is critical for stimulation of genes containing either interferon stimulated response elements (ISRE) that are regulated by type I IFN or gamma-activated sequence (GAS) elements stimulated by type II IFN. STAT1 responsive genes include both PKR and OAS, and differential effects of the two types of IFN on the two antiviral mechanisms have been observed.[112] STAT 1−/− cells are unresponsive to IFN and sensitive to virus infection,[99,337] although the severity of the disease and vaccine derived protection may not be altered for all enteric pathogens.[321] In HAV-infected FrhK4 cells, STAT1 is not phosphorylated and IFNα/β is not induced.[48,126,187] The activation of RNase L and apoptosis in such cells is 2–5A or PKR independent (Figs 15.6 and 15.7). Clearly, the role of

STAT in the replication of enteric viruses needs to be investigated. The enhanced replication of mouse norovirus in dentritic cells and macrophages from STAT1 knockout mice also suggests a larger role of the JAK-STAT pathway in virus replication.[176,337]

15.5 Mechanisms of virus-induced damage to host cell

15.5.1 Apoptosis as a pathogenic mechanism

Considerable evidence has accumulated over the past years indicating that apoptosis plays a key role in viral pathogenicity.[5,41,61,112,204,255,265,272] Even highly cytolytic viruses such as PV and CV have been shown to induce apoptosis both in tissue culture and in animal models.[4,5,80,81,121,255,265] Because many enteric viruses are highly cytolytic in tissue culture cells, induction of apoptosis is only observed under conditions that are restrictive to virus replication.[265] In cultured cells *in vitro*, such restrictive conditions are achieved by the use of certain inhibitors of virus replication or mutant viruses. Restrictive conditions for virus replication occur *in vivo* owing to an IFNα/β response to virus infection. Moreover, poliovirus-induced apoptosis has recently been observed even under permissive conditions in a human promonocytic and enterocytic-like cell lines[204] and in the mouse central nervous system.[121,122] Apoptosis resulting from activation of the caspase pathway by the perforin/granzyme route was reported following vaccination with oral polio vaccine. IFNγ secretion by both CD4+ and CD8+ T cells was involved, again pointing to apoptosis as a mechanism of tissue damage, probably as a result of replication of the vaccine derived virus.[324] In contrast, wild-type and most cell culture-adapted HAV strains produce a noncytolytic persistent infection *in vitro*. A few cytopathic strains of HAV are capable of cell killing *in vitro* as a result of a slowly developing apoptosis.[47,124,126,187] However, unlike the enteroviruses, the relationship between apoptosis and pathogenicity in animal models has not been clearly established for HAV.

Rotavirus infection has been shown to induce apoptosis both *in vitro* and *in vivo*.[46,67,259,316,317] While induction of apoptosis *in vivo* in mice infected with a human rotavirus was correlated with the onset of diarrheal disease, the underlying mechanisms connecting these processes have not been fully elucidated.

15.5.2 Cytopathic effect (CPE)

The development of morphologic changes related to CPE in an infected cell is the subject of numerous reviews.[185,205,289] The secondary effects of viral gene expression/replication on host cell macromolecular structures and/or metabolism can ultimately lead to CPE by effecting changes in cell morphology such as cell rounding, cell lysis, syncytium formation, and inclusion body formation. The induction of CPE in cultured cells may or may not have a direct mechanistic

relationship to the pathogenesis of viral disease. The molecular events responsible for the cytopathogenesis ascribed to a particular virus infection may be delineated through investigations of the effects of viral gene expression and replication on host cell metabolism in culture. For an increasing number of viruses, the CPE observed following virus infection has subsequently been determined to be the consequence of an apoptotic response.

For example, the productive infection of non-neuronal cells (e.g. HeLa) with poliovirus gives rise to CPE but does not lead to DNA laddering that is characteristic of apoptosis. Infection of neuronal or promonocytic cells, or non-neuronal cells under conditions of restricted poliovirus replication, induces molecular events and morphologic changes consistent with cell death by apoptosis.[80,121,204] Enterovirus 71 and coxsackievirus B5 were also reported to induce apoptotic and non-apoptotic cell death depending, in part, on the cell type and multiplicity of infection.[4,60,255,327] A number of investigators have argued for the contribution of viral CPE and possibly apoptosis in the pathology of viral myocarditis and progression to cardiomyopathy.[14,153,238,328] The immunological contribution to the pathology could not be discounted. Clearly, the interplay between viral and cellular factors/mechanisms during enterovirus infections which results in either non-apoptotic CPE or apoptosis induction, is complex, and has yet to be fully elucidated with respect to natural EV infection and potential sequellae such as poliomyelitis, meningitis, and cardiac damage.

Wild-type hepatitis A virus infection in culture does not produce CPE despite replication, assembly, and spread of infectious virus. While the clinical symptoms and pathology of infectious hepatitis are attributed to a T cell mediated destruction of infected cells,[64,319,320] the contribution of virus replication *per se* to hepatic cell destruction remains unclear. There is currently no information regarding the development of either CPE or necrosis in cell culture by human NoV owing to the lack of a cell culture system for this virus. Human volunteer studies reveal upper small intestinal histopathologic lesions and mononuclear cell infiltration of the lamina propria, suggesting virus particle binding to epithelia cells (stomach) and enterocytes (small intestine).[105] While animal rotaviruses can be grown in cell culture quite easily, the culture of human rotaviruses often requires additional methods such as pretreatment and/or incorporation of trypsin in the culture medium possibly aiding in the exposure of viral antigenic epitopes for more efficient binding of the virus to its cell receptor.[174,203]

Although most culturable human (primarily group A) and non-human strains of rotavirus have been reported to develop CPE; human group B and C members have proven more difficult to culture. Histopathologic changes,[132] altered cytoskeletal organization and perturbation of calcium homeostasis,[104,254] are among the reported effects of rotavirus infection. The induction of apoptosis has been described for rotavirus infection in culture.[67,295] DNA fragmentation (not consistently reported during rotavirus infection in culture) has been correlated with the loss of mitochondrial membrane potential and release of cytochrome *c*, as well as shut-off of host macromolecule synthesis. The viral and cellular

mechanism(s) responsible for induction of apoptosis in rotavirus infected cells are not well understood and remain the subject of continuing investigation.

15.5.3 Effects on cellular metabolism: virus inhibition of protein and RNA synthesis

Owing to the limited genome capacity of most enteric viruses (Fig. 15.1), essential viral functions are co-opted to modify or inhibit cellular macromolecule synthesis and function to favor virus replication (see Section 15.2). The study of cellular factors and mechanisms involved in this highly coordinated, regulated, and complex process is the subject of numerous reviews.[120,149]

15.6 Implications for foodborne disease treatment and prevention

15.6.1 Vaccines

Norovirus

Generally, gastroenteritis caused by foodborne viruses of norovirus genus is a rather mild self-limiting disease. Thus, a nationwide program of mass vaccination is probably unwarranted, although specific segments of the population, such as military personnel destined for war zones, or food handlers and agricultural workers, might benefit from an effective vaccine. From volunteer studies it is unclear whether long-term immunity is achievable following immunization with recombinant VLP against NV,[105] or whether immunization with one genogroup confers cross-protection against a different strain of NoV.[200] Besides the lack of a cell culture or small animal host for NoV, the genetic and antigenic diversity within the genera is a great impediment towards the development of effective vaccines.

Poliovirus

The availability of both inactivated (Salk type) and live attenuated virus (Sabin type) vaccines has almost eradicated this disease in developed as well as most developing countries. The disadvantage of a live attenuated vaccine is ensuring the safety of the vaccine strain. Growth of attenuated strains of PV sometimes results in revertant strains that have regained their virulence, requiring rigorous safety testing of each new batch of virus to be used for immunization,[334] especially since VDPV with mutated phenotypes can persist in immunized populations for years.[70,147]

Rotavirus

The picture of success of vaccination programs with live attenuated poliovirus got murkier with reports of serious adverse effects during clinical trial with a live rotavirus vaccine.[33,228] Considerable resources are currently being used to develop new vaccines against rotavirus based on reassortments between human and animal rotaviruses of the capsid proteins VP4 and VP7.[155]

HAV

Two inactivated HAV vaccines are currently licensed for use.[25] They are both highly effective and serious adverse effects are not currently known.

15.6.2 DNA vaccines

DNA vaccines are based on the expression in 'vaccinated' hosts of cDNA encoding protein antigens (viz. viral coat proteins) that have been cloned into plasmid vectors carrying transcription and translation signal sequences utilized by the host's cellular/molecular machinery. Specific genetic elements can be engineered into the vector to permit replication in target cells.[145,246] Expression of the protein antigens generates both humoral (antibodies) and cell-mediated (cytotoxic T lymphocyte or CTL) responses to the antigen, conferring protection against subsequent infection by the same or related pathogen. The advantage of DNA vaccines over inactivated or live attenuated pathogens is that large quantities of highly purified pathogens are not needed, and that both CTL and antibody responses are induced, which are crucial for establishing protective (i.e. relevant) immunity. The advantage of DNA vaccines over immunization with live attenuated pathogens, which also elicit a CTL response, is the reduced risk owing to the absence of virulent pathogen production through unforeseen mutations or recombinations. The disadvantage is that the magnitude of the immune response may be low, requiring boosting of the response with purified antigen, or cytokines (see below).

Technology for the oral administration of DNA vaccines has been developed, resulting in an IgA response at the mucosal surface similar to that achieved following oral administration of live attenuated vaccines. Intramuscular or intradermal administration of DNA vaccines, or inactivated viral vaccines do not generate an IgA response,[145] although, interestingly, immunization of human volunteers with an inactivated HAV vaccine resulted in expression of IFNγ as well as interleukin (IL)-10, and a CTL response, in addition to the normal antibody response.[142] DNA vaccines against several enteric viral pathogens have been developed and tested in animal models. However, none is currently licensed for human use.[145] DNA vaccines so far have not lived up to the initial excitement, particularly when tested in large animals or humans.[102] It remains to be seen whether mucosal adjuvants such as CpG containing DNAs or cytokines will result in improved protection without the toxicity problem of older adjuvants such as cholera toxin. Targeting vaccines to mucosal cells to elicit secretory IgA response by using receptor binding proteins such as reovirus σ1 protein is a promising approach, particularly with regard to the recent development of a model for intestinal Peyer's patch M cells.[50]

15.6.3 Vaccines and cytokines

Cytokines have a profound effect on the pathogenesis of foodborne viral diseases and on innate and adaptive immunity against virus infection. The effects of

interferons, the most studied cytokines in the context of virus infections, have been described in previous sections. The effects of various cytokines may be complementary or antagonistic. The cytokine tumor necrosis factor α (TNFα) was found to down-regulate the inhibitory effect of IFNα on human rhinovirus (a picornavirus) growth, and disease potential.[28] In rotavirus infected children, the severity of the disease correlated with lower levels of IFNγ, IL-6, and IL-10, and higher levels of TNF-α.[166] However, experiments with STAT-1 knockout (Stat-1 $-/-$) mice, which are defective in IFN response showed a potent antibody and T-cell response to rotavirus challenge and were protected against rotavirus infection following immunization with capsid protein VP6.[321]

15.6.4 Inhibitors of replication

Therapeutic control of virus infections have been the subject of intense investigation ever since viruses have been recognized as disease agents, and a full discussion is beyond the scope of this review. Several therapeutic strategies are currently under investigation and include the application of interferons, capsid function inhibitors, replication inhibitors, inhibitors of receptor binding, and protease inhibitors including nitric oxide releasing compounds.[188,344] A promising new field of research is aimed at investigating the effects of virus infection on host cell gene expression with a view to identifying metabolic pathways affected by the virus.[115] Although several picornaviruses have been studied regarding their effects on host gene expression, tangible results using this approach in the form of new antivirals are lacking. The genomic approach probably is more appropriate for viruses that produce latent or chronic infections in the host. Effects on cellular gene expression following infection of FrhK4 cells with the non-apoptotic HAV strain HM175 (clone 1) was compared with the effect of infection with the apoptotic strain HM175/18f.[187] Both transcription factors c-jun (AP-1) and c-myc were significantly up-regulated in 18f infected cells compared with clone 1. However, no transcriptional induction of IFNβ, IFNα2 or IFNγ was observed with either virus. These results are similar to the results reported for echovirus and poliovirus infection.[171,243] In contrast, in a mouse model of coxsackievirus induced myocarditis, more than 150 cellular genes were shown to be affected (> two-fold increase or decrease) as a result of virus infection.[306] Surprisingly, neither IFN nor IFN-stimulated genes (ISGs) such as 2–5 OAS or PKR expression were affected. Rotavirus infection, however, caused marked increase in 2–5 OAS and PKR levels.[85] In the absence of corroborating data on protein expression or activity, the significance of the observed effects remains to be determined.

15.6.5 Other cytokines

It is recognized that cytokines other than interferons play important roles in determining the outcome of viral infections. For example PV inhibits the secretion of IL-6, IL-8 as well as IFN.[92] Tumor necrosis factor TNFα was shown

to transform a trace rhinovirus infection into full blown disease by down-regulation of the IFN response.[28] Henke *et al.*[143] reported protection of mice from a lethal injection of a CVB 3H3 strain when a recombinant CVB3 strain expressing IFNγ was administered prior to or simultaneously. In mouse models, IL-12 was protective against lethal infection by coxsackievirus.[108,248] Undoubtedly IFN response modifiers such as TNF, and interleukins will be targets for future antivirals.

15.6.6 Virus detection in foods

The ability to detect viruses in foods is a significant component of foodborne viral disease control and prevention. This has proved to be difficult for several reasons. Traditional methods for virus detection based on cytopathic effect on infected cells in culture cannot be applied to viruses of the norovirus group because a cell culture host is not available. Similarly, wild-type HAV grows very poorly in the available cell culture hosts and usually without cytopathic effect. Molecular methods based on the detection of virus genomes by RT-PCR (see Fig. 15.3) have been the basic tools for food virologists. However, attempts to detect viruses in foods by RT-PCR have met with limited success because of complicated multi-step processes required to concentrate viruses from foods. Seeding experiments have revealed severe losses of virus during such purification procedures. Most protocols also result in unacceptable levels of contaminants that severely inhibit the enzymatic reactions employed in RT-PCR. Moreover, the level of virus in foods contaminated during production or handling is expected to be low. In most cases, the distribution of virus in foods is not uniform, creating a sampling problem. Also the time lag between food consumption and onset of disease can be days to weeks, so that contaminated food is either totally consumed or discarded.

To date, only a few instances of successful detection of a suspected viral pathogen in foods are known.[35,125,182,195] The significance of these successes has been questioned since viral genomic RNA isolated from inactivated virus often produce positive signals in RT-PCR reactions.[34,230,231]

15.7 Current research frontiers

There is increasing concern that foodborne viruses, because of their resistance to inactivation by environmental factors, could be deliberately added to the food or water supply to spread diseases. It has been known for a number of years that genomes of picornaviruses can be manipulated to express foreign genes.[143,162] It is also possible to completely synthesize infectious picornaviral genomes in the absence of a viral template.[65] Thus, global control of infectious virus stocks may prove limited in effectively preventing such a malicious act, because a viral genome can be synthesized that contains mutations in critical antigenic determinants or incorporates a critical modulator of innate immunity, and therefore

will not be easily amenable to control by currently available vaccines. Major efforts will be needed to develop virus isolation and detection protocols capable of detecting such mutated or recombinant viruses in a short period of time.[63]

As discussed in Section 15.6, vaccine research, specifically DNA vaccines and vaccine cytokine combinations to augment the effectiveness of vaccinations, will remain an important area of investigation. Modulation of cytokine levels (IFN and interleukins) to control viral infections and also nonviral diseases is still in its infancy, and will undoubtedly be an active area of research.[2,108,162,248,315]

15.8 Sources of further information

15.8.1 Recommended reading

The authors suggest the following publications for further reading as sources of additional information relevant to the topics discussed in this chapter.

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