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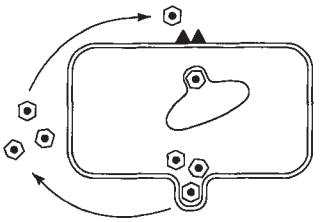
VIRUS–HOST CELL INTERACTIONS



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Introduction

The topic of virus–host cell interactions spans all of virology and provides some of the most important insights into this field. Since viruses are intracellular parasites, they rely on their host cells for the energy, macromolecular synthesis machinery and the work benches for genome replication and particle assembly. Because of this dependence, viruses have evolved a myriad of mechanisms for exploiting normal host cell functions. Often this exploitation is associated with damage to the host cell which may be one of the major factors in the pathology and disease caused by viruses. The material in this entry is confined to model systems of virus–host cell interactions that involve the infection by animal viruses of cells in culture.

The past few decades have witnessed a dramatic expansion of our knowledge of animal viruses. These advances have provided a detailed understanding of the structure and composition of the viral genome and the virus particle as well as insight into the replication strategies used by viruses and the regulation of viral gene expression during infection. Development of an understanding of the virus growth cycle has proved easier than a clear comprehension of the interaction of the virus with the host cell. Owing to the complexity of the cell, many of the effects of virus infection on the host occur by mechanisms yet to be determined.

Types of Virus Infections

When a virus infects a cell, the outcomes that may occur can be grouped into several general categories which are determined by the particular virus involved, as well as by the type of cell and its functional state. Productive infections result in the formation of progeny virus and usually cause the destruction of the host cell. In some cases the host cells are not all destroyed, leading to persistent infections in which the surviving cells multiply and continue to produce progeny viruses. When persistent infections occur in which the viral genome is present but no infectious virus is produced, these infections are referred to as latent infections. In such infections some level of viral gene expression is usually detectable although virions are not produced. When genetic information of the virus is integrated as DNA into the host cell genome or is carried as episomal DNA, transforming infections may take place. Such infections can cause an oncogenic alteration of the growth properties of the cell. Abortive infections occur when viruses infect cells that are nonpermissive or only partially permissive. In this instance, the virus is able to enter the cell but because some step essential for viral replication is absent, the replication cycle does not go to completion and no progeny are produced. Such abortive infections may or may not cause cell death.

A few examples follow which demonstrate that different outcomes of infection are dependent on the particular virus and host cell involved, as well as on the state of the host cell. For example, influenza A virus causes a productive, cytolytic infection of a line of canine kidney cells (MDCK). However, when the same virus infects the L cell line of mouse fibroblasts an abortive infection occurs because of a block at the level of virion RNA replication. The same mouse L cell line supports a productive, cytolytic infection by vesicular stomatitis virus (VSV). However, if the L cells are pretreated with interferon, the functional state of the cells is altered; the VSV replication cycle is blocked at the level of protein synthesis and an abortive infection results. When VSV infects insect cell lines derived from *Aedes* or *Drosophila*, productive noncytolytic infections occur. Continuous passage of the insect cell lines reveals that they have become persistently infected and continuously produce infective virus without any signs of cytopathology. Adeno-associated virus (AAV), a parvovirus, is capable of a productive or a latent infection depending upon whether or not the host cells are co-infected with a helper virus such as adenovirus. In some host cells, AAV can cause a latent infection by integrating its DNA into the host cell genome.

There are instances in which infection with a second unrelated virus can dramatically alter the type of infection produced by certain viruses. As mentioned in the preceding paragraph, adeno-associated viruses are capable of productive, cytolytic infections only in cells co-infected with adenovirus. Human adeno-viruses can multiply in monkey cells only in the presence of SV40, a simian papovavirus that supplies a helper function that permits translation of adenovirus mRNAs. In rabbit corneal cells, co-infection with vaccinia or some other poxviruses can convert nonproductive infections with VSV into cytolytic infections.

Effects of Virus Infection on the Host Cell

Effects on host cell morphology and viability

The most readily recognized effects of viruses on host cells are those that involve morphologic changes or cell death. Enders defined viral cytopathogenicity as 'the capacity to induce any demonstrable departure from the normal either in the morphological or functional properties of cells'. The space available for this entry precludes a comprehensive survey of all the cytopathic effects induced by infection with the various families of animal viruses. However, one of the most striking observations that emerges from an overview of the effects of viruses on host cells is how little is known of the mechanisms by which viruses induce cytopathology. The production of cytopathic effects has been observed with most families of viruses and in many cases the viral gene(s) involved or implicated in these morphological changes has been defined. However, in most cases the mechanisms responsible for cell destruction have not been identified. It is fair to say that one of the most fundamental questions of virology, namely, how viruses kill cells, remains for the most part unanswered.

Effects on host cell macromolecular synthesis

Many of the investigations of the effect of virus infection on the host cell have centered on virus-induced alterations of host cell macromolecular synthesis. While these studies are important to an understanding of the viral growth cycle and have yielded significant insights into the control of host cell gene expression, there is no direct evidence that inhibition at this level is the direct cause of visible cytopathology or cell death. In fact, treatment of host cells with drugs such as actinomycin D and cycloheximide, which inhibit nucleic acid and protein synthesis, does not mimic the morphological changes produced by virus infection. Nevertheless, viruses do employ a variety of strategies to affect the host cell at the level of gene expression.

Effects on host cell DNA and RNA synthesis A variety of DNA and RNA viruses are capable of affecting gene expression by directly altering the host cell genome. For example, the host cell DNA is degraded after infection with poxviruses. Herpes-, picorna- and reoviruses cause a displacement of the cellular chromatin, while an inhibition of host DNA synthesis has been reported following infection with herpes-, pox-, adeno-, picorna-, reo-, alpha- and rhabdoviruses. This inhibition of host DNA synthesis may be a direct effect of a virus factor in the nucleus or a secondary consequence of the inhibition of host cell protein synthesis.

Viral products can directly affect the activity of cellular RNA polymerases and cause an inhibition of host RNA synthesis. Such an inhibition has been seen with VSV and polioviruses. In the case of VSV, both a small viral-encoded RNA molecule (leader RNA) and a viral protein (the matrix M protein) have been implicated in the inhibition of the cellular polymerases at the level of RNA synthesis initiation. Another mechanism to inhibit host RNA synthesis is employed by polioviruses. These agents encode a protease that is capable of cleaving transcription factors required by host RNA polymerases II and III. Reo- and alphaviruses also block host RNA synthesis but the mechanism of this inhibition is not known. Synthesis is not the only level at which viruses can affect host mRNA. Infection with herpes- and poxviruses increases the rate of host mRNA degradation. A unique effect on host cell mRNA is produced by influenza viruses. These agents cleave the cap structure and the first 10–13 nucleotides from the 5′ ends of newly synthesized host mRNAs, and utilize this oligomer as a primer for viral mRNA synthesis. Another mechanism that affects host RNA is seen with adenoviruses; in this instance, infection inhibits the transport of host mRNA out of the nucleus.

Effects on host cell protein synthesis Although much effort has been directed at understanding the effect of virus infection on host protein synthesis, it is unlikely that an inhibition of host protein synthesis is required for successful virus replication. Many viruses, such as paramyxo-, papova- and retroviruses do not normally inhibit host protein synthesis during their replication. Furthermore, mutant viruses that are defective in their ability to shut down host protein synthesis are not necessarily defective for virus growth. In fact, VSV mutants selected during a persistent infection have a reduced ability to inhibit the host's translational machinery; nevertheless, these mutants grow to higher titer during a lytic growth cycle than the parental wild-type virus. With several virus families, infection causes a selective inhibition of the translation of host cell mRNA. Such viruses include picorna-, pox-, herpes-, adeno-, rhabdo-, reo- and orthomyxoviruses. In many cases this inhibition is accompanied by a decrease in the overall rate of protein synthesis in the infected cell. It is likely that this overall inhibition occurs at the level of initiation of protein synthesis since, where it has been examined, the average size of the polysomes in the infected cells is reduced.

The most clearly defined case of virus-induced damage to the translational machinery of the host cell

is the effect of poliovirus on one of the translation initiation factors. Following infection with poliovirus, the cap binding complex responsible for recognition of the capped 5′ end of cellular mRNA is inactivated by a proteolytic cleavage of the p220 component of the complex. It has been speculated that the destruction of the p220 protein confers a selective advantage on the translation of poliovirus messages which are uncapped. Infection with poliovirus also causes the release of host mRNA from the cytoskeleton.

Virus-mediated inactivation of other initiation factors for protein synthesis has also been reported. Translational extracts prepared from VSV-infected cells are deficient in eucaryotic initiation factor 2 (eIF-2) activity in one report and eIF-3 in another, while infection with reoviruses impairs the function of eIF-2. It has recently been shown that vaccinia virus, a poxvirus, encodes a small protein which has significant homology to the α subunit of eIF-2. This protein may function as a replacement initiation factor since there is evidence that it may be important in making the virus resistant to inhibition by interferon.

Another viral strategy to inhibit host protein synthesis involves a direct competition of viral and host RNAs. VSV and reoviruses compete successfully with the host for the translational machinery through sheer abundance of viral transcripts. Mengovirus, a picornavirus, produces mRNA which initiates translation more efficiently than the bulk of the host message and, in addition, synthesizes a factor that causes an overall inhibition of protein synthesis in infected cells.

It has been suggested that selective translation of viral mRNA may also occur following changes in intracellular ion concentrations during infection. Increased plasma membrane permeability is a common cytopathic effect of virus infection which can alter the intracellular levels of sodium and potassium ions. Under conditions that cause increased intracellular sodium ion concentrations, the translation of viral mRNAs may be unimpaired while the translation of host mRNAs is severely reduced. Such a differential effect on virus and host protein synthesis has been reported for cells infected with poliovirus, encephalomyocarditis virus, VSV, reovirus and Sindbis virus. In the case of Sindbis virus, the shutdown of host protein synthesis following infection has been correlated temporally with an increase in permeability of the plasma membrane.

Effects on host cell membranes and cytoskeleton

In addition to altering membrane permeability, virus infection can cause other changes in the membranes of the host cell. Insertion of viral proteins into the plasma membrane can induce syncytia formation by fusing infected cells with neighboring uninfected cells. This fusion can be induced either from without by input virions or from within by newly synthesized viral fusion protein made during infection. The ability to fuse cells, which is characteristic of the paramyxovirus family, is also seen with herpes-, flavi-, lenti-, pox- and coronaviruses. Flaviviruses can also affect internal membranes by causing the proliferation of the rough endoplasmic reticulum, a site associated with the assembly of viral particles. Reo-, picorna- and alphavirus infections frequently produce a significant increase in vesicle formation in the cytoplasm.

Cytolytic virus infections generally cause a progressive loss of integrity of the lysosomal membranes. Two phases of damage are recognized. In the first phase, which in some cases is reversible, the lysosomes become permeable to small molecules and are able to concentrate dyes such as neutral red. Visible evidence of this phenomenon is seen with a mutant strain of Newcastle disease virus, a paramyxovirus, which produces red plaques when assayed using an agar overlay containing neutral red. Concentration of this vital stain in lysosomes can also be detected in cells infected with certain strains of influenza A virus. In this instance a ring of darkly staining cells surrounds a clear area of unstained dead cells. In the second phase of lysosomal damage the membrane becomes so permeable that lysosomal enzymes are released into the cytoplasm. As a rule, this release occurs late in the replicative cycle. The release of lysosomal enzymes into the cytoplasm has been described for a wide variety of viruses such as picorna-, pox-, herpes-, orthomyxo-, paramyxo-, corona-, adeno- and papovaviruses. The mechanism responsible for this type of virus-induced cytopathology and the role it plays in cell death have not been clearly defined.

One of the most common signs of virus-induced cytopathology is cell rounding, a morphological change which has been correlated with alterations in the cytoskeleton. Disruption of one or more of the elements of the cytoskeleton has been described after infection with several viruses. Early gene products of herpes, vaccinia and SV40 viruses produce a disassembly of the actin-containing microfilaments, while infection with polio- and reoviruses causes an alteration and reorganization of the virimentin-containing intermediate filaments of the cytoskeleton. Microtubules, another element of the cytoskeleton, are depolymerized following infection with herpes simplex virus 1 (HSV-1), canine distemper virus and frog virus-3. It has been reported that infection with VSV causes a sequential disassembly of all three filament

components of the cytoskeleton. The mechanisms by which virus infections disrupt the cytoskeleton are not known and it is not clear whether these morphologic changes are a direct effect of some virus product or a secondary consequence of some other aspect of virus-induced cytopathology. It is interesting to note that in normal cells polyribosomes are closely associated with the cytoskeleton, and on the basis of this association it is possible to speculate that some of the effects of virus infection on the host translational apparatus may be caused by virus-induced changes in the integrity of the cytoskeleton.

Viruses also use the structural elements of the cytoskeleton as the work benches for virion assembly and for transport of viral products within the cell. Examples of this function of the cytoskeleton include adenoviruses which appear to use the microtubules for movement within the infected cell; Newcastle disease virus, the viral products of which are associated with actin filaments; and reoviruses which produce inclusion bodies found in association with microtubules and are the site of viral RNA synthesis and virion assembly. It has also been suggested that, in VSV infections, assembly of nucleocapsids occurs in close association with the cytoskeleton.

Inclusion bodies

Another commonly recognized form of virus-induced alteration of the infected host cell is the formation of intracellular masses called inclusion bodies. It should be noted that at the beginning of this century the discovery of a characteristic cytoplasmic inclusion, the Negri body, in cells infected with rabies virus provided an effective diagnostic test for this disease. Depending upon the virus, these intracellular masses may consist of either virions or unassembled viral products. Inclusion bodies may occur in the cytoplasm, as in cells infected with pox-, paramyxo-, orthomyo-, reo-, rubella or rabies viruses, or may be found in the nucleus in cells infected with adeno- and herpesviruses.

Transformation of host cells

In addition to producing various forms of cell destruction, some families of animal viruses are capable of inducing cell transformation. In most cases, transformation is associated with integration of the viral genome into the host cell DNA or maintenance of viral DNA in an episomal state. Only one family of RNA viruses, the retroviruses, is capable of transforming cells. This family of viruses induces transformation through the action of a variety of oncogenes that are cellular in origin and that are not part of or necessary to the virus replicative cycle. There are several families of DNA viruses that are the cause of or are associated with tumor induction in animals and cell transformation in cultured cells. These include polyoma-, adeno-, herpes-, papilloma-, hepadna- and poxviruses. In contrast to the RNA viruses, the genes of DNA viruses responsible for transformation are viral in origin and required for virus replication.

Is It Murder or Suicide?

It is clear from the information reviewed above that the mechanisms responsible for cell death following virus infection have not been clearly defined. Perhaps the reason it has been so difficult to explain how viruses kill cells is that they do not do this directly. An alternative to a direct cell killing is the induction by viruses of a suicide function in infected cells. It would be advantageous for a cell, as part of a metazoan, to induce an apoptosis-like function in response to viral infection rather than to continue on as a factory producing a constant stream of progeny virus. Some recent evidence has appeared that lends support to this possibility. The cytopathic effect of human immunodeficiency virus (HIV) infection has been associated with apoptosis; and in another report, a noncytopathic latent infection of B cells with Epstein–Barr virus (EBV) has been associated with an inhibition of the apoptosis function. In this connection, it is interesting to note that latent infection with EBV blocks the killing of B cells by VSV with little or no effect on the replicative ability of this RNA virus. These observations provide some basis for suggesting that virus-associated cell killing may involve the induction of apoptosis or some other suicide function in the infected cell.

Resistance of Cells to Virus Infection

The major determining factor of the susceptibility of a cell to a particular virus is the ability of the viral attachment proteins to recognize and interact with specific receptors on the cell surface. In many cases, cells are resistant to infection by a particular virus simply because of the lack of appropriate surface receptors. A dramatic example of this type of resistance is seen when chicken fibroblast cells, which lack specific receptor molecules on their plasma membranes, are exposed to poliovirus. Infection does not take place because the viruses cannot adsorb to the cell membrane. However, the avian cells are fully able to support the growth of poliovirus if transfected with the virion RNA rather than infected with intact virions. In addition to cell surface viral receptors, the host range of some viruses can be determined by other

factors such as host cell transcriptional regulators. There is evidence that suggests that viruses from the herpes-, polyoma-, retro- and hepadnavirus families can replicate only in cells that express the appropriate factors that permit recognition of the viral enhancers.

Although viruses have an adaptive advantage in terms of genetic plasticity, cells are not totally powerless to mount a defensive response to viral infection. The best characterized defense that cells have evolved for protection against viral infection is the interferon system. The interferon family of proteins that is produced in response to viral infection promotes the development of an antiviral state through the induction of a second group of proteins. Two of these proteins, the 2′-5′ A synthetase and the protein kinase, have been well characterized and evidence has accumulated that demonstrates their role in the development of the interferon-mediated antiviral state. Perhaps the best evidence to suggest that these proteins are actually involved in the interferon-induced antiviral state comes from the fact that several families of viruses have evolved factors that are capable of blocking the activity of the 2′-5′ A synthetase (herpes- and poxviruses) and the protein kinase (herpes-, pox-, adeno-, reo- and orthomyxoviruses).

Viruses as Tools for Probing the Host Cell

Many of the crucial discoveries concerning cellular processes were offshoots of investigations into the replication cycle of viruses or derived from the use of viruses as model systems. This is particularly true for understanding the mechanisms involved in gene expression. It is apparent that all viruses must use the host cell translational apparatus for the synthesis of viral proteins and that many DNA viruses depend on the host transcriptional and DNA replication machinery as well. Consequently, investigation of the intricacies of viral gene expression has led to the discovery of nearly all identified host factors involved in host genome replication, RNA splicing, enhancer sequences, the scanning model for the initiation of protein synthesis, the use of translational frameshifting for gene expression, and the manner in which proteins are targeted within the cell. This list, which is far from exhaustive, will surely be expanded in the future.

It would be difficult to overestimate the impact of the study of tumor viruses on our understanding of the mechanisms involved in transformation and the nature of the cancer cell. In spite of the fact that most naturally occurring cancers of humans and animals are not caused by viruses, investigation of transforming viruses, and retroviruses in particular, has led to an understanding of the major mechanisms and cellular genes responsible for transformation. A detailed review of this subject can be found elsewhere in this volume.

See also: **Cell structure and function in virus infections; Enteroviruses (*Picornaviridae*): Human enteroviruses (serotypes 68–71); Host genetic resistance; Influenza viruses (*Orthomyxoviridae*): General features; Interferons: Therapy of aids and cancer; Pathogenesis: Animal viruses; Persistent viral infection; Polioviruses (*Picornaviridae*): General features; Replication of viruses.**

Further Reading

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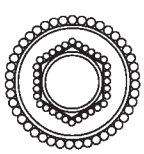
[This article is reproduced from the 1st edn (1994).]

VISNA-MAEDI VIRUSES (*RETROVIRIDAE*)



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History

Visna and maedi are Icelandic terms for two sheep diseases characterized by wasting paralysis and progressive labored breathing respectively. These diseases broke out in epizootic proportions among Icelandic sheep following introduction of European sheep into the local flocks. The newly introduced