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The Pathogenetic Basis of Viral Tropism

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FIFTY years ago it was fashionable to discuss the cell or tissue tropism of a given virus. Vaccinia and other pox viruses were predominantly dermotropic (although vaccinia, for instance, could be adapted to grow in places such as the testis or brain), papillomaviruses were unmistakably dermotropic, and the neurotropism of polioviruses was legendary. But the concept of viral tropism received a severe setback when it was shown that poliovirus grew well in non-neural cells *in vitro*.[1] Trypsinised, cultivated "fibroblasts" from monkey kidney came to provide a standard assay system and source of poliovirus. Growing viruses in cultured cells at the same time opened up a new era in vaccine development and in diagnostic virology, even heralding the birth of modern virology. However, there is no evidence of poliovirus replication in the kidney of the infected host, even when virus is injected directly into this organ. Cells undergo considerable change after trypsinisation and cultivation *in vitro,* and in the case of human amnion cells, susceptibility to poliovirus is not acquired until after approximately 7 days *in vitro*.[2] It is clear that *in vitro* tropisms are not necessarily expressed *in vivo*. Many other viruses have since been shown to be capable of infecting cells in culture that are not infected in the host. Viral tropism is readily determined in cells *in vitro,* but the state of the intact host is more complex; it has also become necessary to consider the question of access. Does the virus have the opportunity to infect susceptible cells? Does it actually reach them *in vivo*? Pathologists are still inclined to ask about viral tropism, because it forms the basis for the clinical and pathologic features of infectious diseases. Why do hepatitis viruses grow in the liver? How does mumps virus select salivary and other glands? Work on virus-specific cell receptors, and more recently studies of transgenic mice, has thrown fresh light on the issue of viral tropism, and in this article the subject is reexamined. When a cell is infected by a virus, it must be considered whether or not the infection is abortive or productive, and whether or not large or very small amounts of virus are produced. This aspect of tropism, however, will not be discussed at length here.

Tropism Based on Virus Receptors

Viruses must attach to cells as a necessary preliminary to entering them, and this is often the result of a specific interaction between molecules on the surface of the virus and receptor molecules on the susceptible cell. Infection or noninfection of a given cell or tissue by a virus thus may result from the presence or absence of specific receptor molecules. Influenza is a classic example, with selected segments of the hemagglutinin molecules in the viral envelope binding to sialic acid receptor on the susceptible respiratory epithelial cell. When receptor molecules are removed from cells by treating mice with neuraminidase intranasally there is substantial protection against intranasal challenge with influenza virus.[3]

Examples of virus-specific receptors are given in Table 1. This table will need to be expanded before long. Work on receptors is moving fast and an atomic model has been published for the interaction on the influenza virus hemagglutinin with its receptor.[4] Receptors, of course, are not displayed on the cell surface for the benefit of the infecting viruses, which must make use of whatever molecules are available. Sometimes the receptor molecule is present on many types of cell, but occasionally the virus uses a molecule present only on one or two types of cell. Indeed, the focusing of infection and damage onto a certain cell type that bears the receptor can then account for the pathology and the disease, as is the case with poliovirus, influenza, rabies, and EB virus infections. The receptor determines the characteristic viral tropism. EB virus attaches to the C3d receptor present on B cells,[12-14] which explains the infection of these cells. Host T cells respond immunologically to the infected B cells, resulting in a type of immunologic civil war with enlarged spleen, lymph nodes, and release of mediators that probably account for the malaise associated with the disease glandular fever. The infected B cells are stimulated to secrete immunoglobulin, and this polyclonal activation of B cells accounts for the heterophile antibodies and other autoantibodies seen with this infection. However, cells other than B cells are susceptible if the virus is given the opportunity to enter them experimentally, either by coat-

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Table 1. *Examples of Virus-Specific Receptors*

Virus	Cell	Mechanism
Influenza	Respiratory epithelial cell (intestinal epithelial cell in birds)	Viral hemagglutinin binds to sialic acid receptor on cell[4]
Parainfluenza virus I (Sendai)	Respiratory epithelial cell	Viral H-N glycoprotein binds to glycoside receptor on cell[5]
Rhinovirus	Nasal mucosal cell	Bind to ICAM-I molecule on cell[6-9]
Poliovirus	Neurone	Bind to ICAM-I type molecule on cell[7,8]
Reovirus type 3*	T lymphocyte, neurone	Viral hemagglutinin binds to beta-adrenergic or other receptor on cell[10,11]
EB virus	B lymphocyte, mucosal epithelial cell	Viral envelope protein binds to C3d receptor on cell[12-15]
HIV	CD4 + T lymphocyte, dendritic cell, Langerhan's cell[16]	Viral gp 120 binds to CD4 molecule on cell[17]
Hepatitis B virus	Hepatocyte	Middle S portion of viral HBs binds to monomeric albumin, which in turn binds to hepatocyte[18]; Large S portion of HBs independently mediates direct attachment to hepatocyte[19]
Rabies virus	Neuromuscular junction	Viral envelope protein binds to acetylcholine receptor on cell[20,21]
Vaccinia virus	Epidermal cell	Viral protein binds to receptor for epidermal growth factor?[22]

* Reovirus type 1 infects ependymal cells *in vitro*[23] and *in vivo*, and can lead to obstructive hydrocephalus.

ing the cell with C3d receptors or introducing viral DNA directly into the cell by microinjection. Also, in the naturally infected host epithelial cells are infected, providing the basis for the shedding of virus into parotid gland secretions and into the throat; the mechanism of infection, however, is not clear.[15]

Usually virus receptors are not molecules with a specialized function that are present only on certain cells. For instance, herpes simplex virus infects a wide range of cells, and recent work indicates that this virus binds to heparan sulphate molecules, which are present on most vertebrate cells. Actual entry into a cell requires additional specific virus–cell interactions.[24] For most viruses, including, eg, important viruses such as varicella-zoster virus, cytomegaloviruses, polioviruses, and measles, the receptors are either not known, or have been isolated and partially purified, but their molecular structure and cellular function is not known.[25] On the other hand, our knowledge of picornavirus receptors is expanding dramatically. We already know much about the site on human rhinovirus 14 that attaches to cells, even its 3-dimensional structure,[7] and recent work[8,9] makes it clear that the major cell surface receptor is the intercellular adhesion molecule (ICAM-I). ICAM-I is widely distributed in cells and, like the receptors for poliovirus, coxsackie B virus, and echoviruses, maps to human chromosome 19. It is a member of the immunoglobulin super family, which includes neural cell adhesion molecular (NCAM) and myelin-associated glycoprotein (MAG). Its expression on cells is enhanced by inflammation, a finding that leads to the interesting possibility that rhinoviruses induce their own receptors on cells by causing local production of inflammatory cytokines. The receptor for poliovirus appears to be a similar type of molecule.[26] That transcripts are found in a wide range of human tissues, whereas poliovirus infects only a limited number of cell types *in vivo*, indicates that additional factors are involved in its tropism.

A given receptor may be used by more than one virus, and studies on HeLa cells many years ago suggested the existence of four different families of receptors used by various picornavirses and adenoviruses[27]; the interpretation of these results, however, has been questioned.[28] Also, it is conceivable that a given virus could have more than one receptor, enabling it to infect different types of cells at different key stages in pathogenesis. Thus, at the site of initial infection, rabies virus may bind to acetylcholine receptors at the neuromuscular junction, but at a later stage to ganglioside receptors on neural cells.[29]

Mere binding of virus to the host cell does not ensure productive infection, which depends on successful completion of a subsequent series of events including, for example, penetration into the cell and uncoating. Transfected mouse cells or HeLa cells expressing the human CD4 molecule on their surface bind HIV but do not thereby become susceptible to HIV infection. Also, cells lacking the specific receptor can sometimes be infected. There are alternative receptors or alternative modes of entry into the cell. For instance, virus particles coated with specific antibody could bind to Fc receptors rather than to virus-specific receptors on macrophages. If these cells are inherently susceptible, they are then infected, with the virus-specific antibody enhancing rather than preventing infection. This is a well-established phenomenon, which is important in the pathogenesis of dengue hemorrhagic fever.[30]

Tropism Based on Postpenetration Events

Even when the virus has attached to the cell and entered it, there is no guarantee that this leads to productive replication. Three examples of this will be discussed.

Cell Differentiation and Susceptibility

Many viruses enter cells but subsequent expression of the virus is determined by the state of differentiation of the cell. This is probably the reason why mouse embryo or newborn mouse cells are susceptible to such a wide variety of viruses compared with adult cells or adult animals. A classic example of cell differentiation and susceptibility is seen with papillomaviruses. In a papillomavirus skin lesion in cottontail rabbits, basal epidermal cells may contain the viral genome, but viral antigens and finally virus particles are produced only as the differentiating cells become keratinized and squamified, and as they move to the surface layers.[31] This is true for human papillomaviruses such as HPV1[32] and for adenovirus type II.[33] We understand nothing of the biochemical basis for this.

Viral dependence on cell differentiation can be especially important when immune cells are infected or when latent infection becomes productive only as cells differentiate. It has long been known that measles, which fails to replicate in normal (resting) human peripheral blood lymphocyte cultures, does so when the cells undergo differentiation.[34] Cells to which virus has been added can be maintained *in vitro* for a week or more but productive replication does not occur until mitogen (PHA) is added to induce differentiation. T cells then become permissive, but fail to divide because of a virus-induced block in the G1 stage of the cell cycle.[35] Similar phenomena are seen with B cells.[36] HIV infection of CD4-positive T cells becomes more efficient as these cells are activated during the course of an immune response and express an increased density of CD4 molecules on their surfaces.[17] Visna, another retrovirus, infects monocytes abortively with low level transcription of viral RNA, but the infection becomes more productive as the cells differentiate and become macrophages.[37,38] The expression of yet another retrovirus is increased when B lymphoma cells differentiate into immunoglobulin-producing cells.[39]

Hepatitis B virus expression is controlled by the combined action of an enhancer and a viral core gene promoter.[47] The enhancer is preferentially expressed in hepatocytes, with the promoter active only in differentiated hepatocytes explaining the greater susceptibility of these cells.

Examples of the influence of cell differentiation on virus replication are included in Table 2. The mechanisms are unknown. Dependence of viral replication on the state of differentiation of the host cell may explain other tropisms. For instance the vulnerability of cells to parvoviruses depends on their mitotic state. Feline panleukopenia virus preferentially infects mitotic cells in bone marrow and intestinal epithelium giving rise to leukopenia and diarrhea, and in the cat fetus the mitotic germinal cells of the cerebellum are destroyed giving rise to cerebellar hypoplasia.[50] The human parvovirus, B19, preferentially infects hemopoietic (erythroid) progenitor cells in the bone marrow,[51] with severe consequences if there is a pre-existing chronic anemia.[52]

Transgenic Mice

Work with transgenic mice makes it clear that, no matter how many different types of cells it actually gets into, a virus can replicate only in certain cells of a given host. To produce transgenic mice, viral DNA is injected into the nucleus of fertilized eggs that have been washed out from the oviduct of mice. The eggs are then implanted into pseudopregnant females. Some of them develop normally, and offspring can be obtained in which the injected DNA is integrated into the genome of all cells, as determined by analysis of DNA in a small piece of tissue taken from the end of the tail. From these founder mice a colony is formed. Small et al[53] produced transgenic mice in which every cell contained the early region of the JC (papovavirus) genome. This codes for the large T and small t antigens and contains the viral enhancer sequences. JC virus is known to infect human oligodendrocytes, and as a result causes progressive multifocal leucoencephalopathy. The mice appeared normal at birth but developed a neurologic disease at 2 to 3 weeks, with visible abnormalities in oligodendrocytes and in the myelin sheaths formed by these cells. There were no detectable abnormalities in the peripheral nervous system or elsewhere in the body. Transcription of viral DNA was detected especially in the brain. Evidently the viral sequences, although present in all cells, were recognized and expressed predominantly in oligodendrocytes, as shown by the presence of T antigen and T antigen mRNA by immunochemistry and *in situ* hybridisation.[54] As a result, oligodendrocyte function was impaired and myelin production inhibited, giving rise to the disease. It is believed that specific recognition of JC virus enhancer sequences by the oligodendrocyte[55] results in expression of the associated sequences and forms a basis for the striking cell tropism shown by this virus.

The same technique has been applied to hepatitis B virus. Burk and colleagues[56] produced mice in which every cell contained greater than genome length hepatitis B DNA sequences. All mice have HBs antigen in serum, and the viral sequences are preferentially expressed in the liver, kidney, and pancreas, with HBs antigen RNA transcripts detected by Northern (RNA) blot analysis. Again, specific recognition means that only certain cells are susceptible no matter how many contain the virus. Of interest, the kidney and pancreas are sites of growth for the related hepadnavirus that infects ducks.[57]

The work with transgenic mice identifies blocks in viral transcription that form the basis for tissue tropism. Even

Table 2. *Examples of Influence of Cell Differentiation on Virus*

Virus	Nonproductive infection	Productive infection	Reference
HIV	Resting CD4 + T cell	Activated CD4 + T cell*	42 17
HPV	Basal epidermal cell	Keratinised epidermal cell	32
Visna	Monocyte	Macrophage	38
Measles†, VSV, HSV	Resting T cell	Activated T cell	40, 41
Mouse CMV	Undifferentiated teratocarcinoma cell Latently infected spleen cell	Differentiated teratocarcinoma cell Differentiating (DMSO treated) cell	43 44 45
Mouse polyoma virus	Embryonic carcinoma cells	Differentiating (retinoic acid treated) cells	46
Hepatitis B	Undifferentiated hepatocyte	Differentiated hepatocyte	47

* Viral transcription is also stimulated by defined proteins from HSV and adenovirus.[49]
† Measles virus also inhibits DNA synthesis in T cells[48].

when transcripts are formed, there is the possibility of translational restriction. For instance, mRNA may fail to associate with polysomes in the infected cell, so that there is no viral protein synthesis. This occurs in mouse L cells infected with an avian reovirus, and explains the host range restriction of this virus, which multiplies in avian but not in mouse cells.[58]

Posttranslational Cleavage

In the cases of orthomyxoviruses (influenza) and paramyxoviruses (eg, parainfluenza viruses and respiratory syncytial virus), a large envelope protein is produced in the infected cell that must be cleaved if the progeny virus is to be fully infectious. A host cell protease is responsible for cleavage and unless the correct protease is present the virus particles formed will be noninfectious. Thus, influenza A virus infects Martin-Derby Canine Kidney (MDCK) cells, but in these cells the primary hemagglutinin polypeptide (Ho) is not cleaved to form HAl and HA2. The infection is nonproductive unless trypsin is added to the culture medium. This is not an irrelevant *in vitro* phenomenon. The virulence of avian influenza virus (H5N2) in chickens has been explained in terms of the ability of host proteases to cleave the hemagglutinin molecule. A single amino acid change at residue 23 of hemagglutinin, probably by affecting glycosylation, results in a change in susceptibility to protease, and thus a change in virulence.[59-61] More virulent strains of virus have a hemagglutinin that is cleaved more readily and in a greater variety of cells, so that these strains are more likely to reach suitable cells during their spread through the birds' body from primary replication sites in the gastrointestinal tract.

A mutant of Sendai (parainfluenza type 1) virus that is cleaved by trypsin replicates in the mouse lung where trypsin is locally available and causes pulmonary disease, whereas a strain that needs chymotrypsin for cleavage fails to replicate and cause disease. Even when pretreated with chymotrypsin, which enables it to infect an initial set of cells, this strain was unable to establish successive cycles of growth and was nonpathogenic.[62] A similar mechanism may determine the virulence of Newcastle Disease virus[63] and possibly respiratory syncytial virus virulence in humans.[64]

The requirement for a suitable protease has also provided an interesting mechanism for the increased pathogenicity of influenza virus in the presence of secondary bacterial infection. Some strains of *Staphylococcus aureus* produce the correct protease, and in mice concurrent infection with *S. aureus* can convert an otherwise avirulent influenza virus infection into a lethal one, with a striking increase in the extent of virus replication in the lung.[65] The enhancing effect of *S. aureus* was prevented when a protease-inhibitor was given.[66]

Virus Tropism Determined by Temperature, Chemical, or pH Barriers

The above phenomena showed how restriction of viral replication can operate after penetration into the cell and contribute to the observed tropism. There are also other types of restrictions that can provide a basis for viral tropism.

Temperature

It is well known that optimum multiplication of *Mycobacterium leprae* takes place a few degrees below central body temperature. This helps explain the striking disease pattern in lepromatous leprosy, that exhibits extensive multiplication of bacteria in nasal mucosa, skin, and superficial nerves. The tropism of rhinoviruses for the upper respiratory tract is also at least partly attributable to their optimal

replication at 34 to 35 C rather than at 37 C. During the course of a natural infection, rhinoviruses are constantly introduced into the lower respiratory tract by, for instance, aspiration during sleep,[67] but they fail to replicate here.

At febrile body temperatures the replication of some but not all viruses is reduced, and in the case of influenza virus the ability to replicate at pyrexial temperature may contribute to virulence.[68] Perhaps the polymerase of virulent virus strains is less temperature dependent.

pH

After influenza virus has been taken up into a phagosome in a susceptible cell, the hemagglutinin binding the virus to the cell must be converted into a fusion molecule that can fuse the viral envelope to the host cell membrane and introduce viral nucleocapsid into the cytoplasm.[69] The conversion of the hemagglutinin takes place as the pH in the vacuole falls, and if it fails to do so the infection may be blocked at this stage. Virus strains whose hemagglutinin has a changed pH optimum for fusion may show changes in replication.[70] This requirement is specific for influenza, certain togaviruses, and rhabdoviruses, and does not apply to paramyxoviruses (eg, parainfluenza, measles, and mumps), herpes simplex, or HIV, in which fusion occurs at neutral pH. Because most cells are capable of producing acidic conditions in endosomes, however, it is not strictly a determinant of tropism.

Viruses may show a tropism for certain body surfaces as a result of pH restrictions. For instance, picornaviruses that infect through the alimentary canal (polioviruses, coxsackie viruses, and echoviruses) tend to be resistent to low pH. In contrast, those picornaviruses that infect the respiratory tract (rhinoviruses and foot and mouth disease virus) are inactivated by acid pH. Similar comments can be made about bile salts, to which enveloped viruses are sensitive. Viruses that infect through the alimentary canal tend to be nonenveloped and bile resistant, (adenoviruses, enteroviruses, and rotaviruses). These viruses, some of which replicate elsewhere in the body (eg, enterovirus 72, alias hepatitis A), can then be shed into the alimentary canal from the biliary tract.[71]

Apparent Tropism Based on Failure to Arrive; Local Barriers

A cell may be susceptible to a virus but escape infection because the virus fails to reach it. In a systemic viral infection, there are generally multiple steps in pathogenesis that involve replication in different body sites before the virus has access to a target organ involved in the disease. For instance, polioviruses reach the blood in many infected individuals, but fail to invade the central nervous system, although neural cells are susceptible. The barrier is at the blood–brain or blood–CSF junction. The exact mechanism is not known, but in the case of the blood–brain barrier it could be, among others, a failure of the circulating virus to attach to capillary endothelium, a failure to infect or be transported across this endothelium, a failure to traverse basement membrane, or failure to infect perivasular astrocytes. Similar possibilities based on ultrastructure apply to the blood–CSF barrier. The blood–brain barrier has been invoked in many classic studies of the pathogenesis of viral infections in laboratory animals.[72–74] For instance, adult mice, unlike infant mice, are resistant to extraneurally inoculated yellow fever (17D) virus, but develop encephalitis when virus is injected directly into the brain. The concept of a blood–brain barrier was highlighted when it was shown that intraperitoneally inoculated virus spread to the brain and caused encephalitis in adult mice when an intracranial injection of starch was given at the same time.[75] Mere insertion of a needle into the brain was effective. This formed the basis of the intraperitoneal protection test for antibody that was extensively used in world surveys of immunity to yellow fever in the 1930s.

Within the central nervous system, apparent targeting of infection and pathology can result from cell-to-cell spread of the virus. For instance, in experimental infection of animals with herpes simplex virus, nearly all neural cells seem susceptible, but specific areas of the brain and spinal cord are involved because of transneuronal spread. The pattern of infection depends especially on the route of inoculation.[76] Indeed, herpes simplex virus could be used as a transneuronal tracer. Agents of the scrapie group have also been shown to target certain areas of the CNS, not because the cells in these areas are particularly susceptible, but because of spread along neural pathways.[77] Spread of rabies virus along axons targets infection from the local site of infection to the central nervous system, and then from the central nervous system to the salivary gland and dermis. If the lacrimal nerve of an experimentally infected fox is removed, the virus fails to infect the salivary gland.

A similar failure to arrive lies behind the apparent lack of hepatotropism shown by certain viruses in mice. After intravenous injection, viruses are rapidly taken up by Kupffer or endothelial cells in liver sinusoids. Viruses that then replicate in these cells can reach and infect the neighboring hepatic cells and cause hepatitis.[78] Those viruses that fail to replicate in Kupffer or endothelial cells (eg, white strains of vaccinia virus, influenza, and myxoma viruses) do not infect hepatic cells, although their ability to do so *in vivo* is revealed when the virus is introduced directly into hepatic cells as a result of injection up the bile duct.[79] Clearly no circulating virus can express its hepato-

tropism unless it first localizes in sinusoids. Throughout evolution the reticulo–endothelial system, by taking up circulating virus particles, has constantly given them the opportunity to evade destruction in Kupffer cells and infect hepatic cells.

Failure to arrive is strikingly exemplified in the case of the fetus.[80] Most viruses are capable of replication in fetal tissues, but only a few are given the opportunity. The requirement is that circulating virus or virus-containing leukocytes first localize in placental vessels and after replication in the placenta the virus reaches the fetal circulation. Fetal invasion occurs regularly with rubella and cytomegalovirus in humans, and with parvoviruses and certain togaviruses in animals, but the mechanisms, for instance, in terms of virus receptors on vascular endothelium or placental cells, are not understood.

Cytomegalovirus (CMV) infects a variety of cells and tissues during natural infection of humans, but displays an even greater pantropism after infecting children with severely impaired immune responses. In these individuals CMV causes lethal disease with infection, as demonstrated by *in situ* hybridization with biotinylated DNA probes, in, for example, hepatocytes, pancreatic acinar cells, myometrium, cardiac muscle cells, and anterior pituitary cells.[81] The catastrophic failure to control the infection gives CMV a rarely offered opportunity to infect these cells, presumably as a sequel to localization and infection in vascular endothelium.[82]

Many other viruses are capable of infecting vascular endothelium *in vitro*[83] and probably *in vivo*. Under normal circumstances, however, this is often prevented because the circulating virus is rapidly removed by macrophages of the reticuloendothelial system. When reticuloendothelial function is depressed, circulating virus has the opportunity to infect vascular endothelium elsewhere in the body.[84]

Epithelia on the body surfaces provide a final example of failure to arrive. The pathogenesis of influenza virus has long been studied in ferrets, in which the respiratory infection is more similar to that of man than is the case of the laboratory mouse. It was found that influenza virus, when given the opportunity, is also able to infect the epithelium of the urinogenital tract in ferrets.[68] Under normal circumstances expression of this tropism is unlikely, but in humans it is not beyond the bounds of possibility. It would be interesting to know whether human urethral epithelium is susceptible *in vitro,* because this could conceivably provide a basis for a new type of sexually transmitted disease. It may be noted that many microorganisms can move from the urethra to conjunctiva and vice versa. Among these are gonococci, meningococci (occasionally isolated from the urethra), chlamydia, and adenovirus type 19.[85]

Virus Localization in Vascular Beds of Specific Organs

Circulating viruses reach distant organs and tissues after localization in capillaries and venules. There is a real possibility that viruses show preferential localization in the vascular bed of certain organs. In other words, mumps virus, for instance, might bind to and infect specifically the vascular endothelial cells in parotid glands (and also in meninges, mammary glands, and pancreas), whereas measles virus localizes in and infects capillary endothelium in the dermis[86] and in subepithelial sites in the respiratory tract and elsewhere. A possible basis for this is provided by *in vitro* studies with various viruses in endothelium from different sites in the body.[87] It was found that when measles virus grew in endothelium from the pulmonary artery of the bovine fetus, the yield of virus was 500 times greater than in the case of endothelium from the inferior vena cava.

It is possible that in the intact host viruses preferentially infect endothelium in certain tissues, although there is no direct evidence for this. An alternative explanation is that the circulating virus localizes equally well in all vascular beds, but that subsequent events (eg, transit or growth across endothelial cells and invasion of adjacent parenchymal cells) only occur in certain tissues.

The circulating virus may be free in the plasma (eg, poliovirus and yellow fever virus) or present in infected leukocytes or platelets (eg, herpesviruses, measles, and HIV); localization will follow different rules. In a recent study, various fractions of distemper virus-infected blood were infused into the carotid artery of a dog, and it was found that infected platelets were more than a 100 times more effective than mononuclear cells in initiating infection in cerebral vascular endothelium.[88]

Recent work on the site-specific localization of circulating immune cells gives fresh interest in the possible site-specific localization of circulating viruses. An effective immune response depends on selective trafficking of lymphocytes between tissues, and the localization of circulating lymphocytes in lymph nodes occurs in postcapillary venules, where there is a special type of high endothelium. On venular endothelium in Peyers' patches, intestinal lamina propria, and lactating mammary gland a mucosal "vascular addressin" is selectively expressed, and the binding of lymphocytes to this molecule can be blocked by a specific antibody.[89,90] The adhesion molecule (addressin) that is selectively expressed on venular endothelium in peripheral lymph nodes was defined by monoclonal antibodies[91] and others have been described.[92] The molecules on lymphocytes that control their tissue specific homing are now being identified.[93]

Conclusions

Viral tropism remains an intriguing problem, and recent advances throw fresh light on possible mechanisms. Many aspects of virology are now being illuminated with speed and precision by molecular biological methods. The analysis of virulence is a key target, and viral tropism forms an important part of this. Determinants of viral virulence tend to be multiple, but guilty viral gene segments and gene products are being identified. But we still do not understand their mode of action *in vivo*. The interplay with host defences must be understood, although the immune system at present seems choked with a surfeit of mediators of possible pathogenic and protective pathways. Host immune defences are complex, and some clarification is needed. It will be essential to give continued attention to pathogenesis and its biochemistry and physiology if we are to understand the action of viral gene products and their relationship to host defences, and thus enjoy the full fruits of the molecular biological revolution.

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