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1

Viruses, virulence and pathogenicity

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Virus, a Latin word meaning poison, was once used as a generic term for agents of disease. After the discovery of bacteria in the 19th century, 'viruses' became those agents which passed through filters known to remove bacteria. Identification of viral diseases such as smallpox dates back to the 24th century B.C.E., greatly preceding characterization of viruses themselves (Lwoff, 1957). Several millenia later, Stanley crystallized the 'protein' which causes tobacco mosaic disease (Stanley, 1935). Interest in viral disease continues to be the driving force behind much of virology (Smith, 1972).

Two terms dominate discussion of the relationship between viruses and disease: pathogenicity and virulence. Pathogenicity is a categorical term describing the ability of an agent to cause disease. Virulence is a comparative or quantitative term describing the relative probability that ill effects to the host will result from exposure to an agent (Miles, 1955). Pathogenicity refers to those characteristics of a virus which make disease possible; virulence those which make it likely.

In order to cause disease, viruses generally must enter the host, multiply in host tissues, and damage host cells (Smith, 1972). In addition, agents of chronic infection also require a means of evading host defences (Smith, 1980). Thus, these simplest of pathogens have complex requirements for pathogenicity, and only a minority are pathogenic in particular species of host. Even a pathogenic virus may have quite limited virulence for a particular host species. In humans, for example, clinically apparent illness results from only a minority of infections with such dreaded agents as poliovirus (Ray, 1991) dengue (Guzman et al, 1990) and the encephalitis viruses (Centers for Disease Control, 1994). The proportion of cases per exposure is even lower, since not all those exposed become infected. With these and other viruses, host factors appear to play a major role in determining who will suffer disease as a result of exposure. Among the several factors contributing to pathogenicity, this chapter will emphasize mechanisms of damage to host cells and their role in determining virulence.

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ENTRY INTO TARGET CELLS

Entry into the host usually requires binding between a molecule on the viral surface and a cellular receptor molecule on membranes of host cells (Williams et al, 1986; Lentz, 1988). There is experimental evidence to characterize biochemically only a handful of human cellular receptors for viruses (Lentz, 1990). In addition to binding studies, further functional evidence is required to implicate a particular molecule as a cellular viral receptor. Such evidence includes abrogation of infection by specific antibody blockade, competition with free receptor molecules, genetic absence of the receptor, or biochemical inactivation of the receptor. Transfer of susceptibility to cells provided with the receptor molecule or the gene encoding it provides excellent proof in some cases. Human viruses whose cellular receptors have been characterized include Epstein–Barr virus (EBV), echoviruses, human immunodeficiency virus (HIV), poliovirus, parvovirus B19, rabies virus, and rhinoviruses (Table 1).

The distribution of specific receptors contributes to species tropism, since a virus cannot infect a cell to which it has no means of entry. Poliovirus, for example, is confined to primates because its cellular receptor is not found in nonprimate species. Transgenic mice which express human poliovirus receptor can be infected with the poliovirus and develop paralysis (Koike et al, 1991), which does not occur in wild-type mice.

Receptor distribution can also limit pathogenicity within species. SJL/J mice make a truncated allotype of the 110 kDa murine coronavirus receptor, and they cannot be infected with murine hepatitis virus (Williams et al, 1990). The receptor for parvovirus B19 is absent from some members of an inbred human community, who are resistant to infection with this virus (Brown et al, 1994).

Among susceptible individuals, receptor distribution limits tissue tropism. EBV can only be grown in vitro in cells which express complement receptor 2 (CR2, also CD21). Resting B-cells express CR2 and can be infected readily, but after proliferation begins the cells lose CR2 expression and can no longer be infected (Inghirami et al, 1988). Since EBV causes transformation of nasopharyngeal epithelial cells in vivo, and these cells do not constitutively express CR2, there must be an alternate means of entry into these cells. IgA may act as a Trojan horse to conduct antibody-coated virions into epithelial cells through IgA receptors (Sixbey and Yao, 1992).

Cellular receptors represent a potential weak point in virulence to be exploited therapeutically (Lentz, 1990; Colonno, 1992). The use of unbound receptors as decoys has been advocated for therapy of viral infections, most notably HIV (Capon and Ward, 1989; Anonymous, 1990; Chaldakov, 1990). This approach appears effective in vitro (Smith et al, 1987) but disappointing in vivo. Higher soluble receptor concentrations are required to block infection by wild-type virus, as opposed to laboratory isolates (Daar et al, 1990; Daar and Ho, 1991). Although CD4 is the principal cellular receptor for HIV, it does not appear to be the unique receptor (Clapham et al, 1989; Clapham, 1991), a situation likely with other viruses as well.

Table 1. Early descriptions of selected cellular virus receptors.

Virus	Receptor	Evidence	Selected references
Echovirus 1	Integrin VLA-2 (collagen-binding protein)	Blockade; transfer	Bergelson et al (1992)
Echovirus 7	CD55 (decay accelerating factor)	Blockade; inactivation	Bergelson et al (1994)
Epstein–Barr virus	CD21 (complement receptor 2)	Blockade; transfer	Fingeroth et al (1984)
Human immunodeficiency virus	CD4	Blockade	Dalgleish et al (1984); Klatzmann et al (1984)
Parvovirus B19	Erythrocyte P antigen	Blockade; competition; genetic defect	Brown et al (1993); Brown et al (1994)
Poliovirus	Poliovirus receptor*	Transfer	Mendelsohn et al (1989); Bernhardt et al (1994)
Rabies virus	Acetylcholine receptor	Inactivation	Lentz et al (1982)
Rhinovirus	Intracellular adhesion molecule 1 (ICAM-1)	Blockade; transfer	Greve et al (1989); Staunton et al (1989)

*The poliovirus receptor is an 80 kDa glycopeptide of the immunoglobulin superfamily, whose physiological role remains under investigation

REPLICATION

Molecular mechanisms of viral replication are plentiful and diverse and beyond the scope of this chapter to review in their entirety. Recent reviews of specific viral replication schemes may of interest to the reader (Garcia-Blanco and Cullen, 1991; Lambert, 1991; Mergia and Lucia, 1991; Nibert et al, 1991; Porter, 1993; Snijder and Horzinek, 1993).

The dependence of viral replication on host cell factors further narrows the tropism of viral infection. The receptor for parvovirus B19, for example, is found on endothelial and myocardial cells in vivo (Von dem Borne et al, 1986; Rouger et al, 1987), but replication in vitro has only been observed in erythroid progenitors (Mortimer et al, 1983; Young et al, 1984) and cell lines originating from megakaryocytic leukaemias (Shimomura et al, 1992; Munshi et al, 1993). B19 genes are transcribed in nonpermissive cells, but replication does not occur (Liu et al, 1992). This finding implies that a required post-transcriptional replication factor is found only in haematopoeitic progenitors, or that a post-transcriptional blocking factor is present in all other cells. In this and most cases, the specific cellular factors necessary for viral replication remain unknown. Viral growth in cell-free systems is therefore difficult or impossible for most viruses.

The site of viral replication does not always determine the site of disease. For example, Cas-Br-E is a retrovirus which causes spongiform degeneration of the murine central nervous system. Immunohistochemical staining for the viral envelope protein shows that it is synthesized in the thymus and spleen, but not neurons, of infected animals—indicating that complete replication occurs in the former but not in the target tissues (Sharpe et al, 1990). Central nervous system pathology in Cas-Br-E infection is presumed to be mediated by infected cells of the immune system, not by a direct effect of the virus on nervous system parenchyma. Similarly, the virulence of murine hepatitis virus correlates with 1000-fold strain-to-strain variation of replication potential in macrophages. Replication in hepatocytes remains relatively constant from strain to strain (Taguchi et al, 1983).

Although viruses must usually replicate in order to cause disease, in rare instances replication is not required. Very large intranasal doses of human adenovirus type 5, for instance, cause pneumonia in mice, even though the virus is unable to replicate in this host (Ginsberg et al, 1991).

DAMAGE TO HOST CELLS

Once established, viral infection can damage the host directly or indirectly (see Table 2). Direct damage occurs when the infecting virus itself transforms, kills, or disrupts the metabolism of infected cells. Indirect damage is mediated by the response of the host to the virus. Examples of indirect damage include immune responses directed against either infected or uninfected cells. In some cases, indirect damage results from viral peptides which resemble host hormones or cytokines and harm by dysregulating host physiology.

Table 2. Mechanisms of host injury during viral infection.

Mechanisms	Example	Selected references
Direct		
Transformation	Human papilloma virus E7 oncoprotein binds to retinoblastoma gene product	Dyson et al (1989)
Inactivation of suppressor gene		
Activation of protective gene	Epstein–Barr virus induces *bcl-2* expression	Henderson et al (1991)
Suppression of cell metabolism	Lymphocytic choriomeningitis virus suppresses growth hormone production by murine pituitary cells	Oldstone et al (1984)
Apoptosis	Lytic Epstein–Barr virus infection	Kawanishi (1993)
Indirect		
Autoimmune		
Directed against infected cells	Coxsackievirus B3 myocarditis	Wolfgram et al (1985); Kandolf et al (1987); Neumann et al (1992)
Directed against uninfected tissues	Hepatitis B e antigen causes membranous glomerulonephritis	Lai et al (1991)
Molecular minicry		
Hormonal	Friend spleen focus-forming virus 55 kDa glycopeptide mimics erythropoietin	Li et al (1990); D'Andrea et al (1992)
Cytokine	Epstein–Barr virus BCRF1 product mimics interleukin-10	Moore et al (1991); Vieira et al (1991)

TRANSFORMATION

Neoplastic transformation was first attributed to a filterable agent by Rous (1911), who transmitted a sarcoma to four of ten inoculated chickens. Viral transformation may occur by inactivation of host genes or gene products whose normal function is to kill the infected cell. Viruses can also immortalize cells by upregulation of genes whose products protect the cell from physiological death. Examples of genes whose inactivation results in transformation include the retinoblastoma gene and *p53* (DeCaprio et al, 1988; Whyte et al, 1988; Dyson et al, 1989; Levine et al, 1991; Nevins, 1992). *Bcl-2* is a gene whose upregulation is important in the immortalization of EBV-infected cells (Henderson et al, 1991). Transformation is the topic of an immense literature and several recent reviews (Lentz, 1990; Colonno, 1992; Joske and Knecht, 1993; Khoobyarian and Marczynska, 1993; Nevins, 1993; McDougall, 1994; Ullrich et al, 1994) and cannot be discussed extensively in this chapter. Other chapters in this volume deal with transforming viral

infections of the marrow and reticuloendothelial system (see chapters 4, 6 and 10).

SUPPRESSION OF CELLULAR METABOLISM

In contrast to transformation, directly toxic effects of viruses resulting in host cell death are sparsely described at the molecular level. Such effects of viruses on cells can best be defined in vitro, in the absence of the host immune system, where any observed cytopathological effect (CPE) can be attributed to the virus itself. The mechanism of damage is seldom defined in CPEs. The death of infected cells has been blamed on overwhelming burdens of viral material or starvation due to the hijacking of cellular metabolism by the invading virus (Oldstone, 1989; Welsh and McFarland, 1993).

Specific viral gene products have been identified which downregulate cellular metabolism. The *S4* gene of reovirus, for example, codes for a protein (σ3) which impedes cellular transcription and translation (Sharpe and Fields, 1982), while the *S1* gene of the same virus downregulates replication of cellular DNA (Sharpe and Fields, 1981). It is not clear that these effects by themselves are sufficient to bring about the death of the host cell.

Damage to cellular metabolism may cause significant pathology without cell death and even without a CPE. An example is the runting syndrome of mice, in which lymphocytic choriomeningitis virus (LCMV) suppresses growth hormone production by the pituitary without causing microscopically evident damage to pituitary tissue (Fields, 1984; Oldstone et al, 1984).

CELL DEATH

More recent literature distinguishes a programmed form of cell death, called apoptosis (Kerr et al, 1972), which can occur in, response to viral infections. Apoptosis is cellular suicide in which chromatin degradation precedes loss of membrane integrity (Cohen, 1993). Apoptosis causes DNA cleavage between nucleosomes, and DNA from apoptotic cells is present in multimers of the nucleosomal unit, about 180 bp, seen as a characteristic ladder on electrophoresis (Wyllie, 1980). Flow cytometry using a stain which intercalates with DNA, such as propidium iodide or acridine orange, identifies an apoptotic population of small cells with minimal light scatter (Dive et al, 1992). Apoptosis is promoted by *p53* and other 'tumour suppressor' genes which are inactivated in transformed cells (Levine et al, 1991; Debbas and White, 1993; Fujiwara et al, 1993). The apoptotic program is arrested by the *bcl-2* gene product, which antagonizes *p53* and other apoptosis-inducing gene products (Chiou et al, 1994).

Because apoptosis involves destruction of genetic material prior to disruption of the membrane, it can provide a physiological defence mechan-

ism against intracellular pathogens (Cohen, 1991). Viral DNA is destroyed along with the host DNA prior to membrane rupture of the apoptotic cell (Sellins and Cohen, 1989; Martz and Gamble, 1992). Another advantage to the host is that apoptosis avoids necrotic cell death and accompanying inflammation. The destruction of marrow cells by parvovirus B19, for example, appears to occur by means of apoptosis, which may explain the relative absence of inflammation in infected marrow (Morey et al, 1993).

In most instances of virally mediated apoptosis, cell death appears to be an active response of the host. Virally induced apoptosis often requires protein synthesis and is susceptible to cycloheximide blockade (Groux et al, 1992; Kawanishi, 1993; Takizawa et al, 1993). In addition to being a direct response of infected cells, apoptosis is also the means by which cytotoxic T-lymphocytes kill their targets (Duke et al, 1983; Cohen et al, 1985; Allbritton et al, 1988; Moss et al, 1991), including cells expressing viral target antigens (Welsh et al, 1990; Ando et al, 1993).

Apoptosis can be induced by infection of cells with intact virus (Terai et al, 1991; Groux et al, 1992; Kawanishi, 1993; Takizawa et al, 1993; De Rossi et al, 1994; Hinshaw et al, 1994; Martin et al, 1994) or expression of viral genes in vitro. Apoptosis follows expression of the HIV glycoprotein gp160 in transfected human monocytoid cells (Lu et al, 1994) and of a single coat protein of the chicken anaemia virus in lymphoid and myeloid progenitors (Noteborn et al, 1994).

Apoptosis can be triggered by viral infection but depends upon the presence or absence of host factors for completion. Viral pathogenicity may modify or be modified by the apoptotic program of the host cell. Influenza viruses infecting many species induce apoptosis in canine kidney cells in vitro (Takizawa et al, 1993; Hinshaw et al, 1994). Apoptosis correlates with cytopathic effect and can be blocked with transfection of *bcl-2* into the infected cell (Hinshaw et al, 1994). Sindbis virus, a togavirus, causes apoptosis in non-neuronal cells. In contrast, Sindbis virus establishes a latent infection in neurons (which express *bcl-2* constitutively) or in non-neuronal cells into which the gene for *bcl-2* has been transfected (Levine et al, 1993). Apoptosis occurs during EBV infection when latent virus is activated by *n*-butyrate and tetradecanoyl phorbol acetate or when latently infected cells are superinfected with exogenous EBV (Kawanishi, 1993). Cellular expression of adenovirus E1A proteins induce apoptosis, but further expression of a 19 kDa viral E1B protein blocks apoptosis of the infected cell, as does *bcl-2* expression (Rao et al, 1992; Chiou et al, 1994). These results are consistent with viral evolution of a countermeasure to this cellular defence mechanism.

SPECIFIC IMMUNE RESPONSES DIRECTED AGAINST INFECTED CELLS

Viral infection in vivo frequently results in tissue damage mediated by the host immune system. The immune response is influenced by the genetic background of the host. In the New Zealand black mouse, which is predisposed to autoimmune disease, viral infection increases the expression of

autoantibodies and the incidence of autoimmune pathology (Tonietti et al, 1970).

Immune effects can be specific to infected tissues, as in coxsackievirus B3 (CB3) myocarditis. CB3 is cardiotropic (Woodruff, 1980). In situ hybridization studies reveal that almost one-third of human myocarditis patients have the genome of CB3 or related enteroviruses present in heart tissue (Kandolf et al, 1987). In mice, CB3 infection leads to production of antibodies which bind to the heart muscle (Wolfgram et al, 1985), including antibodies to cardiac myosin (Alvarez et al, 1987; Neu et al, 1987a; Neumann et al, 1992). Myocarditis can be induced in A/J mice by two subcutaneous injections of myosin or by inoculation with CB3—either treatment leads to production of antibodies against myosin as well as other cardiac autoantigens (Neumann et al, 1994).

Coxsackie virus itself does not appear to be the principal target of the immune response in this animal model. Myocarditis-associated antibodies found in CB3-induced disease fail to crossreact with CB3 antigens (Neu et al, 1987b), and maximum pathology is visible after viral concentrations in target tissue have fallen (Lodge et al, 1987). It appears that CB3 infection is one of a number of noxious stimuli which lead to expression by the target cell of heat shock proteins, which provoke a cytotoxic T-lymphocyte (CTL) response (Ioannides et al, 1993). The pathogenicity of CB3 is not entirely governed by antigen-specific components of the immune system, however, since CB3 also induces myocyte death and nonspecific inflammatory infiltrates in the hearts of mice with severe combined immunodeficiency (Chow et al, 1992).

Immunological attack on infected tissue is also a pathogenic mechanism of viral hepatitis. Viral and autoimmune hepatitis share a number of features (Peters et al, 1991; Rehermann et al, 1994), including the production of anti-smooth muscle antibodies (Toh et al, 1979) and CTL infiltration (Koziel et al, 1992). Rarely, chronic hepatitis may result from autoimmune responses to cells injured during acute infection with hepatitis A virus (Vento et al, 1991). Transgenic mice expressing the hepatitis B surface antigen (HBsAg) under control of an albumin promoter develop CTL-mediated hepatitis when they are given spleen cells from animals previously immunized against HbsAg (Moriyama et al, 1990).

The genetic background of the host is a significant determinant of virulence in virally initiated autoimmune disease. Human T-cell leukaemia virus I (HTLV-I), a retrovirus, infects neuronal cells in vitro and is associated with inflammatory destruction of neuronal tissue in vivo (Gessain et al, 1985; Osame et al, 1986). An intriguing feature of HTLV-I-associated myelopathy is its apparent racial predilection: the vast majority of reported patients are of Asian or African descent, although HTLV-I-associated leukaemia occurs sporadically in people of European descent. This implies that a combination of host allotype and viral infection is required to bring about inflammatory damage to the nervous system.

The lifetime incidence of infection with some viruses is nearly 100%, but the incidence of autoimmune sequelae is very low. Subacute sclerosing panencephalitis is a disease in which blindness and severe neurological

deterioration accompany elevated immunoglobulin levels in the cerebrospinal fluid as well as lymphocytic and monocytic infiltration of the cerebral vasculature. Latent measles virus infection appears to be the cause (Degre et al, 1972; Link et al, 1972; Salmi et al, 1972; Thormar et al, 1973). The very low incidence of subacute sclerosing panencephalitis compared with the nearly universal incidence of measles prior to 1957 emphasizes the poorly defined but certain role of host factors in virulence.

OTHER IMMUNE RESPONSES

Previous examples have described immune responses directed against virally infected tissues. Autoimmune viral pathogenesis need not be so limited, however. Virally initiated immune responses may result in tissue damage remote from the infecting virus. One means by which this can occur is immune complex deposition, a good example of which is membranous glomerulonephropathy due to hepatitis B virus. The virus infects the liver, but e antigen is deposited in the glomerulus, causing thickening of the basement membranes and, in adults, irreversible renal damage (Lai et al, 1991). Some cases of mixed (type II) cryoglobulinaemia appear to be associated with hepatitis C (Ferri et al, 1991a,b,c), although the specific antigen responsible has not been identified. In 129/J mice, mucosal exposure to Sendai virus antigen or wild-type virus infection leads to glomerular IgA deposition—mice receiving mucosal immunization followed by a live virus challenge developed haematuria and pathological findings compatible with IgA nephropathy (Jessen et al, 1992).

Cytokine production is critical to tissue damage in some virally mediated diseases. In the murine model of adenovirus pneumonia mentioned earlier, tissue damage is accompanied by high levels of tumour necrosis factor-α, interleukin-1, and interleukin-6 in the target organ as well as high blood levels of interleukin-6 (Ginsberg et al, 1991). A more complex example is LCMV, which causes fatal encephalitis in mice. There is a 'docile' strain of LCMV that reproduces to high virus titre but causes limited or no disease and is associated with negligible interferon-γ production by the host (Jacobson et al, 1981; Pfau et al, 1983; Leist et al, 1987). Virulent strains reproduce to a lower titre but are much more likely to cause encephalitis because they trigger interferon production by the host; death can be averted by giving anti-interferon antibodies (Pfau et al, 1983). The 'nonvirulent' LCMV strain is lethal in some strains of mice, however. Susceptibility is dominant, and linked both to the major histocompatibility complex (MHC) and non-MHC determinants (Eyler et al, 1989). These results are consistent with an autoimmune mechanism of death in LCMV encephalitis.

In the murine LCMV model, immune activation is a two-edged sword. The combination of LCMV with specific allotypes triggers a massive T-lymphocyte response, overproduction of interferon-γ in the central nervous system, and neuronal death in consequence. Immunization of susceptible mice prevents subcutaneously injected virus from reaching the central nervous system. If docile virus, is introduced into the central nervous system

directly, however, previously immunized mice die while their unimmunized cohorts survive (Battegay et al, 1992).

The B10.A mouse is another example of an animal in which immune activation may work against the host. These mice are normally resistant to the CB3 model of murine myocarditis mentioned above. Even these mice will develop myocarditis if they are inoculated with lipopolysaccharide, interleukin-1, or tumour necrosis factor along with CB3. Inoculation with the cytokines or the virus alone fails to produce myocarditis (Lane et al, 1992, 1993). In the hearts of diseased mice, inflammatory cells secrete interleukin-1 and tumour necrosis factor. The authors of these studies suggest that circulating cytokines activate macrophages at the site of infection, which in turn activate CTL to release more cytokines, leading to a 'vicious cycle' of local inflammation in place of the benign natural history of infection in these animals (Lane et al, 1992, 1993). In similar experiments, normally refractory BALB/c mice were treated with the docile H310A1 strain of CB3. These mice also got CB3-induced myocarditis if they were pretreated with interleukin-1 or interleukin-2 (Huber et al, 1994).

Soluble factors and direct cell–cell communication are implicated in retroviral pathogenicity. Brain tissue exposed to culture fluids from HIV-infected macrophages shows cytoplasmic vacuolation; vacuolation is not seen in tissue exposed to supernatants from infected T-cells nor from uninfected macrophages (Pulliam et al, 1991). HIV-induced CPEs among neuronal cells in vitro may require contact between neurons and cytokine-producing macrophages (Genis et al, 1992), as well as local production of nitric oxide (Dawson et al, 1994). Tumour necrosis factor-α induces apoptosis in fibroblasts infected with feline immunodeficiency virus but not uninfected control cells (Ohno et al, 1993).

A more subtle but perhaps more clinically significant example of cytokine-mediated HIV pathogenesis concerns the cells of the immune system itself. T-lymphocytes from asymptomatic HIV-infected individuals undergo apoptosis when antigenically stimulated in vitro. Under these circumstances, the percentage of apoptotic cells is far greater than the percentage of infected lymphocytes, and the process involves $CD8^+$ as well as $CD4^+$ cells (Groux et al, 1992; Meyaard et al, 1992). This reveals an immune response deficit which does not depend directly on infection. Apoptosis of these cells may be prevented by antibodies to CD28 (Groux et al, 1992), the receptor for an antigen-presenting cell ligand. Transient immunodeficient states have been noted during infections with other viruses, so this effect does not appear to be unique to HIV. T-lymphocytes from LCMV-infected mice also undergo apoptosis upon antigen stimulation, and cell defect is enhanced by preincubating the cells in interleukin-2 (Razvi and Welsh, 1993).

MOLECULAR MIMICRY

A more elegant set of pathogenic mechanisms emerge when the similarity between viral and host cell antigens is considered (Oldstone, 1989; Barnett and Fujinami, 1992; Murphy, 1994). Damien (1964) first coined the term

'molecular mimicry' to describe the resemblance between parasites and their animal hosts. Most examples of molecular mimicry discovered since then have involved components of the host immune system (Gooding, 1992; Murphy, 1994).

In some cases, the evolutionary advantage of molecular mimicry to the virus is obvious and involves disruption of the host immune system. The BCRF1 reading frame of EBV, for example, contains significant homology to the human gene for interleukin-10—which impairs cellular immunity by downregulating interferon-γ and interleukin-2 production (Moore et al, 1991; Vieira et al, 1991). Other viral products with homology to immunoregulatory peptides include the vaccinia *B15R* gene (with homology to interleukin-1 receptors (Alcami and Smith, 1992)), the swinepox virus C6L gene (interferon-γ receptor (Massung et al, 1993)), the rabbit myxoma virus T2 and T7 genes (tumour necrosis factor receptor (Upton et al, 1991) and interferon-γ receptor (Upton et al, 1992), respectively) and IE2 protein of cytomegalovirus, (human and murine major histocompatibility complex class II β chains (Fujinami et al, 1988)).

Dysregulation of the immune system is not the only means by which molecular mimicry may work to the disadvantage of the host. EBV also codes for a nuclear antigen with a glycine–alanine repeat common to a number of host proteins, and autoantibodies directed against this motif are proposed as a means by which EBV might cause rheumatoid arthritis (Baboonian et al, 1991). In addition to inflammatory sequelae, neoplastic transformation can occur when viral peptides mimic a stimulatory cytokine or hormone. This is the mechanism used by the Friend spleen focus-forming virus, whose 55 kDa glycopeptide triggers the erythropoietin receptor and can induce erythroleukaemia (Li et al, 1990; D'Andrea et al, 1992).

VIRUSES AND DISEASES OF UNCERTAIN AETIOLOGY

Diseases of problematic aetiology have been attributed to autoimmune sequelae of viral infection. Generally, the supporting evidence consists of findings consistent with activation of the cellular immune system. Since cellular immunity is of particular importance in defence against viral infection, activation of the cellular immune system is attributed to infection with an unknown virus. Examples include diabetes mellitus, multiple sclerosis, and aplastic anaemia, as well as various other diseases of uncertain cause.

An infectious cause for diabetes has been sought since the early part of this century, when Gundersen (1927) noted an association between mumps epidemics and deaths due to diabetes in Norway. There is a slight seasonality to diabetes incidence, favouring winter months when many viral infections also peak (Gleason et al, 1982). It has been hypothesized that viral damage to islet cells provokes a CTL attack on the islets with subsequent development of diabetes (Craighead, 1981). Diabetes can be induced in mice by infection with the encephalomyocarditis virus (Craighead and Steinke, 1971), an effect which is lost in athymic mice (Buschard et al, 1976). In juvenile diabetes mellitus of recent onset in humans, there is infiltration of

$CD8^+$ CTL around the islets of Langerhans (Dalgleish et al, 1984; Santamaria et al, 1992), and γδ-T-lymphocytes within them (Santamaria et al, 1992). Early treatment with anti-T-lymphocyte therapy such as cyclosporin A can diminish and postpone the need for insulin therapy in recent onset juvenile diabetes (Feutren et al, 1986; Dupre et al, 1990). In newly diagnosed, untreated juvenile diabetes patients 21% of IgG-secreting cells were committed to production of anti-insulin IgG, compared with less than 4% among controls (Casali et al, 1990). Peripheral blood cells from diabetic patients or persons predisposed to diabetes show reactivity to the β cell enzyme glutamate decarboxylase; the major determinant recognized by T-cells has significant sequence similarity to the P2-C protein of Coxsackie B virus (Atkinson et al, 1994), although the precise role of this virus in the origin of diabetes is unknown.

Elegantly constructed transgenic models also show how diabetes can be induced by an autoimmune attack on infected tissue. Mice with transgenes for an LCMV glycopeptide gene under control of the insulin promoter do not become diabetic spontaneously but do develop insulitis and diabetes when exposed to LCMV infection later in life (Oldstone et al, 1991). Similarly, spontaneous diabetes does not develop in mice receiving transgenes for an LCMV glycopeptide and also a T-cell receptor specific for the viral peptide: infection is still required to produce diabetes in these mice (Ohashi et al, 1991). Infection is not required for development of diabetes in these animals if they also receive a transgene for the antigen presenting cell ligand B7 under control of the insulin promoter (Harlan et al, 1994). Expression of viral antigens on target cells can cause autoimmune disease in the host but only if the antigens are displayed in the appropriate immunological context.

It has long been known that the injection of brain and spinal cord extracts causes demyelinating disease in monkeys (Rivers et al, 1933) and other animals. The encephalitogenic fraction of these extracts was identified as a basic peptide of approximately 3000 Da (Carnegie and Lumsden,1966) referred to as myelin basic protein. Enhanced cellular immune response to myelin basic protein is a characteristic shared by multiple sclerosis and other demyelinating diseases (Gorny et al, 1983; Ota et al, 1990).

The reason this response develops in otherwise healthy human adults remains obscure. One possibility is that neurons are infected by a neurotropic virus such as the JC virus (Stoner, 1991), measles virus (McDermott et al, 1974), human herpes virus 6 (Wilborn et al, 1994) or possibly a retrovirus related to HTLV-I (Koprowski et al, 1985). According to this theory, infection of the neurons exposes antigens which provoke an attack by the cellular immune system (Allen and Brankin, 1993), somewhat analogous to the murine myocarditis model. In a related model, molecular mimicry between the virus and a native protein is responsible for an autoimmune CTL response.

Geographic and temporal clustering of multiple sclerosis (Riise et al, 1991) implies an infectious or environmental cause, while the 20-fold higher incidence of multiple sclerosis in kindreds with an affected member emphasizes the importance of genetic background (Compton, 1991). Both of these

epidemiological observations are consistent with the viral-autoimmune hypothesis (Brody, 1972).

There is also cross-reactivity between antibodies to measles virus and myelin basic protein (McDermott et al, 1974). Measles is an appealing candidate cause because of a study involving seven discordant twin pairs, in which the twin with multiple sclerosis was more likely to have a vigorous lymphoproliferative response to measles virus (Greenstein et al, 1984).

Aplastic anaemia (AA) is another disease in which there is evidence for enhanced CTL activity. Most AA patients respond to anti-T-lymphocyte therapy (Champlin et al, 1983; Bacigalupo et al, 1988). CTLs from AA patients are activated at the time of presentation (Zoumbos et al, 1984). There is increased production of bone marrow IFN-γ messenger RNA in AA (Nisticò and Young, 1994). Broad geographic differences in the incidence of aplastic anaemia exist on presentation (Linet et al, 1985; Young et al, 1986; Issaragrisil et al, 1991), supporting an infectious or environmental antecedent. No specific virus, however, has emerged as a likely cause.

Many diseases of unknown aetiology have autoimmune features. Evidence has been presented linking antecedent viral infections to rheumatoid arthritis (possibly associated with HTLV-I (Di Giovine et al, 1994) or EBV (Fox et al, 1992)), lupus erythematosus (with HTLV-I (Blomberg et al, 1994)), Sjögren's syndrome (with EBV (Inoue et al, 1991), HTLV-I (Garry, 1994; Sumida et al, 1994), or hepatitis C virus (Haddad et al, 1992)), idiopathic pulmonary fibrosis (with herpes viruses (Geist and Hunninghake, 1993)), Crohn's disease (with an unknown picorna virus (Gitnick and Rosen, 1976), and a host of other diseases.

When initial hypotheses have been refined to test specific viruses as antecedents to putative autoimmune sequelae, results have often disappointed. In Japan, where HTLV-I infection is relatively common, none of 34 multiple sclerosis patients had HTLV-I provirus genome detectable in genomic DNA by polymerase chain reaction (Nishimura et al, 1990; Kaneko et al, 1991); similar results were obtained in studies from Italy (French et al, 1991) and Denmark (Lisby, 1993). Also, none of 23 English multiple sclerosis patients had herpes simplex DNA detectable in their brains by polymerase chain reaction (Nicoll et al, 1992). None of 492 measles-reactive T-lymphocyte lines obtained from 12 multiple sclerosis patients reacted with myelin basic protein (Pette et al, 1993), casting doubt on this model of multiple sclerosis as well.

Ugly data have slain many other beautiful hypotheses linking specific viruses to autoimmune diseases. Examples of hypothetical associations undermined by controlled studies include hepatitis C with AA (Hibbs et al, 1992a,b), hepatitis C with Sjögren's syndrome (Aceti et al, 1992), cytomegalovirus (Tamm et al, 1993) with rheumatoid arthritis, HTLV (Di Giovine et al, 1994) with rheumatoid arthritis, or a novel parvovirus (Simpson et al, 1984) with rheumatoid arthritis. Such results are discouraging. They cannot disprove the paradigm of autoimmune disease provoked by viral infections, but data such as these make it clear how difficult it will be to substantiate that paradigm with associations between specific pathogens and specific diseases.

It is fruitless to search for associations between specific viruses and specific diseases if the virus one seeks is the wrong one. Recently, a previously unknown human retrovirus was identified, first in the cerebrospinal fluid of a single multiple sclerosis patient (Perron et al, 1989), then from the macrophages of 10 of 18 multiple sclerosis patients but none of 14 controls (four of whom had other neurological diseases) (Perron et al, 1991). Koprowski's original article setting forth the retroviral hypothesis specifically cited a virus 'related to, but distinct from' HTLV-I (Koprowski et al, 1985), but much effort was spent attempting to prove or disprove that HTLV-I was itself the cause of multiple sclerosis. It is therefore possible that an important association with an unknown virus has been obscured by focus on a known one. Moreover, expression of the putative new retrovirus appears to be upregulated by coinfection with a herpes virus (Perron et al, 1993). If coinfection is required for pathogenesis, efforts to associate a single virus with disease are likely to result in failure.

The discovery of associations between viruses and diseases of unknown aetiology is unlikely to be straightforward, and will involve previously unknown agents as well as unsuspected host factors in multiple combinations. It should be noted that erythroblastopenic crises were suspected of being caused by an infectious agent for more than 30 years (Owren, 1948) before parvovirus B19 was established as the cause (Chorba et al, 1986; Young et al, 1986).

SUMMARY

Pathogenicity is a complex process with stringent requirements of both the host cell and the infecting virion. Among these requirements are a port of entry into host cells, a means of replication for the virus, and a means by which infection damages host cells. Damage to the host can result from multiple mechanisms including transformation, suppression of cellular metabolism, apoptosis, autoimmune responses directed against infected or uninfected tissues, or by molecular mimicry. In the attempt to identify new associations between viral infection and disease, investigators should be mindful that variable host factors as well as viral infection may be required for pathogenesis. Efforts to associate specific viral infections with specific diseases may be obscured by final common pathways through which multiple agents damage host cells in similar ways.

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