Mechanisms of viral pathogenesis in rheumatic disease

Considerable evidence indicates that viruses may be important environmental factors in the pathogenesis of autoimmune rheumatic diseases. A concordance rate of 25% for the most common illnesses, such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) in monozygotic twins shows that genetic factors influence susceptibility to autoimmune diseases. Alternatively, a 70% discordance rate emphasises the importance of environmental factors. Forensic studies of archeological sites revealed the presence of RA-like erosive bony changes in pre-Columbian New World populations dating back 6500 years and the absence of RA in the Old World before the 18th century. This geographical distribution suggests that RA may have spread from the Americas through environmental factors, possibly by a virus, another microorganism, or an antigen. Viruses can elicit acute or subacute and, less often, chronic forms of arthritis. These viral arthritis syndromes can be diagnosed by recognition of well defined clinical signs and detection of viral antibodies and nucleic acids. Viral elements may also play a part in the pathogenesis of idiopathic autoimmune rheumatic diseases. This editorial will assess mechanisms of viral pathogenesis in rheumatic disease by focusing on known viruses capable of causing inflammatory arthritis syndromes and comparing virally induced immunological aberrations with those noted in rheumatic disease patients.

Well defined virus induced rheumatic diseases

Viral infections often lead to inflammatory syndromes where arthralgias or arthritis may represent a major manifestation. Most cases of viral arthritis, such as rubella or parvovirus B19 arthropathies are short-term and self limited as a result of an efficient elimination of the organism by the immune system. Chronic arthropathies have been associated with persistent or latent viral infections, virus induced autoimmunity, polyclonal B cell activation, and immunodeficiency resulting in opportunistic infections, largely because of an inability of the immune system to eliminate the pathogen. This latter group of viruses include human immunodeficiency virus I (HIV-1), human T-cell lymphotropic virus type I (HTLV-I), and hepatitis C virus (HCV).

VIRUS INDUCED TRANSIENT ARTHRITIS SYNDROMES

Parvovirus B19

Parvovirus B19 is one of the most frequent causes of viral arthritis.1 Joint manifestations are temporally associated with production of anti-B19 IgM antibodies. While involvement of B19 has been repeatedly raised in classic RA, large surveys failed to demonstrate an association between erosive RA and parvovirus B19.3

Rubella virus

Rubella is known to cause mild and self limited arthralgias and acute arthritis.1 Chronic arthropathy was reported in 1–4% of postpartum female recipients of the RA27/3 vaccine strain.5 Other studies found no increase of chronic arthritis in women receiving the RA27/3 rubella vaccine.6 Moreover, no rubella virus can be recovered from peripheral blood lymphocytes of persons with chronic arthropathy following rubella infection or vaccination.7 Therefore, continued vaccination of rubella susceptible women to reduce the risk of congenital malformations seems warranted.

Alphaviruses

These are arthropod borne viruses that include the chikungunya, o’nyong-nyong, Mayaro, Sindbis, Okelbo, Barmah Forest (BF) and Ross River (RR) viruses. Similar to the rubella virus, they belong to the Togavirus family containing a positive strand RNA genome. The viruses are spread by mosquitoes in endemic areas of Australia (Sindbis, BF, and RR), South America (Mayaro), northern Europe (Okelbo), Asia and sub-Saharan Africa (chikungunya). They can cause an acute infectious illness with rash, fever, arthritis, myalgia and/or encephalitis. RR virus is the aetiological agent of the best studied epidemic polyarthritis (EPA) affecting up to 7800 Australians annually.8 Persistent infections are believed to be responsible for chronic arthritis. CD4+ T cells dominate mononuclear synovial effusions of EPA patients in contrast with CD8+ T cell infiltrate in rashes of RR virus infected patients who made early and complete recoveries.9 10 EPA involves the small joint of the hand and often causes tendonitis. Symptoms may persist for months. No erosive changes have been reported. The diagnosis is made by demonstrating IgM antibodies to RR virus.11

Adenoviruses

These viruses are a common cause of acute respiratory infections. Symmetric polyarthritis of small and large joints may occur within a week of respiratory symptoms.12 Recurrent chronic oligoarthritis because of adenovirus infection was rarely reported.13 14

Coxackieviruses

They belong to the group of enteroviruses. More than 90% of coxsackievirus infections are asymptomatic or manifest in undifferentiated febrile illness. Spectrum and severity of disease manifestations vary with age, sex, and immune status of the host.15 Coxackievirus arthritis, usually caused by Group B virus, occurs with fever, serositis, pleurodynia, and rash. The arthritis is usually symmetric and polyarticular, involving both small and large joints.

Herpesviruses

After initial infection, viruses of the Herpesviridae family persist in the host with lifelong latency. Therefore, several of these viruses have been considered as aetiological agents in autoimmune diseases, such as systemic lupus erythematosus (SLE), RA, or Sjögren’s syndrome (see below). Epstein-Barr virus (EBV) infection causes arthralgias lasting for up to four months in 2% of patients with mononucleosis.16 Recently, EBV positive lymphomas were described in methotrexate treated RA patients.17 18 Interestingly, remission of lymphomas was noted after discontinuation of methotrexate.19 HSV-1 arthritis rarely lasts longer.
Polyarteritis nodosa and cryoglobulinaemia.

Hepatitis B virus (HBV)

HBV can cause arthralgias and arthritis early after infection. Arthritis resolves in 2–6 weeks with the onset of jaundice. Hepatitis B virus has been also associated with polycleritisis nodosa and cryoglobulinemia.

VIRUS INDUCED CHRONIC RHEUMATIC DISEASES

Hepatitis C virus (HCV)

HCV has a wide pathogenic potential that is not limited to diseases of the liver. Despite high titre antibody concentrations, > 80% of infected people become chronic virus carriers. Cryoglobulinaemia is detectable in up to 40–50% of HCV infected patients. Identification of HCV as the causal agent of most (>90%) type II or essential mixed cryoglobulinemias (EMC) has been a major breakthrough of rheumatology in the past decade. Type II cryoglobulins are immune complexes comprised of a monoclonal IgM/k rheumatoid factor and polyclonal IgG. The clinical syndrome of EMC is an immune complex vasculitis characterised by purpura, arthritis, inflammatory arthritis, peripheral neuropathy, and glomerulonephritis. IgM/k bearing B cells are clonally expanded in the peripheral blood of EMC patients. Identification by HCV may be directly responsible for the clonal expansion of B cells, which may lead to development of B-cell non-Hodgkin’s lymphomas. HCV infection is associated with production of autoantibodies. Up to 75% of the patients have high titre rheumatoid factors, presumably produced by HCV infected and clonally expanded B lymphocytes. Fifty per cent or more of the patients have anti-smooth muscle antibodies. Low titre antinuclear antibodies and anticardiolipin antibodies were noted in 10–30% of HCV infected patients. Five per cent of patients may develop Sjögren’s syndrome, SLE, autoimmune thyroiditis, or scleroderma. Erosive/rheumatoid arthritis, and polymyositis/dermatomyositis were rarely documented.

Human T cell lymphotropic virus I (HTLV-I)

Infection by HTLV-I has been associated with adult T cell leukaemia (ATL), mycosis fungoides/Sézary syndrome, HTLV-I associated myelopathy/tropic spastic paraparesis (HAM/TSP), HTLV-I associated arthritis (HAA), polymyositis, and Sjögren’s syndrome. CD4+ T cells infiltrating the synovium of HTLV-I infected T lymphocytes. HAA is characterised by erosive symmetrical polyarthritis most often involving the hands. The patients may have rheumatoid factor or antinuclear antibodies and usually satisfy the diagnostic criteria for RA. Arthritis in ATL may lead to development of B-cell non-Hodgkin’s lymphomas. Up to 40% of infected goats develop chronic arthritis characterised by infiltration of the synovium by macrophages, B lymphocytes, plasma cells, CD4+ and CD8+ T cells. CAEV induced arthritis leads to erosions of articular surfaces. CD4+ T cells infiltrating the arthritis joints are predominantly of TH1 helper type 2. Similar to RA, tumour necrosis factor (TNFα) concentrations are increased in synovial fluid of CAEV infected arthritis goats. Many naturally or experimentally infected goats are long term non-progressors, characterised by relatively low virus loads and a dominance of viral envelope protein specific TH1 type CD4+ T helper cells in the peripheral blood. Viral pathogenesis in idiopathic autoimmune diseases

Independent lines of evidence suggest a viral aetiology in autoimmune rheumatic diseases. The possibility of a viral aetiology was raised by findings of virion-like tubuloreticular structures in endothelial cells and lymphocytes as well as demonstration of increased serum concentrations of type I
programmed cell death has been reported in HIV infected40 I; HIV-1, human immunodeficiency virus I. VZV, varicella-zoster virus; EBV, Epstein-Barr virus = human herpesvirus 4; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV-I, human T cell lymphotropic virus

mune patients have not been successful.43 Nevertheless, it is isolation and transmission attempts from tissues of autoim-
teins have profound e

interferon (IFN) in lupus patients.38 Virus-like particles were also noted in RA synovium.45 Many viral infections are accompanied by production of autoantibodies and viral proteins have profound effects on both antigen presentation and effector functions of the immune system. Dysregulation of programmed cell death has been reported in HIV infected40 and lupus patients as well.41 Similar to SLE, anaemia, leucopenia, thrombocytopenia, polyarthritis, and vasculitis have been widely reported in patients with AIDS.38 Direct virus isolation and transmission attempts from tissues of autoimmune patients have not been successful.43 Nevertheless, it is possible that a (retro)virus, responsible for provoking an immune response cross reactive with self antigens, has been cleared from the host, so the absence of viral particles is not conclusive. An alternative retroviral aetiology—that is, activation of endogenous retroviral sequences (ERS) was initially proposed by a study of the New Zealand mouse model of SLE.44 Endogenous retroviral envelope glycoprotein, gp 70, was found in immune complex deposits of autoimmune lupus prone NZB/NZW mice. Abnormal expression of an ERS was noted in the thymus of lupus prone mouse strains.45 More recently, expression and autoantigenicity of human ERS has been demonstrated in patients with SLE.46–50

Below, two possible mechanisms of viral pathogenesis will be discussed. The first scenario involves molecular mimicry causing abnormal self reactivity.51 Naturally, viral infections elicit potent antiviral immunity that may lead to cross reactivity against self antigens. Analysis of molecular mimics that is delineation of autoantigenic epitopes of self antigens may provide clues to the identity of viral antigens responsible for triggering the cross reactive immune responses. Secondly, infection of genetically susceptible hosts by a potentially large number of commonly occurring viruses may lead to T and B cell dysfunction and autoimmune. Immunoregulatory aberrations triggered by well defined viral proteins at the level of antigen presentation, modulation of cytokine activities, and disruption of cell death pathways, will be discussed.

Table 1 Virus induced rheumatic diseases

<table>
<thead>
<tr>
<th>Virus</th>
<th>Arthritis frequency</th>
<th>Arthritis type</th>
<th>Duration</th>
<th>Erosion</th>
<th>Other</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>Children: 5–10% Adults: 50–70% Female: male = 2:1</td>
<td>Polyparticular, small and large joints, symmetrical</td>
<td>2–8 weeks, rarely chronic</td>
<td>No</td>
<td>Anemia</td>
<td>(3) (90)</td>
</tr>
<tr>
<td>Rubella</td>
<td>10–30%</td>
<td>Multiple small joints</td>
<td>5–10 days</td>
<td>No</td>
<td>Vaccine strain</td>
<td>(4,43)</td>
</tr>
<tr>
<td>VZV</td>
<td>&lt;1%</td>
<td>Mononarthritis</td>
<td>1–7 days</td>
<td>No</td>
<td>Life long latency</td>
<td>(19)</td>
</tr>
<tr>
<td>EBV</td>
<td>1–5%</td>
<td>Poly or mononarthritis</td>
<td>1–12 weeks</td>
<td>No</td>
<td>Autoimmunities</td>
<td>(16)</td>
</tr>
<tr>
<td>HIV</td>
<td>10–25%</td>
<td>Symmetrical, migratory</td>
<td>1–3 weeks</td>
<td>No</td>
<td>Vasculitis</td>
<td>(43)</td>
</tr>
<tr>
<td>HCV</td>
<td>10–50%</td>
<td>Polyparticular, symmetrical</td>
<td>Chronic</td>
<td>No</td>
<td>Vasculitis</td>
<td>(23)</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>&lt;1%</td>
<td>Oligoarthritis, large joints</td>
<td>Chronic</td>
<td>Yes</td>
<td>Sjögren’s Autoimmunities</td>
<td>(28)</td>
</tr>
<tr>
<td>HIV-1</td>
<td>10–50%</td>
<td>Painful joint syndrome</td>
<td>1–2 days</td>
<td>No</td>
<td>Promotion of CD8 T cell expansion</td>
<td>(32)</td>
</tr>
<tr>
<td>Alphavirus</td>
<td>&gt;50%</td>
<td>Reiter’s syndrome</td>
<td>Chronic</td>
<td>Yes</td>
<td>mediated autoimmunity</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>rare</td>
<td>Symmetrical, small joints</td>
<td>1 week to months</td>
<td>No</td>
<td>fever, myalgia encephalitis</td>
<td>(11)</td>
</tr>
<tr>
<td>Coxsackie</td>
<td>rare</td>
<td>Small and large joints</td>
<td>transient or chronic</td>
<td>No</td>
<td>Pharyngitis</td>
<td>(12–14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symmetric, small and large joints</td>
<td>acute or chronic</td>
<td>No</td>
<td>Myocarditis, Serositis, pleurodynia</td>
<td>(15)</td>
</tr>
</tbody>
</table>

The ERS capable of triggering antibodies cross reactive with the 70K protein and, subsequently, recognition could expand to additional 70K epitopes.

Table 2 Molecular mimicry between viral proteins and autoantigens

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>Prevalence (%)</th>
<th>Virus protein</th>
<th>Virus</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>70kU1 snRNP</td>
<td>30</td>
<td>gag</td>
<td>MoMLV, HRES-1</td>
<td>(47,53)</td>
</tr>
<tr>
<td>HRES-1</td>
<td>21–52</td>
<td>gag, gag24</td>
<td>HTLV-I</td>
<td>(46–49)</td>
</tr>
<tr>
<td>Sm B’</td>
<td>30</td>
<td>gag24</td>
<td>HIV-1</td>
<td>(59)</td>
</tr>
<tr>
<td>C/U1 snRNP</td>
<td>30</td>
<td>ICP4</td>
<td>HIV-1</td>
<td>(64)</td>
</tr>
<tr>
<td>Sm D</td>
<td>36</td>
<td>EBNA-1</td>
<td>EBV</td>
<td>(60)</td>
</tr>
<tr>
<td>Sm B’</td>
<td>25–40</td>
<td>EBNA-1</td>
<td>EBV</td>
<td>(63)</td>
</tr>
<tr>
<td>La</td>
<td>15</td>
<td>gag</td>
<td>FSV</td>
<td>(65)</td>
</tr>
<tr>
<td>p34</td>
<td>10–50</td>
<td>EBNA-1</td>
<td>EBV</td>
<td>(61)</td>
</tr>
<tr>
<td>ERV-3</td>
<td>32</td>
<td>env</td>
<td>MoMLV</td>
<td>(50)</td>
</tr>
</tbody>
</table>

*Prevalence of antibodies in patients with SLE.

interferon (IFN) in lupus patients.38 Virus-like particles were also noted in RA synovium.50 Many viral infections are accompanied by production of autoantibodies and viral proteins have profound effects on both antigen presentation and effector functions of the immune system. Dysregulation of programmed cell death has been reported in HIV infected40 and lupus patients as well.41 Similar to SLE, anaemia, leucopenia, thrombocytopenia, polyarthritis, and vasculitis have been widely reported in patients with AIDS.38 Direct virus isolation and transmission attempts from tissues of autoimmune patients have not been successful.43 Nevertheless, it is possible that a (retro)virus, responsible for provoking an immune response cross reactive with self antigens, has been cleared from the host, so the absence of viral particles is not conclusive. An alternative retroviral aetiology—that is, activation of endogenous retroviral sequences (ERS) was initially proposed by a study of the New Zealand mouse model of SLE.44 Endogenous retroviral envelope glycoprotein, gp 70, was found in immune complex deposits of autoimmune lupus prone NZB/NZW mice. Abnormal expression of an ERS was noted in the thymus of lupus prone mouse strains.45 More recently, expression and autoantigenicity of human ERS has been demonstrated in patients with SLE.46–50

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STRUCTURAL MIMICRY AND CROSS REACTIVITY BETWEEN VIRAL PROTEIN AND AUTOANTIGENS

Under normal conditions, the immune system develops a potent virus specific immune response that rapidly eliminates the virus with only minimal tissue injury. Only minimal amounts of self antigens are released, which are insufficient to induce autoreactive B and T lymphocytes and autoimmune disease will not ensue. However, in the event that the host and the virus share antigenic determinants, virus infection may result in autoimmunity as virus specific T cells and antibodies are cross reactive with self antigens. This scenario does not preclude the possibility that the infecting virus is eliminated by the immune response. Alternatively, similarities between proteins of the major histocompatibility complex (MHC) and microbial antigens, especially viral antigens, may allow the host to regard an infectious agent as self and, thus, forego an immune response. The “shared epitope” QKRAAA sequence from the third hypervariable region of HLA DRB1*0401, which has been found in numerous human pathogens, is associated with susceptibility to RA.52 The 70K protein of U1snRNP was the first lupus autoantigen shown to contain a region of homology and immunological cross reactivity with a conserved p30 gag protein of most mammalian type C retroviruses (table 2). Based on this observation, Query and Keene proposed that autoimmunity to U1RNP may be triggered by expression by an endogenous retroviral gag protein.53 Anti-gag antibodies elicited by the ERS could cross react with the 70K protein and, subsequently, recognition could expand to additional 70K epitopes.

The ERS capable of triggering antibodies cross reactive with the 70K protein may correspond to HRES-1, a human T-cell lymphotropic virus related endogenous retrovirus.54 In different laboratories, prevalence of HRES-1 antibodies may be as high as 52%55 or as low as 21%56 in patients with SLE. Fifty nine per cent (10 of 15)
common fragile site of chromosome 1 at q42.56 The pres-

ent per haploid genome that has been mapped to a

nity. HRES-1 is represented as a single copy

Y

charged amino acids in the mimicking epitopes may have
SLE.57 The q41

locus—that is, a relative decrease of genotype I and

V

can elicit high titre antibodies.55 Therefore, the presence of

protein. It is well known that highly charged polypeptides

residues 248–250, 418–420, and 477–479, respectively

RRE triplet is repeated three times in the 70K protein at

were suggested to be the core of cross reactive

gag

gag

gag

gag

gag

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gag

Leader

(Table 3 Viral proteins mimic immunoregulatory abnormalities of rheumatic disease

<table>
<thead>
<tr>
<th>Virus/viral product</th>
<th>Mechanism/effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in lymphokine milieu</td>
<td>induction of IFNs</td>
<td>(108)</td>
</tr>
<tr>
<td>HTLV-I p40/tax</td>
<td>increases IL2R expression</td>
<td>(109)</td>
</tr>
<tr>
<td>HIV-1 gp41 (aa591-597)</td>
<td>stimulates apoptosis through bcl2</td>
<td>(98)</td>
</tr>
<tr>
<td>HIV-1 env</td>
<td>inhibits apoptosis through Fas and oxidative stress</td>
<td>(99,100)</td>
</tr>
<tr>
<td>CMV US28</td>
<td>inhibits PKC activity and IL2 production</td>
<td>(75)</td>
</tr>
<tr>
<td>CMV ORF636</td>
<td>binds lck, inhibits Th1 cytokine production</td>
<td>(110)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>binds Th1 cytokine IL12 production</td>
<td>(111)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>inhibits Th1 cytokine production</td>
<td>(66)</td>
</tr>
<tr>
<td>HSV/EBV</td>
<td>inhibits MHC class II binding</td>
<td>(81)</td>
</tr>
<tr>
<td>Adenovirus/E1A</td>
<td>inhibits MHC class I expression</td>
<td>(80)</td>
</tr>
<tr>
<td>Adenovirus/E3 gp19</td>
<td>inhibits MHC class I binding to antigen</td>
<td>(79)</td>
</tr>
<tr>
<td>HSVC/ICP4</td>
<td>inhibits TAP (MHC) function</td>
<td>(78)</td>
</tr>
<tr>
<td>Apoptosis pathways</td>
<td>stimulation through blocking bcl-2</td>
<td>(98)</td>
</tr>
<tr>
<td>HTLV-I p40/tax</td>
<td>inhibition of Fas and oxidative stress pathways</td>
<td>(99,100)</td>
</tr>
<tr>
<td>HIV-1 tat</td>
<td>stimulation through Fas and oxidative stress</td>
<td>(84,86)</td>
</tr>
<tr>
<td>HIV-1 protease</td>
<td>Stimulation by cleavage of bcl-2</td>
<td>(87)</td>
</tr>
<tr>
<td>HIV-1 vpr</td>
<td>Stimulation through mitotic arrest</td>
<td>(93,94)</td>
</tr>
<tr>
<td>Parovirus B19</td>
<td>Stimulation by unknown mechanism</td>
<td>(88)</td>
</tr>
<tr>
<td>Influenza NS1</td>
<td>Stimulation through Fas and bcl-2 pathways</td>
<td>(89)</td>
</tr>
<tr>
<td>Adenovirus E1B 19K</td>
<td>Bcl-2 homologue, inhibits apoptosis</td>
<td>(95)</td>
</tr>
<tr>
<td>EBV BHRF1</td>
<td>Bcl-2 homologue, inhibits apoptosis</td>
<td>(96)</td>
</tr>
<tr>
<td>HSV-7</td>
<td>Inhibition by unknown mechanism</td>
<td>(97)</td>
</tr>
<tr>
<td>HBV</td>
<td>Inhibition, p53 antagonist</td>
<td>(92)</td>
</tr>
<tr>
<td>HIV-2 23 K E8 + FLIP</td>
<td>Inhibition of Fas pathway</td>
<td>(104,105)</td>
</tr>
<tr>
<td>MCV ORF159L + FLIP</td>
<td>Inhibition of Fas pathway</td>
<td>(104,105)</td>
</tr>
<tr>
<td>HVs ORF17 + FLIP</td>
<td>Inhibition of Fas pathway</td>
<td>(104,105)</td>
</tr>
<tr>
<td>HHV8 ORF189 + FLIP</td>
<td>Inhibition of Fas pathway</td>
<td>(104,105)</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Inhibition of Fas pathway</td>
<td>(104,105)</td>
</tr>
</tbody>
</table>
locus resulted in dysregulation of this apoptosis pathway in lupus prone MRL/lpr mice.

**VIRAL PROTEINS MODULATE CYTOKINE PRODUCTION**

Functional abnormalities of T and B cells have been correlated with an altered cytokine production profile in patients with rheumatic disease. Secretion of T helper type 1 (Th1) cytokines, interleukin 2 (IL2), interferon-γ (IFNγ), and IL12, necessary for maintenance of a classic T cellmediated immunity, is diminished while production of Th2 cytokines, in particular, IL4, IL5, IL6 and IL10, promoting B cell function, is increased in patients with SLE. This marked shift in cytokine production may be related to a fundamental biochemical defect manifested in deficiencies of protein kinase A activity, increased phosphatidylinositol turnover and diminished protein kinase C activities in lupus T cells.

Changes in production of cytokines similar to those in patients with SLE, a shift from a Th1 to a Th2 type cytokine profile, have been described as a result of HIV-1 infection. CD4 T cell decline is mediated by an increased rate of apoptosis or programmed cell death (PCD). Interestingly, Th1 type cytokines protect against apoptosis while Th2 cytokines increase PCD. Accelerated apoptosis has also been described in SLE. Moreover, apoptosis has been associated with a compartmentalised release of autoantigens in patients with SLE. These observations raise the possibility that increased apoptosis and autoantibody production may be mediated by somewhat similar mechanisms both in AIDS and SLE. The nef and tat genes of HIV-1 are thought to mediate a Th1 to Th2 shift in cytokine production (table 3). A synthetic env heptadcapeptide, CKS-17 down regulates cell mediated immune responses, possibly via suppression of Th1 type cytokine production. The CKS-17 motif was found to be highly conserved among infectious and endogenous retroviruses. Down regulation of IL2 production in HIV infected cells was also linked with inhibition of protein kinase C (PKC) activity and influx of Ca++. US28 of HCMV binds members of the α or C-C family of chemokines. Polymorphisms of chemokine receptors are important factors determining sensitivity to infection by HIV-1. Development of CAEV induced arthritis is also associated with a Th1 to Th2 shift in cytokine production.

**VIRAL PROTEINS MODULATE ANTIGEN PRESENTATION**

MHC haplotypes have been associated with susceptibility to rheumatic diseases and recognition of specific autoantigens. This is consistent with a dominant role of the MHC in selection and presentation of antigenic peptides. Interestingly, viral peptides influence expression of MHC class I and class II antigens as well as the function of TAP proteins (transporters associated with antigen presentation). Thus, herpes simplex virus (HSV) encodes a cytosolic protein, ICP47, which interferes with the function of the TAP1/TAP2 complex, prevents association of peptide with MHC class I, and leads to degradation of empty class I molecules. E3 gp19 of adenosine type 2 and E1A of adenovirus type 2 also inhibit expression of MHC class I. E1A was shown to directly interfere with negative regulatory elements in the MHC class I promoter. The B2LF2 protein of EBV recognises the peptide binding pocket of the HLA-DR β chain and interferes with class II directed antigen presentation. In addition, expression of MHC proteins is dependent on production of cytokines, such as IFNγ and TNFα, production of which is often inhibited by viral infections. The above data indicate that viruses commonly infecting the general population, including patients with rheumatic diseases, affect antigen presentation and modulate the cytokine milieu, which may in turn play a part in initiation or perpetuation of autoimmunity.

**REGULATION OF APOPTOSIS BY VIRAL PROTEINS**

Apoptosis or programmed cell death (PCD) represents a physiological mechanism for elimination of autoreactive lymphocytes during development. Viral infections may have a role in dysregulation of apoptosis in autoimmune patients. Many viruses have evolved genes that can selectively inhibit or stimulate PCD. The suicide of an infected cell by internal activation of apoptosis or the killing of an infected cell by a cytotoxic T lymphocyte or NK cell may be viewed as a defense mechanism of the host to prevent viral propagation. In the early stages of infection, viral inhibitors of apoptosis allow for more extensive production of progeny. At later stages, viral inducers of apoptosis facilitate spread of progeny to uninfected cells.

HIV may use several mechanism to deplete CD4+ T cells at the later stages of disease (table 3). The tat protein induces oxidative stress, and increases surface expression of the Fas ligand resulting in accelerated signaling through the Fas pathway. In addition, cleavage of bcl-2 by HIV protease may expose the cell to a variety of apoptotic signals. Parovirus B19 depletes erythroid progenitor cells by apoptosis. Cells infected by influenza virus undergo PCD that can be inhibited by bcl-2 and facilitated through the Fas pathway. It is intriguing to consider the possibility that viruses causing common cold may stimulate antinuclear autoantibody production through periodic release of nucleosomes from apoptotic cells. Thus, chronic parovirus B19 infection was recently associated with production of a wide array of autoantibodies. Replication of CAEV is also associated with induction of apoptosis.
Inhibition of apoptosis by viral proteins help infected cells to evade inflammatory responses, such as killing by cytoytic T cells through the Fas and TNF pathways (fig 1). As with hepatitis B virus (HBV) and hepatitis C virus (HCV), hepatitis D virus (HDV) inhibits binding of p53 to DNA. The e7 gene of HIV-1 causes cells to arrest in the G2 phase of the cell cycle when virus expression is highest. Viral homologues of bcl-2 can functionally substitute for bcl-2 in binding to the apoptosis accelerating proteins, bax, bad, and bag. Persistence of herpes simplex virus (HSV) in neurons has been linked to its apoptosis inhibitory protein γ 34.5. The p40/tax protein of HTLV-I seems to possess both apoptosis inducing and inhibiting capabilities. Up regulation of thioredoxin, a NADPH dependent antioxidant and inhibition of Fas dependent signalling have been implicated in the anti-apoptotic effect of HTLV-I tax protein. These two mechanisms not mutually exclusive as Fas induced cell death is accompanied by the formation of reactive oxygen intermediates (ROI) and is subject to regulation by enzymes of the pentose phosphate pathway providing NADPH as a source of reducing equivalent for intracellular antioxidants. p40/tax may mediate autoimmune arthropathy and Sjögren’s syndrome by blocking Fas dependent cell death in HTLV-I/tax transgenic mice. A new family of viral infectors, designated as vFLIPs (viral FLICE inhibitory proteins), has recently been discovered. vFLIPs are produced by several γ -herpesviruses, including the Kaposis-sarcoma associated human herpes virus 8 (HHV-8), the tumorigenic human melanocytic virus (MCV), and equine herpes virus 2 (EHV-2). vFLIPs block the early signalling events triggered through the death receptors Fas, TRAMP, TRAIL-R and TNFR1. Thus, herpesviruses evolved a series of genes that allow selective blocking of the Fas and TNF signalling pathways.

Conclusion and future directions

The experimental evidence presented above shows immunological cross reactivities between autoantigens and viruses. The concept that autoimmunity is triggered in genetically susceptible hosts by trivial environmental factors, possibly different from patient to patient, is consistent with the general epidemiology—that is, a relatively sporadic occurrence, of the disease. Moreover, proteins of commonly occurring viruses have profound effects on the cytokine milieu, antigen recognition, and lymphocyte cell survival. Thus, molecular mimicry and immunomodulation by viral proteins may account for both cross-reactivity with autoimmune responses and abnormal TH1, TH2 and TH17 cell functions in autoimmune disorders. Causal association of HCV with type II cryoglobulinemias and of HTLV-I with polyomysitis, Sjogren’s syndrome, and erosive arthritis represent significant discoveries for rheumatology. Patients infected with HCV or HTLV-I invariably have high titres of antiviral antibodies. Likewise, serum samples of autoimmune patients are likely to contain antibodies specific for viruses of pathogenic significance. Thus, autoimmune serum samples could be used as tools for isolating viral nucleic acids by careful screening of expression libraries of differential display. Alternatively, further studies on previously characterised infectious and endogenous viral elements are needed. Continued research on viral pathogenesis is likely to provide future breakthroughs for the diagnosis and treatment of rheumatic diseases.

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