CMLS, Cell. Mol. Life Sci. 57 (2000) 552–560
1420-682X/00/040552-09 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Evidence for mimicry by viral antigens in animal models of autoimmune disease including myocarditis

C. M. Lawson

Division of Veterinary and Biomedical Sciences, Murdoch University, South Street, Murdoch, 6150 Western Australia (Australia) Fax + 618 9310 4144, e-mail: cassiel@numbat.murdoch.edu.au

Abstract. Molecular mimicry of viral antigens with self determinants has been proposed as one of the pathogenic mechanisms in autoimmune disease. Evidence of viral mimicry in animal models of autoimmunity is accumulating. Murine adenovirus, Semliki forest virus, lactate dehydrogenase-elevating virus, herpes simplex virus type-1, hepatitis B virus, encephalomyocarditis virus, Theiler's murine encephalomyelitis virus, Coxsackievirus and cytomegalovirus have been found to mimic physiologically important host proteins. However, epitope homology of a viral and self determinant is not in itself strong evidence for mimicry as a pathogenic mechanism. The mimicking determinant must also be capable of inducing disease in the absence of replicative virus. Animal models provide evaluation of the viral trigger, and development and therapy for autoimmune diseases. Identification of host proteins that can induce disease together with the knowledge of immune system dysregulation, genetic association and environmental factors may lead to improved immunotherapeutic strategies for human autoimmune diseases.

Key words. Epitope; mimicry; viral proteins; autoimmunity; animal models.

Viruses and autoimmune disease

Viruses have been implicated as a trigger for autoimmune diseases over the last 15 years [reviewed in refs 1–4]. Various immunological mechanisms induced by viral infections are mostly beneficial for the host, playing a major role clearing the infectious agent. However, certain anti-viral immune responses can be reactive against self. The outcome may cause injury to the host, with progression of a protective immune response into an autoaggressive immune response. This may lead to chronic autoimmune disease. The mechanisms of loss of self-non-self discrimination triggered by a viral infection are incompletely understood but evidence favours molecular mimicry in select cases of autoimmune disease. Mechanisms other than mimicry include tissue damage and release of sequestered autoantigens by persistent virus infection, activation signals provided by virus infection which lead to a loss of self tolerance, epitope spreading of the anti-viral immune response and dysregulation of the production of cytokines such as tumour necrosis factor-α (TNF-α). This review will focus on experimental evidence for viral mimics of self in animal models of autoimmune disease including myocarditis. Experiments in which transgenic animals expressing viral ('self') antigens can be stimulated by virus infection to respond to the expressed viral transgene illustrate the autoreactive potential of the immune response [reviewed in ref. 4]. Furthermore, these models allow investigations of the induction, progression and regulation of molecular mimicry. There are very few established animal models providing conclusive proof of the phenomenon of mimicry in the precipitation and potentiation of autoimmune disease. However, the search to identify viruses in autoimmunity operating through molecular mimicry is far from complete. This review will illustrate the cytomegalovirus (CMV) myocarditis model [5–7] in the pursuit for evidence of novel viral mimics. Finally, clinical autoimmune diseases and the relevance of suspected human viral mimicry will be discussed.

Emphasis needs to be placed on the nature of the antigenic mimic of the viral and self proteins and their importance in the pathology of disease. Cross-reactivity of an immune response requires a disease-inducing epi-

tope that can be tissue specific or, occasionally, systemic. The form and valence of the antigenic determinant is responsible for inducing autoimmunity in experiments involving spreading of the T-cell-mediated immune response [8]. Other factors including viral tropism, viral genetic sequences, host genetic background and environmental conditions play important pathogenic roles in disease establishment. Virus-induced autoimmunity through molecular mimicry may involve the production of autoantibodies and/or the stimulation of autoreactive T cell responses, which are usually $CD4^+$ T cell dependent. These autoimmune responses may either initiate disease or potentiate an established disease [reviewed in ref. 9]. Most often, the autoimmune disease is inflammatory in nature with chronic tissue injury in the absence of detectable infectious viral replication. No single mechanism can explain the extremely varied phenomena of autoimmunity, but there is clear evidence in animal models that some viral infections may lead to autoimmune disease.

Animal models of viral mimicry in autoimmune disease

Several viruses have been directly associated with the development of autoimmunity leading to disease in experimental models through molecular mimicry (table 1). Analysis of animal models can provide evidence for the role of viruses in initiating disease, the influence of genetic factors, viral persistence in chronic autoimmunity, the immunopathogenic responses involved in disease, and the antigenic mimic of the viral and self protein. The genetic nature of the mimic may be of several types. Not every residue in a linear sequence need be identical between the viral antigen and the self peptide recognised by the T cell. Indeed, non-linear epitopes may stimulate autoreactive B cells which predominantly recognise conformational determinants, including α-helical coiled-coil structures [10, 11]. Furthermore, the length of the peptide and the flanking sequences of the homologous region may influence MHC binding and subsequently the type of cell-mediated immune response ($CD4^+$ or $CD8^+$ T cells) stimulated in autoimmunity.

Adenovirus

Murine adenovirus type I infection of mice induces experimental autoimmune thyroiditis [12]. A viral E1B peptide (residues 368–381) which exhibits homology with a thyroglobulin peptide (residues 2695–2706) was found to be a poor immunogen but could act as an agonist for activated autoreactive T cells, suggesting a role for mimicry in the enhancement of the pathogenesis of autoimmune disease.

Semliki forest virus

Mice infected with Semliki forest virus develop encephalomyelitis followed by demyelination of the brain [13]. There is sequence similarity between the viral E2 protein (residues 115–129) and myelin oligodendrocyte glycoprotein (residues 18–32) and immunisation with either peptide elicits an experimental allergic encephalomyelitis-like disease with vacuolation of the central nervous system (fig. 1).

Table 1. Animal models of viral mimicry in autoimmune disease.

Virus	Epitope mimic		Autoimmune disease	Animal model
	viral	self		
Murine adenovirus type I	E1B protein	thyroglobulin	experimental autoimmune thyroiditis	mouse [12]
Semliki forest virus	E2 protein	myelin oligodendrocyte glycoprotein	encephalomyelitis	mouse [13]
Lactate dehydrogenase-elevating virus	VP3 protein	intermediate filaments	motor neuron disease	mouse [14]
Herpes simplex virus type-1	coat protein (UL6)	corneal antigens, IgG2a	stromal keratitis	mouse [17, 18]
Hepatitis B virus	polymerase	myelin basic protein	experimental allergic encephalitis	rabbit [1]
Encephalomyocarditis virus	VP1 protein	histidyl tRNA synthetase	polymyositis	mouse [24]
Coxsackievirus B3	VP1 protein	myosin, tropomyosin, vimentin	myocarditis	mouse [31, 32]
Coxsackievirus B3	unknown	adenine translocator protein	myocarditis	mouse [35]
Coxsackievirus B4	VP1 protein	cardiac myosin heavy chain	myocarditis	mouse [36]
Murine cytomegalovirus	unknown	cardiac myosin heavy chain	myocarditis	mouse [6, 7]

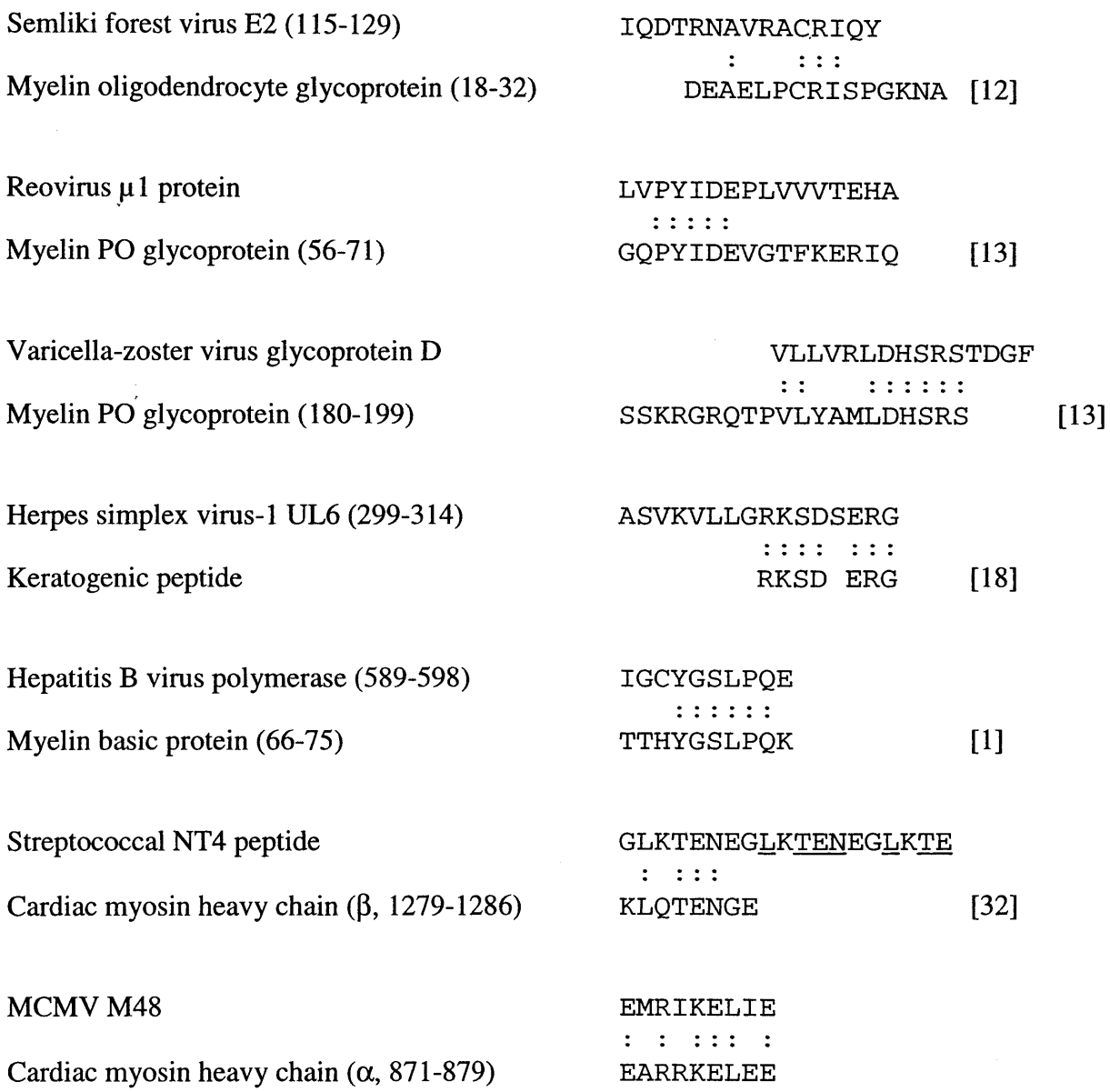

Figure 1. Sequence alignments of viral mimics with host proteins. Identical residues in the peptides are shown with a full colon and the repetitive homologous sequences in the streptococcal NT4 peptide are underlined.

Lactate dehydrogenase-elevating virus

Infection of mice with lactate dehydrogenase-elevating virus induces motor neuron disease with the production of autoantibodies to intermediate filaments [14]. Furthermore, monoclonal antibodies directed against the virus cross-react with VP3 envelope protein and determinants of intermediate filaments, implicating molecular mimicry.

Reovirus, herpesviruses and HIV-1

Experimental allergic neuritis is a demyelinating disease of the peripheral nervous system and can be induced in Lewis rats by immunisation with myelin P0 glycoprotein [15]. This experimental animal disease represents the human autoimmune disease, Guillain-Barré syndrome [16]. Homologous sequences of five or more consecutive amino acids between several viral proteins

and myelin have been found. Reovirus, Epstein Barr virus, CMV, varicella zoster virus, and HIV-1 all share sequence homologies with peptides of myelin. Certain T cell epitopes of myelin elicited disease in the rat; however, immunisation of rats with either viral peptides of reovirus μ1 protein or varicella zoster virus glycoprotein D with sequence similarities to the neuritogenic determinants of myelin P0 glycoprotein (residues 56–71 and 180–199, respectively) did not induce disease (fig. 1). Thus, the pathogenicity of peptides is not always associated with sequence homology but must be tested in the induction of autoimmune responses in vivo.

Another member of the herpesvirus family, herpes simplex virus type-1, induces herpes stromal keratitis in mice [17, 18]. Molecular mimicry between the viral coat protein (UL6, residues 299–314) and corneal antigens leads to autoreactive $CD4^+$ T cells in C.AL-20 mice (fig. 1). Furthermore, mice can be tolerised by vaccination with the peptide before corneal challenge with herpes simplex virus type-1.

Hepatitis B virus

The encephalitogenic protein, myelin basic protein, shares sequence homology with the hepatitis B virus [1]. The viral mimic shares six out of the ten amino acid residues with myelin and this peptide can elicit experimental allergic encephalomyelitis in rabbits (fig. 1). A cross-reactive antibody response was generated in rabbits immunised with either the peptide from hepatitis B virus or the encephalitogenic peptide of myelin basic protein. However, only five out of seven rabbits immunised with the viral polymerase peptides, having sequence homologies with myelin basic protein, developed immune responses characterised by cellular infiltrates in the central nervous system. In addition, peripheral blood lymphocytes from the immunised rabbits were stimulated to proliferate after recognition of either myelin basic protein or the viral polymerase. This model is an example of molecular mimicry operating to perpetuate tissue injury in the central nervous system that can persist beyond complete resolution of the infectious virus that initiated the autoimmune response. Furthermore, acute demyelinating transverse myelitis associated with circulating immune complexes of hepatitis B surface antigen has been documented in humans [19].

Encephalomyocarditis virus

Polymyositis is an inflammatory disease of skeletal muscle. It has long been associated with the development of autoimmune responses, including the production of autoantibodies to amino acid transfer RNA synthetases. In particular, the predominance of antibodies reactive to histidyl transfer RNA synthetase (HRS) in a select group of myositis patients has led to the study of the role of this candidate autoantigen in myositis [20]. Mice immunised with HRS protein develop a high-titre-antibody response to HRS but do not develop myositis [21]. In contrast, studies transferring the gene encoding HRS, by injection of a mammalian expression plasmid into skeletal muscle, which allows persistent expression of the transgene in vivo, showed the induction of myositis with a low-titre-antibody response to HRS [22]. Inoculation of mice with the blank expression vector induced neither myositis nor the anti-HRS antibody response. Furthermore, immunisation with an unrelated antigenic determinant, the haemagglutinin of influenza A virus, did not induce myositis. The cellular infiltrate was predominantly mononuclear and was localised to the DNA-inoculated muscle. However, the loss of self tolerance to HRS remains to be established in this animal model. Encephalomyocarditis viral infection of mice induces polymyositis [23]. Interestingly, sequence similarities between the VP1 protein of encephalomyocarditis virus and HRS may be important in viral mimicry in this disease [24].

Theiler's murine encephalomyelitis virus

Infection of mice with Theiler's murine encephalomyelitis virus provides a model for multiple sclerosis, a T-cell-mediated autoimmune demyelinating human disease. This experimental model is characterised by a chronic $CD4^+$ T cell response which is initially directed at viral determinants but persists in the central nervous system and is directed against multiple myelin autoepitopes [25]. However, unlike the above-mentioned autoimmune responses, kinetic studies of the autoepitopes recognised by T cells show an ordered progression to sequestered autoantigens that are released subsequent to viral-specific immune responses to myelin. Although there is no involvement of mimicry at the T cell level, other investigators have reported antibody cross-reactivity including that of a monoclonal antibody cross-reactive with Theiler's murine encephalomyelitis virus and myelin basic protein which augments disease pathogenicity [26]. Molecular mimicry by such viruses may initiate spreading of an autoimmune response [reviewed in ref. 27].

Coxsackievirus

Coxsackieviruses have been implicated in autoimmune myocarditis [reviewed in refs 28, 29]. Post-viral myocarditis can be found in genetically susceptible mice in the absence of detectable Coxsackievirus DNA [30]. Mouse models of myocarditis induced by Coxsackievirus B3 infection have demonstrated a major role for

an autoimmune response directed against VP1 polypeptides and heart antigens, including myosin, tropomyosin and vimentin [31]. Furthermore, a three-way cross-reactivity exists between heart antigens, Coxsackievirus B3 and group A streptococcus M5 [32]. Neutralising monoclonal antibodies to Coxsackievirus B3 which cross-react with cardiac myosin have been found to be pathogenic in mice [33]. In this murine model, certain strains of inbred mice are susceptible to myocarditis which is also dependent on the virus variant. No differences in the viral titre in the heart were noted with any of the virus strains, however, cytolytic activity of T cells derived from the lymph nodes correlated with disease severity. This experimental model allowed the testing of defined viral VP1 peptides as vaccines to prevent the development of autoimmune myocarditis following viral infection [31]. Pre-immunisation with certain VP1 peptides either resulted in partial protection from viral-induced myocarditis (peptide 1) or exacerbation of the severity of myocarditis (peptides 3 and 21) when compared to mice that were not immunised with the various VP1 peptides before challenge with Coxsackievirus B3. Furthermore, vaccination with NT4, a mimicking peptide from streptococcal M5 protein, coupled to syngeneic splenocytes protected mice from Coxsackievirus B3-induced myocarditis [34] (fig. 1). Tolerance induced by peptide vaccination may be due to immunomodulation by switching a predominant Th1-type response to a Th2-type response. These findings indicate the importance of cross-reactive immune responses ($CD4^+$ T cell dependent) to infectious agents and cardiac myosin in the development of heart disease.

Coxsackievirus B3 also has cross-reactive epitopes with adenine translocator protein [35]. Since immunisation with adenine translocator protein can induce myocarditis, mimicry between this self protein and Coxsackievirus B3 variants is postulated as a possible trigger for disease. A variant of Coxsackievirus B3 (Woodruff) has been found to induce myocarditis that is mediated by cytolytic T cells. Mice infected with parental virus (Coxsackievirus B3) develop myocarditis which is mediated by cytotoxic autoreactive T lymphocytes. In this model, a virus variant H3-10A1 that induces very mild disease compared to the parental virus was investigated. Such suppression of myocarditis was mediated by the action of immunoregulatory lymphocytes. These cells were found in H3-10A1 virus-infected animals but not in animals infected with the parental Coxsackievirus B3. Furthermore, myocarditis could be transferred with the T cells from Coxsackievirus B3-infected mice but not with T cells from H3-10A1 virus-infected mice.

Immunological cross-reactivity between Coxsackievirus B4, the VP1 protein, and the α cardiac myosin molecule, the heavy chain (residues 1632–1647), also leads to myocarditis in a mouse model [36]. A monoclonal antibody found to neutralise Coxsackievirus B4 through recognition of VP1 was shown to cross-react with murine α cardiac myosin. Epitope mapping using antibody screening of an expression library showed that sequences within the light meromyosin fragment of cardiac myosin were recognised. The overlapping peptides all contained a common sequence (residues 1299–1647) and the above-mentioned monoclonal antibody reacted to the epitope (residues 1632–1647) within this region of the molecule. In summary, the above Coxsackievirus models have provided clues to the mechanisms of pathogenesis for myocarditis and have indicated that multiple proteins are involved in the autoimmune response.

Cytomegalovirus

Prognosis of viral myocarditis in humans is dependent on the correct diagnosis of the patient. Presenting symptoms must be characterised into either the acute or chronic stage of the disease. Treatment is mutifactorial and may involve anti-viral, immunomodulatory and immunosuppressive agents. Since, cytomegaloviruses are species specific, human CMV cannot be studied in experimental animal models. Animal models such as MCMV-induced myocarditis allow the detailed study of this natural mouse pathogen, MCMV, as a trigger for autoimmune disease.

MCMV infection of mice induces the inflammatory heart disease myocarditis [37]. Cells bearing viral inclusions can be found in the heart tissue by immunohistochemistry during the acute phase of the infection (days 3–10 post-infection) and infectious virus can also be detected by plaque assay at days 3 to 10 post-infection [38]. Although replicative virus is never detected in the heart beyond day 10, certain strains of inbred mice develop chronic myocarditis out to day 100 post-infection in the absence of infectious virus in the heart. Myocarditis in MCMV-infected animals is characterised by a mixed cellular infiltrate during the acute phase and an infiltrate of predominantly mononuclear cells during the chronic phase of the disease. Inflammation may be associated with necrosis of myofibres within the areas of myocardial inflammation, which can vary from focal to diffuse infiltration. Degenerative changes range from loss of striations, vacuolation to myofibre drop out. Immunopathogenicity may be associated with effector mechanisms of the virus, immune cells and/or cytokines.

Genetic factors of the host and virus influence the susceptibility of the murine host to MCMV-induced myocarditis [38]. MCMV-induced myocarditis is biphasic in susceptible BALB/c mice with an acute phase occurring at days 3–21 and a second chronic phase occurring at days 28–100 post-infection [38; D. Fair-

weather, G. R. Shellam and C. M. Lawson, unpublished observations). In contrast, C57BL/6 mice only develop mild myocarditis at days 5–7 with no evidence of myocarditis beyond day 7 post-infection. These two mouse strains thus represent hosts that are either susceptible or resistant to viral-induced myocarditis. The possession of the *b* or *d* allele at the H-2 complex confers susceptibility to disease, whereas possession of the *k* allele confers resistance. Non-H-2 genes are also involved. Most interestingly, viral replication does not correlate with susceptibility to myocarditis. Indeed, increasing the viral inoculum in C57BL/6 mice does not induce chronic myocarditis. Viral genome (*ie1* and *gB* genes) persists in the heart as determined by nested polymerase chain reaction out to day 100 post-infection in both BALB/c and C57BL/6 mice [D. Fairweather, G. R. Shellam and C. M. Lawson, unpublished observations]. However, viral transcripts for *ie1* but not for *gB* genes are detected out to day 70 post-infection in both mouse strains. Genetically different isolates of MCMV obtained from wild-trapped *Mus domesticus* can induce myocarditis in inbred BALB/c mice [39]. Myocarditis was detected in approximately 30% of wild mice (n = 17) and 100% of these animals were seropositive for MCMV. However, this observation does not necessarily imply that the observed myocarditis was directly due to MCMV infection. Taken together, it appears that different MCMV isolates induce myocardial disease and that replicative virus is not solely responsible for chronic disease.

Athymic nude mice do not develop myocarditis following MCMV infection even though they disseminate the viral infection and produce higher titres of virus in many tissues [40]. Mice immunosuppressed with cyclosporin A showed a delayed onset of myocarditis by about 4 days and also produced higher titres of virus with an increased organ distribution of viral infection compared with untreated MCMV-infected mice [41].

In addition to antibodies reactive to MCMV antigens, autoantibodies to heart antigens, including reactivity to the heart contractile proteins, troponin, tropomyosin, myosin, and actin are found during acute MCMV infection of mice [6, 42]. During the chronic phase of the disease, BALB/c mice produce predominantly autoantibodies reactive to the heavy chain of cardiac myosin (200-kDa protein) [6, 7]. Autoantibodies to cardiac myosin which cross-react with skeletal myosin are found in both BALB/c and C57BL/6 mouse strains during acute infection. However, only the BALB/c mice produce a subpopulation of autoantibodies specific for the cardiac isoform of myosin during the chronic stage of disease in addition to the cross-reactive population of autoantibodies to cardiac and skeletal myosins. Of importance was our finding that some neutralising monoclonal antibodies (IgG2b subclass) directed against structural determinants of MCMV react with cardiac myosin [43]. Indeed, these monoclonal antibodies recognised murine, rat and human cardiac myosin peptides [D. Fairweather, M. Cunningham, G. R. Shellam and C. M. Lawson, unpublished observations]. These findings imply the possible mechanism of mimicry between the virus and cardiac myosin molecule in the genesis of myocarditis following MCMV infection. The isoform-specific autoantibodies directed against cardiac myosin obtained from MCMV-infected BALB/c mice (taken at day 56 post-infection) can passively transfer disease to uninfected BALB/c mice. This is in contrast to the lack of myocarditis transfer with normal mouse sera or from BALB/c sera taken at day 10 post-infection which does not contain the isoform-specific antibodies [7]. Immune sera, from MCMV-infected C57BL/6 mice, enriched for cardiac-myosin-reactive antibodies, did not transfer disease to BALB/c recipients.

Indeed, cardiac myosin itself can induce myocarditis in the absence of viral infection, indicating the physiological importance of this molecule in autoimmunity [7, 44]. High titres of autoantibodies to cardiac myosin are produced in myosin-immunised BALB/c mice. Thus the candidate autoantigen, cardiac myosin, is capable of inducing immunopathology in the heart. This points to a possible pathogenic role of viral mimicry with cardiac myosin in the disease pathogenesis, since many other infectious agents have been implicated in myocarditis with an established mimic to the cardiac myosin molecule. Computer analysis of sequence homologies between cardiac myosin and MCMV revealed a region of six out of nine amino acids in the large tegument protein M48 of MCMV and murine cardiac myosin heavy chain (residues 869–877; fig. 1). This peptide sequence is identical in the rat and human CMV large tegument protein and in the rat and human cardiac myosin molecules with predicted high α helix amphiphilicity. This intriguing experimental model can be studied for the role of new viral mimics with cardiac myosin resulting in autoreactive immune responses in chronic myocarditis. However, certain selection criteria [reviewed in ref. 45] would need to be met before the antigenic determinant is classified as a proven mimic in the induction of autoimmunity. These include direct evidence of disease mediation by transfer of pathogenic antibody and/or T cells directed against the mimicking determinant(s), reproduction of disease by administration of the viral mimic, and immunomodulation of disease via the route of administration and/or dosage of the mimic. Nonetheless, increased knowledge of autoreactive immune responses in myocarditis will provide improved strategies for the development of immunotherapies for the inflammatory heart diseases.

Human autoimmune disease with putative viral mimics

There are many other clinical autoimmune diseases for which viral mimicry of human antigenic determinants is a suspected cause. Several of these human viruses including Coxsackievirus, rotavirus, CMV, hepatitis viruses, HIV-1, human T-cell-lymphotropic virus type I (HTLV-1), Epstein-Barr virus and influenza A virus will be discussed briefly (table 2).

Coxsackievirus infections are strongly associated with myocarditis in humans [reviewed in ref. 46]. Cytotoxic and viral neutralizing antibodies have been reported to cross-react with the enteroviruses, streptococcal M proteins and cardiac myosin [32]. Molecular mimicry between viruses and islet cell antigens appears to be important in the development of insulin-dependent diabetes mellitus [47]. Recently, rotavirus infections have been associated with insulin-dependent diabetes in children [48]. A tyrosine phosphatase IA-2 peptide shares sequence homology with a VP7 peptide of rotavirus and such peptides bind to HLA-DR4*0401. Interestingly, the VP4 peptide has similarity with another type I diabetes autoantigen, glutamic acid decarboxylase. Other viruses with known sequence homology to the IA-2 immunodominant peptide include dengue, CMV, measles, hepatitis C and canine distemper virus. Therefore, several viruses may be involved in the activation of autoimmunity to islet cells through mimicry of β cell peptides in type I diabetes.

CMV is an aetiological agent in the autoimmune condition, chronic graft-versus-host disease, which is a complication of immunocompromised allogeneic bone marrow transplant recipients [3]. The aminopeptidase N (CD13) molecule (self antigen) which is incorporated into the viral envelope induces an anti-viral antibody response which also reacts with the host CD13. A correlation between the presence of serum CMV DNA and antibody directed against myelin-associated glycoprotein with neuropathy has been reported [49].

Hepatitis B virus infection has been associated with acute demyelinating transverse myelitis in a hepatitis B surface antigen carrier [19]. The hepatitis B surface antigen has sequence homology with myelin basic protein, a molecule that is well established in this disease process. Hepatitis C virus infection may induce autoimmune hepatitis and cytochrome P4502D6 has been implicated as a possible mimic in this disease [50].

HIV-1 infection may trigger an autoimmune response to the CD40-binding site of the MHC class II molecule which has been found to mimic HIV-1 gp120 envelope in patients with AIDS [51]. Human HTLV-1 has sequence homologies in the viral core proteins with transaldolase TAL-H a molecule expressed selectively by oligodendrocytes, in which autoreactivity may lead to oligodendrocyte destruction in multiple sclerosis [52].

Epstein-Barr virus shares homologous regions between the glycine/alanine repeat of the viral nuclear antigen-1 and epidermal keratin, collagen type II, and actin proteins [53]. Rheumatoid arthritis may result from such autoimmune responses in patients. Recently, human cytotoxic T cell clones reactive against the immediate-early antigen of Epstein-Barr virus were shown to

Table 2. Human autoimmune disease with putative viral mimics.

Virus	Epitope mimic		Autoimmune disease
	viral	self	
Coxsackie B viruses	VP1 protein	cardiac myosin heavy chain	myocarditis [32, 36]
Coxsackievirus B4	P2-C protein	β cell E1, E2, glutamate decarboxylase 65, 67	insulin-dependent diabetes mellitus [47]
Rotavirus	VP7	tyrosine phohsphatase IA-2	insulin-dependent diabetes mellitus [48]
Cytomegalovirus	CD13 envelope	aminopeptidase N (CD13)	chronic graft-versus-host disease [3]
Cytomegalovirus	unknown	myelin-associated protein	chronic polyneuropathy [49]
Hepatitis B virus	hepatitis B surface antigen	myelin basic protein	acute demyelinating transverse myelitis [19]
Hepatitis C virus	unknown	cytochrome P4502D6	autoimmune hepatitis [50]
HIV-1	gp120 envelope	CD40-binding site MHC class II	AIDS [51]
HTLV-I	core proteins	transaldolase (TAL-H)	multiple sclerosis [52]
Epstein-Barr virus	nuclear antigen-1	epidermal keratin, collagen type II, actin	rheumatoid arthritis [53]
Influenza B virus	matrix protein (M1)	(U1) RNA-small nuclear ribonucleoprotein (p68)	systemic rheumatic diseases [55]

cross-react with a self peptide of a serine/threonine kinase and a replication initiation peptide of S*taphylococcus aureus* [54]. Influenza B virus is involved in systemic rheumatic diseases in patients, and the suspected viral mimic lies within the nucleus transporter signal of the viral matrix (M1) protein which has homology with (U1) RNA-small nuclear ribonucleoprotein [55].

Concluding remarks

In this review, strong evidence of viral mimicry in the pathogenesis of autoimmune disease is illustrated using several animal models. These examples of molecular mimicry point to the elaborate immune evasion strategies employed by viruses to replicate effectively in their host. It must be emphasised that for autoimmune disease to occur, the cross-reactive autoimmune response needs to be directed at self determinants capable of eliciting disease, as distinct from the many non-pathogenic cross-reactive immune responses which may be generated. New sequence homologies found between viral and self determinants should not necessarily be proposed in eliciting autoimmune responses [2, 56]. In addition, induced autoimmune responses may not necessarily be critical for the development of disease. The development of autoimmune disease is appreciated to be a multifactorial process [reviewed in ref. 44]. Actual involvement of viral mimics in the onset, progression and control of autoimmune diseases requires careful examination in experimental animal models using the candidate peptide(s) as immunogens in the induction of loss of tolerance. Approaches utilising naked DNA for gene transfer and the creation of transgenic mouse lines will aid research endeavours [1, 2]. In the future, the evidence may expand and provide valuable information to clarify as yet controversial clinical cases of autoimmune disease, as outlined in this review. Viral mimicry will be placed in perspective as a mechanism of induction of known autoimmune conditions and will no doubt be proposed in further diseases triggered by virus infections.

Acknowledgements. I sincerely thank Dr. Malcolm Lawson for his discussions and critical review of this manuscript.

1 Fujinami R. S. and Oldstone M. B. (1985) Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science **230:** 1043–1045
2 Weise M. J. and Carnegie P. R. (1988) An approach to searching protein sequences for superfamily relationships or chance similarities relevant to the molecular mimicry hypothesis: application to the basic proteins of myelin. J. Neurochem. **51:** 1267–1273
3 Naucler C. S., Larsson S. and Moller E. (1996) A novel mechanism for virus-induced autoimmunity in humans. Immunol. Rev. **152:** 175–192
4 Herrath M. G. von, Holz A., Homann D. and Oldstone M. B. (1998) Role of viruses in type I diabetes. Semin. Immunol. **10:** 87–100
5 Hengel H., Brune W. and Koszinowski U. H. (1998) Immune evasion by cytomegalovirus-survival strategies of a highly adapted opportunist. Trends Mircobiol. **6:** 190–197
6 O'Donoghue H. L., Lawson C. M. and Reed W. D. (1990) Autoantibodies to cardiac myosin in mouse cytomegalovirus induced myocarditis. Immunology **71:** 20–28
7 Lawson C. M., O'Donoghue H. L. and Reed W. D. (1992) Mouse cytomegalovirus infection induces antibodies which cross-react with virus and cardiac myosin: a model for the study of molecular mimicry in the pathogenesis of viral myocarditis. Immunology **75:** 513–519
8 Farris A. D., Brown L., Reynolds P., Harley J. B., James J. A., Scofield R. H. et al. (1999) Induction of autoimmunity by multivalent immunodominant and subdominant T cell determinants of La (SS-B). J. Immunol. **162:** 3079–3087
9 Rose N. R. and Bona C. (1993) Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol. Today **14:** 426–430
10 Dohlman J. G., Lupas A. and Carson M. (1993) Long charge-rich alpha-helices in systemic autoantigens. Biochem. Biophys. Res. Commun. **195:** 686–696
11 Cunningham M. W., Antone S. M., Gulizia J. M., McManus B. A. and Gauntt C. J. (1993) Alpha-helical coiled-coil molecules: a role in autoimmunity against the heart. Clin. Immunol. Immunopathol. **68:** 118–123
12 Rao V. P., Kajon A. E., Spindler K. R. and Carayanniotis G. (1999) Involvement of epitope mimicry in potentiation but not initiation of autoimmune disease. J. Immunol. **15:** 5888–5893
13 Mokhtarian F., Zhang Z., Shi Y., Gonzales E. and Sobel A. (1999) Molecular mimicry between a viral peptide and a myelin oligodendrocyte glycoprotein peptide induces autoimmune demyelinating disease in mice. J. Neuroimmunol. **95:** 43–54
14 Grossmann A. and Weiland E. (1991) Immunization with inactivated lactate dehydrogenase-elevating virus followed by virus infection favors the selection of hybridomas synthesizing antibodies cross-reacting with intermediate filaments and the LDV envelope protein VP3. Autoimmunity **8:** 329–333
15 Adelmann M. and Linington C. (1992) Molecular mimicry and the autoimmune response to the peripheral nerve myelin P0 glycoprotein. Neurochem. Res. **17:** 887–891
16 Yuki N. (2000) Current cases in which epitope mimicry is considered a component cause of autoimmune disease: Guillain-Barré syndrome. Cell. Mol. Life. Sci. **57:** 527–533
17 Avery A. C., Zhao Z.-S., Rodriguez A., Bikoff E. K., Soheilian M., Foster C. S. et al. (1995) Resistance to herpes stromal keratitis conferred by an IgG2a-derived peptide. Nature **376:** 431–434
18 Zhao Z.-S., Granucci F., Yeh L., Schaffer P. A. and Cantor H. (1998) Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection. Science **279:** 1344–1347
19 Matsui M., Kakigi R., Watanabe S. and Kuroda Y. (1996) Recurrent demyelinating transverse myelitis in a high titer HBs-antigen carrier. J. Neurol. Sci. **139:** 235–237
20 Love L. A., Leff R. L., Fraser D. D., Targoff I. N., Dalakas M., Plotz P. H. et al. (1991) A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine **70:** 360–374
21 Miller F. W., Waite K. A., Biswas T. and Plotz P. H. (1990) The role of an autoantigen, histidyl-tRNA synthetase, in the induction and maintenance of autoimmunity. Proc. Natl Acad. Sci. USA **87:** 9933–9937
22 Blechynden L. M., Lawson M. A., Tabarias H., Garlepp M. J., Sherman J., Raben N. et al. (1997) Myositis induced by

naked DNA immunization with the gene for histidyl-tRNA synthetase. Human Gene Ther. **8:** 1469–1480
23 Miller F. W., Lover L. A., Biswas T., McClintock P. R., Notkins A. N. and Plotz P. H. (1987) Viral and host genetic factors influence encephalomyocarditis virus-induced polymyositis in adult mice. Arth. Rheum. **30:** 549–556
24 Walker E. J. and Jeffrey P. D. (1988) Sequence homology between encephalomyocarditis virus protein VP1 and histidyl-tRNA synthetase supports a hypothesis of molecular mimicry in polymyositis. Med. Hypoth. **25:** 21–25
25 Miller S. D., Vanderlugt C. L., Begolka W. S., Pao W., Yauch R. L., Neville K. L. et al. (1997) Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. Nat. Med. **3:** 1133–1136
26 Yamada M., Zurbriggen A. and Fujinami R. S. (1990) Monoclonal antibody to Theiler's murine encephalomyelitis virus defines a determinant on myelin and oligodendrocytes, and augments demyelination in experimental allergic encephalomyelitis. J. Exp. Med. **171:** 1893–1907
27 McCluskey J., Farris A. D., Keech C. L., Purcell A. W., Rischmueller M., Kinoshita G. et al. (1998) Determinant spreading: lessons from animal models and human disease. Immunol. Rev. **164:** 209–229
28 Rose N. R. (1998) The role of infection in the pathogenesis of autoimmune disease. Semin. Immunol. **10:** 5–13
29 Rose N. R. and Mackay I. R. (2000) Molecular mimicry: a critical look at exemplary instances in human diseases. Cell. Mol. Life Sci. **57:** 542–551
30 Gauntt C. J., Tracy S. M., Chapman N., Wood H. J., Kolbeck P. C., Karaganis A. G. et al. (1995) Coxsackievirus-induced chronic myocarditis in murine models. Eur. Heart J. Suppl. **16:** 56–58
31 Huber S., Polgar J., Moraska A., Cunningham M., Schwimmbeck P. and Schultheiss P. (1993) T lymphocyte responses in CVB3-induced murine myocarditis. Scand. J. Infect. Dis. Suppl. **88:** 67–78
32 Cunningham M. W., Antone S. M., Gulizia J. M., McManus B. M., Fischetti V. A. and Gauntt C. J. (1992) Cytotoxic and viral neutralizing antibodies crossreact with streptococcal M protein, enteroviruses, and human cardiac myosin. Proc. Natl. Acad. Sci. USA **89:** 1320–1324
33 Gauntt C. J., Arizpe H. M., Higdon A. L., Wood H. J., Bowers D. F., Rozek M. M. et al. (1995) Molecular mimicry, anti-coxsackievirus B3 neutralizing monoclonal antibodies, and myocarditis. J. Immunol. **154:** 2983–2995
34 Huber S. A. and Cunningham M. W. (1996) Streptococcal M protein peptide with similarity to myosin induces $CD4^+$ T cell-dependent myocarditis in MRL/++ mice and induces partial tolerance against coxsackieviral myocarditis. J. Immunol. **156:** 3528–3534
35 Loudon R. P., Moraska A. F., Huber S. A., Schwimmbeck P. and Schultheiss P. (1991) An attenuated variant of Coxsackievirus B3 preferentially induces immunoregulatory T cells in vivo. J. Virol. **65:** 5813–5819
36 Beisel K. W., Srinivasappa J. and Prabhakar B. S. (1991) Identification of a putative shared epitope between Coxsackievirus B4 and alpha cardiac myosin heavy chain. Clin. Exp. Immunol. **86:** 49–55
37 Bartholomaeus W. N., O'Donoghue H., Foti D., Lawson C. M., Shellam G. R. and Reed W. D. (1988) Multiple autoantibodies following cytomegalovirus infection: virus distribution and specificity of autoantibodies. Immunology **64:** 397–405
38 Lawson C. M., O'Donoghue H., Bartholomaeus W. N. and Reed W. D. (1990) Genetic control of cytomegalovirus induced myocarditis. Immunology **69:** 20–26
39 Fairweather D., Lawson C. M., Chapman A. J., Brown C. M. S., Booth T. W. M., Papadimitriou J. M. et al. (1998) Wild isolates of murine cytomegalovirus induce myocarditis and antibodies which cross-react with myosin. Immunology **94:** 263–270
40 Lawson C. M., O'Donoghue H. and Reed W. D. (1989) The role of T cells in mouse cytomegalovirus myocarditis. Immunology **67:** 132–134
41 Lawson C. M., Hodgkin P. and Shellam G. R. (1990) The effect of cyclosporin A on major histocompatibility-linked resistance to murine cytomegalovirus. J. Gen. Virol. **70:** 1253–1259
42 Lawson C. M., Grundy J. E. and Shellam G. R. (1988) Antibody responses to murine cytomegalovirus in genetically resistant and susceptible strains of mice. J. Gen. Virol. **69:** 1987–1998
43 Lawson C. M., O'Donoghue H. L., Farrell H. E., Shellam G. R. and Reed W. D. (1991) Murine anti-cytomegalovirus monoclonal antibodies with autoreactivity. Immunology **72:** 427–433
44 Penninger J. M., Neu N. and Bachmaier K. (1996) A genetic map of autoimmune heart disease. Immunologist **4:** 131–141
45 Harrison L. C. and McColl G. J. (1998) Infection and autoimmune disease. In: The Autoimmune Diseases, pp. 127–140, Rose N. (ed.), Academic Press, New York
46 Rose N. R., Herskowitz A. and Neumann D. A. (1993) Autoimmunity in myocarditis: models and mechanisms. Clin. Immunol. Immunopathol. **68:** 95–99
47 Kukreja A. and MacLaren N. K. (2000) Current cases in which epitope mimicry is considered as a component cause of autoimmune disease: immune-mediated (type 1) diabetes. Cell. Mol. Life Sci. **57:** 534–541
48 Honeyman M. C., Stine N. L. and Harrison L. C. (1998) T-cell epitopes in type I diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. Mol. Med. **4:** 231–239
49 Yuki N., Yamamoto T. and Hirata K. (1998) Correlation between cytomegalovirus infection and IgM anti-MAG/SGPG antibody-associated neuropathy. Ann. Neurol. **44:** 408–410
50 Ma Y., Peakman M., Lobo-Yeo A., Wen L., Lenzi M., Gaken J. et al. (1994) Differences in immune recognition of cytochrome P4502D6 by liver kidney microsomal (LKM) antibody in autoimmune hepatitis and chronic hepatitis C virus infection. Clin. Exp. Immunol. **97:** 94–99
51 Bisset L. R. (1994) Molecular mimicry in the pathogenesis of AIDS: the HIV/MHC/mycoplasma triangle. Med. Hypoth. **43:** 388–396
52 Banki K., Colombo E., Sia F., Halladay D., Mattson D. H., Tatum A. H. et al. (1994) Oligodendrocyte-specific expression and autoantigenicity of transaldolase in multiple sclerosis. J. Exp. Med. **180:** 1649–1663
53 Baboonian C., Venables P. J., Williams D. G., Williams R. O. and Maini R. N. (1991) Cross reaction of antibodies to a glycine/alanine repeat sequence of Epstein-Barr virus nuclear antigen-1 with collagen, cytokeratin, and actin. Ann. Rheum. Dis. **50:** 772–775
54 Misko I. S., Cross S. M., Khanna R., Elliott S. L., Schmidt C., Pye S. J. et al. (1999) Crossreactive recognition of viral, self, and bacterial peptide ligands by human class I-restricted cytotoxic T lymphocyte clonotypes: implications for molecular mimicry in autoimmune disease. Proc. Natl Acad. Sci. USA **96:** 2279–2284
55 Guldner H. H., Netter H. J., Szostecki C., Jaeger E. and Will H. (1990) Human anti-p68 autoantibodies recognize a common epitope of U1 RNA containing small nuclear ribonucleoprotein and influenza B virus. J. Exp. Med. **171:** 819–829
56 Dyrberg T. and Oldstone M. B. (1986) Peptides as probes to study molecular mimicry and virus-induced autoimmunity. Curr. Topics Microbiol. Immunol. **130:** 25–37