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Viruses and autoimmunity

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Abstract
Viruses have been suspected as causes and contributors of human autoimmune diseases (AID), although direct evidence for the association is lacking. However, several animal models provide strong evidence that viruses can induce AIDs as well as act to accelerate and exacerbate lesions in situations where self-tolerance is broken. Many models support the hypothesis by acting as molecular mimics that stimulate self-reactive lymphocytes. Mimicry alone is usually inadequate and with human AID, no compelling evidence supports a role for viruses that are acting as molecular mimics. Alternative mechanisms by which viruses participate in autoimmunity are non-specific, involving a mechanistically poorly understood process termed bystander activation or perhaps viral interference with regulatory cell control systems. This review briefly discusses examples where viruses are involved, taking the view point that molecular mimicry is over emphasized as a critical mechanism during AID pathogenesis.

Keywords: *Autoimmune diseases, self tolerance, molecular mimicry, bystander activation*

Introduction

Autoimmune diseases (AID) affect 3–5% of our population. They occur when self-reactive lymphocytes escape immunological tolerance and are activated. Currently, we have little understanding of the mechanisms that cause escape and activation but they are assumed to involve a combination of usually complex intrinsic genetic factors as well as acquired environmental triggers that include infectious agents. In human AID, several viruses are suspected to act as triggers for lesion production but fortunately no known virus has been proven to regularly induce or promote AID. In consequence, even the genetically prone are in no apparent danger of catching AID from other patients. No prospects for bioterrorists in this field! Apart from attempting to establish an association between viruses and human AID by epidemiological or statistical studies, our understanding of how viruses relate to autoimmunity comes from experiments in animal models. Such studies have revealed several mechanisms by which viruses could contribute to the pathogenesis of AID.

There are basically two situations where viruses could participate [1–5]. They could act in some way to break immunological tolerance to self and hence induce autoimmunity. Alternatively, they might be involved in causing disease expression in individuals in which the autoimmune process is already established for genetic or other reasons. A third scenario indicates that viruses might in some situations protect against clinical AID [6]. In most, but not all systems analyzed with mouse models, the induction and expression phases are not investigated separately. This could result in a misleading story since with human AID it appears that clinical lesions become evident long after events which result in tolerance breakdown have occurred [1]. In fact, with human AID the best evidence for virus participation is to act as triggers or accelerators of clinical disease rather than as instigators of tolerance breakdown. If viruses do cause tolerance breakdown, a process described

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Table I. Associations of viruses with AIDs.

Human diseases	Animal models	Autoantigen/ cross-reactive antigen	Viruses implicated	References
Multiple sclerosis	EAE	Myelin proteins	Measles, HSV, HHV6, Corona virus, TMEV, HTLV, Parainfluenza virus, Simian virus 5	[41–49]
IDDM-1	IDDM NOD	Islet antigens	Coxsackie virus 4, Rotavirus, Herpes, Rhino, Hanta, Favivirus, Retro virus	[50–53]
Myocarditis	Myocarditis	Myosin proteins	Hepatitis C	[54]
HSK	HSK	Cornea derived autoantigens	HSV	[20,6]
Myasthenia gravis	EAMG	Acetyl choline receptrs, neurofilaments	HSV, Hepatitis C	[55,56]
Lupus erythematosus	Cutaneous LE, systemic LE	dsDNA spliceosome protein	EBV, CMV	[57,58]
Rheumatoid arthritis	Collagen induced arthritis	Joint antigen, ubiquitin protein	Hepatitis C, Hepatitis B, EBV, Retrovirus	[59–63]

poetically by Lindsay Whitton et al. as the "fertile field" phase [1], then tracing the culprit after a prolonged period would be problematic. However, associating viruses responsible during the "crop nurturing" phase is far easier especially since the suspects were recently around or are still present. In multiple sclerosis (MS), for example, numerous viruses have been advocated as probable causes of disease expression (Table I), although none have been unequivocally proven to play such a role.

Role of viruses in initiating aid: Breakdown of tolerance

Several experimental systems in animal models have clearly shown that viruses can cause tolerance breakdown and resultant AID. The favorite explanation for tolerance breakdown is that the agent responsible provides a cross-reactive molecular mimic of self-protein or peptides [1,2,4,7]. In addition, properties such as potent activation of innate immunity may also be necessary [8,9]. Classical studies from the Oldstone and Zinkernagel laboratories using transgenic mice provided convincing evidence for a causative role for viruses in autoimmunity [10,11]. Their mice were engineered to express a viral protein as surrogate self in the beta cells of the islets of Langerhans. Such animals remained clinically normal, but upon subsequent exposure to the surrogate self antigen in the form of virus infection, islet destruction occurred and the mice developed insulin dependent diabetes mellitus (IDDM) [10–12]. Whilst the initial studies were not strictly speaking molecular mimicry since the molecules involved in induction and tolerance breakdown were identical, subsequent modifications demonstrated that IDDM could also be initiated by exposure to viruses that possessed cross-reactive epitopes [13]. These observations strongly support the molecular mimicry hypothesis [4].

Perhaps the most convincing support for molecular mimicry as an explanation of viral-induced AID comes from the observations of a former skeptic, Steve Miller. This group used Theiler's virus, an agent that causes an MS-like lesion (EAE) in the brain of susceptible mouse strains [14]. Characteristically, intracranial infection with TMEV induces a viral immunopathological lesion that subsequently, as a consequence of a process referred to as epitope spreading [15], becomes autoreactive and includes reactivity to myelin components [16]. In this model, EAE is initially viral immunopathology but it eventually becomes mainly autoimmunity. The Miller group modified their system by engineering recombinant strains of TMEV that expressed different types of recombinant proteins. They demonstrated that recombinants expressing the myelin peptide PLP, or of even more interest a pathogen derived molecular mimic of PLP, induced rapid EAE. However, control recombinants, expressing brain-irrelevant proteins, did not produce rapid disease [14,17]. The Miller experiment made a compelling case for molecular mimicry as the cause of tolerance breakdown, but their system may not translate to understanding MS, the disease they are attempting to model. Thus their recombinant viruses were proinflammatory and persisted indefinitely in the target tissue with the recombinants that expressed brain-unrelated peptides eventually producing the EAE syndrome [14]. The group also showed that additional properties of the persistent virus were necessary to induce EAE such as its potent stimulatory effects on the innate immune system and upregulation of costimulatory molecules on cells of the brain involved in antigen presentation [14,18]. Thus the Miller model shows what could occur but it is doubtful if such a situation actually happens at least with MS where lesions do not usually contain any chronic virus infection.

Table II. Summary of observations that implicate molecular mimicry between HSV and a corneal autoantigen as the explanation for the development of Stromal Keratitis lesions [19–21].

	Mice models*		
Virus infection or inoculation	Susceptible lacks self peptide	Resistant possess self peptide	Transgenic express the TCR specific for self peptide
HSV-1 KOS strain WT	+++	±	++++
HSV-1 KOS strain UL6 − /− replication competent	±	ND†	+++
LPS + Scratch	−	−	+++
HSV-1 KOS strain UL6 − /−‡	±	ND	ND
HSV-1 KOS strain gB − /−‡	+++	ND	ND

* Naive mice were infected on scarified cornea with virus or inoculated with LPS, respectively. SK was scored based on severity of ocular lesion. † Not done. ‡ HSV immune T-cells from susceptible mice were adoptively transferred into nude recipients and infected with the mutant viruses.

Other models have also been taken to support the molecular mimicry hypothesis. An intriguing example was suggested by the Cantor group [19,20]. It is stromal keratitis (SK), a blinding lesion in the eye caused by herpes simplex virus (HSV) infection. The group's fascinating observations were performed initially in two closely related congenic mice strains that differed in the isotype of IgG they produced [19]. It turned out that a peptide sequence of one of the IgG isotypes was expressed in the cornea after HSV infection. Moreover, this peptide appeared to act as the dominant-target antigen for the ocular inflammatory response in susceptible mice [19]. In support of this, $CD4^+$T-cell clones reactive with the self-peptide could adoptively transfer SK susceptibility to immunocompromised animals infected with HSV [19]. The basis of susceptibility to HSV infection was seemingly the consequence of cross-reactivity (molecular mimicry) between a peptide component of the HSV UL-6 protein and the corneal peptide responsible for driving the inflammatory reaction in susceptible mice [20]. Resistant mice, on the other hand, were tolerant of the peptide and so virus infection failed to induce severe SK. This story was further substantiated by showing that HSV mutants lacking UL-6, but not mutants for other proteins (HSV gB − /−), were non-disease producing in nude recipients of T-cells from the susceptible mice [20]. Furthermore, tolerization of susceptible mice with IgG from resistant animal or the UL6 peptide, conferred resistance to SK development [19,20]. Moreover, mice made TCR transgenic with their $CD4^+$T-cells recognizing the corneal peptide were extremely susceptible to wild-type infection [21]. In fact, these animals were highly susceptible to developing SK upon infection with HSV UL6 − /− or inoculation with LPS onto scratched corneas [21]. These observations were interpreted to suggest that innate immune mechanisms are sufficient to trigger disease in animals containing expanded number of autoreactive T-cells. These fascinating observations are summarized in Table II.

The idea that HSV represents an autoinflammatory response set off by cross-reactivity between the viral UL-6 protein and a corneal peptide has been examined in other mouse strains as well as with human tissue. Independent support has not been forthcoming nor have additional proteins of HSV been found to act as molecular mimics of host proteins. For example, BALB/c and C57BL/6 mice fail to generate $CD4^+$T-cell responses to UL-6 upon infection with wild type virus [22]. Moreover, reaction of UL-6 specific T-cells, generated by immunization with recombinant vaccinia expressing UL-6, failed to respond to stimulation by HSV-infected antigen presenting cells *in vitro* [22]. Several groups have also attempted to isolate UL-6 reactive $CD4^+$T-cells from corneal buttons removed from human SK patients [23]. Reactivity to UL-6 was not detected, but cell lines were obtained that reacted with HSV but notably not with corneal extracts [23]. Results thus far indicate that the human disease, and SK in other mouse strains, does not appear to be an autoinflammatory response set off by the UL-6 protein of HSV. Conceivably other viral proteins could play such a role but proving this hypothesis will be highly problematic. Moreover, in human SK there is no known association with MHC genotype nor are females more susceptible, as is frequently the case for organ-specific AID. If indeed HSV, a common infection of mankind, serves to break tolerance in the eye, resulting in autoimmune inflammatory lesions, this stands as a unique and perhaps troublesome example. Thus, it would represent a readily transmissible AID.

Bystander activation-role of viruses in induction and expression of aid

Whereas molecular mimicry by cross-reactive antigens is widely considered as a likely means by which viruses could break tolerance, and result in the expansion and activation of autoreactive lymphocytes, alternative ideas have also been advanced. The most popular idea is referred to as bystander activation [1,5,14,24].

Here, the concept is that autoreactive cells may be expanded and activated by non-specific means or by a combination of non-specific effects with self antigens being released and presented in an inflammatory environment created by virus infection. Possible examples of inflammatory products involved include TLR ligand activity of viruses [25], breakdown products of infected cells, or possibly inflammatory molecules generated by chronically virus-infected tissues [16,26]. The idea that viruses can break tolerance by a bystander activation mechanism has few advocates. However, there is more support for the notion that the bystander activation mechanism provides an explanation for the means by which viruses cause the "fertile field" to flourish and yield crops (lesions) (Figure 1) [1]. In this view point, viruses may act like rain causing all fertile seeds (include autoreactive clones) to grow. The fact that multiple viruses appear to trigger MS is better explained by a bystander activation rather than a molecular mimicry type mechanism. Indeed the epitope spreading phenomenon noted in the wild type TMEV system would seem not to involve molecular mimicry.

Whereas it is conceptually easy to explain and understand how cross-reactive peptides could trigger self-reactive lymphocytes to expand and become activated, bystander activation is less easily explained. Thus, the idea is that self reactive lymphocytes are expanded and activated not by ligands received from their antigen receptors but instead via other triggering mechanisms. Alternatively, they could be presented with their cognate self antigen but by an antigen presenting cell system that has been highly activated by the inflammatory environment created by virus infection. As noted with the TMEV studies, viruses that are more proinflammatory are more likely to induce EAE [8]. In the HSV system too, the Cantor group noted that some strains of HSV can induce SK in some TCR transgenic mouse models in which the HSV KOS strain is inactive [27]. A further mechanism by which viruses could cause autoreactivity to become tissue damaging is that they impair regulatory cell systems. Such systems were shown recently to play a significant role in containing AID [28,29]. Moreover, our group has shown that T regulatory cells serve to modulate the severity of SK [30,31].

Evidence for the operation of bystander mechanisms has been obtained in several systems [16,26,32–34]. Our group, for example, has studied SK in animals lacking lymphocytes that recognize HSV antigens. These were T-cell receptor transgenic mice back-crossed to SCID or RAG $-/-$. In such animals, $>95\%$ of their lymphocytes recognized a known peptide that could not be shown to be cross-reactive to HSV [22,32,33,35,36]. Unlike SCID or RAG $-/-$ mice without lymphocytes, all TCR transgenic SCID or RAG $-/-$ mice studied developed apparently

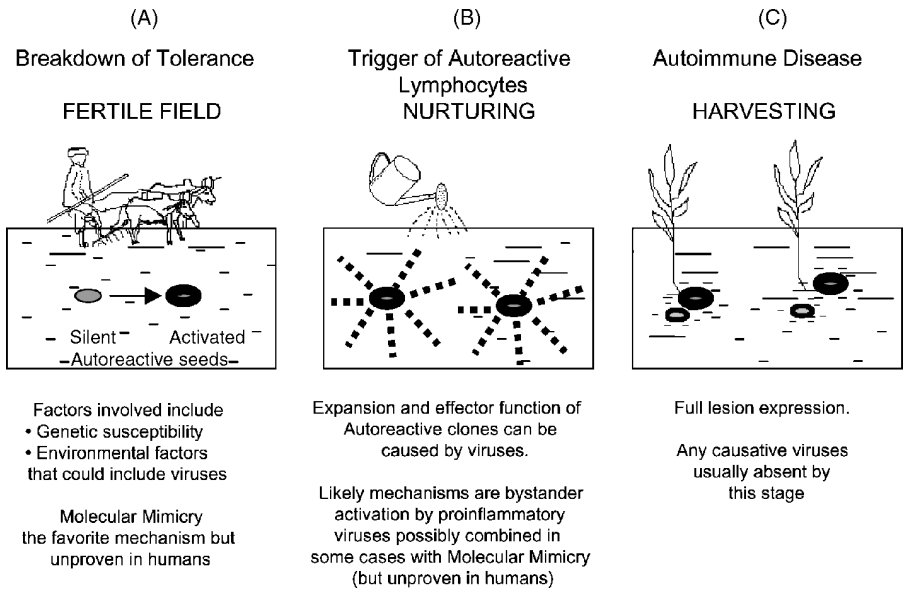

Figure 1. Events likely involved in the expression of AID. (A) Breakdown of tolerance: depicts an individual susceptible to AID as a "fertile field" already containing silent autoreactive seeds and genetic susceptibility. Exposure to environmental factors, which may include virus infection, may result in breakdown of tolerance of the autoreactive lymphocytes, possibly by the mechanism of molecular mimicry. Such an individual with autoreactive lymphocytes is now susceptible to developing AID. There may, however, be a time lapse between breakdown of tolerance, i.e. initiation of AID to actual disease expression; (B) triggering of autoreactive lymphocytes: nurturing of the seeds in the fertile field or the expansion of autoreactive lymphocytes may be set off by virus infection by the bystander activation or the molecular mimicry mechanism. Molecular mimics of the self peptide encoded by the virus may cause expansion and further activation of the autoreactive lymphocytes. Additionally or alternatively, proinflammatory virus infections can cause bystander activation of the autoreactive lymphocytes via generation of inflammatory cytokine/chemokine milieu and superactivation of antigen presenting cells; (C) Expression of AID: harvesting of the fertile field in the absence of the causative virus.

normal SK lesions upon ocular infection with HSV. Since such animals failed to develop HSV specific T-cells and in fact eventually died from infection, the T-cells involved in orchestrating the inflammatory lesions were assumed to be participating non-specifically in a bystander activation mechanism. Although, we assume that similar bystander activation could be responsible for autoimmunity, we do not claim the SK lesions produced in the TCR transgenic model to represent actual autoreactivity.

It also remains to be shown how the virus serves to activate the lesion producing T-cells since TCR engagement by viral proteins appears to be ruled out. It was hypothesized that the activation involved a non TCR mediated bystander activation process possibly mediated by viral products or perhaps more likely by inflammatory molecules generated in the tissue by virus infection. One line of evidence arguing against TCR activation (as occurs with the molecular mimicry mechanism) was that the SK reaction was refractory to cyclosporine A treatment [37]. However, rapamycin, an inhibitor of cytokine mediated signaling, did result in lesion inhibition [37]. Additionally, it was shown that persistence of replicating virus in lesions appeared to be necessary [22,33], a situation reminiscent of EAE induced by TMEV [16]. Accordingly, removal of virus by drugs or antibody or the use of viral mutants, unable to traffic to the stromal lesion site, markedly diminished lesion severity [32,37].

The SK model serves to demonstrate that bystander activation events can alone be responsible for tissue damage. Alas, the observations at present do not explain mechanistically how it occurs or can we assume the response respresents autoimmunity. We suspect a complex of events participate which may include the TLR ligand activity of the virus [38] and the fact that HSV infection results in the vascularization of a normally avascular structure [39,40]. Whereas it is unlikely that any self proteins released from the inflamed site would be recognized by the transgenic T-cells, other self proteins, such as stress molecules might well contribute to the activating effect. Some ideas about the mechanism at play in the bystander system are depicted in Figure 2.

Finally, we realize that showing immunological events with transgenic T-cells can be potentially misleading since the transgenic cells may be more excitable than normal cells during inflammatory events. We have, however, additionally demonstrated the participation of normal T-cells as bystanders in SK lesions [37], but whether or not such cells are functionally contributing to the lesions or in fact are autoreactive requires further study.

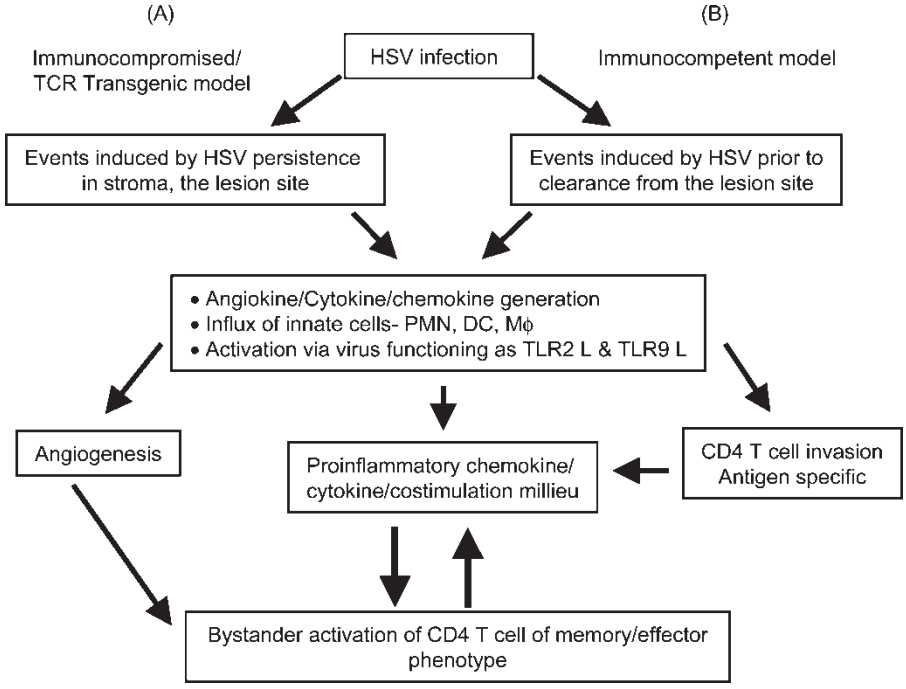

Figure 2. Bystander activation in herpetic stromal keratitis (HSK), HSV infections in the corneas of immunocompetent or immunocompromised, TCR transgenic mice may result in stromal keratitis by the mechanism of bystander activation. (A) In immunocompromised model, virus persists in the corneal stroma, the site of lesion expression, which may lead to complex events, involving angiogenesis and a proinflammatory cytokine milieu which may cause bystander activation of non antigen specific $CD4^{+}$T-cells of memory/effector phenotype; (B) In immunocompetent mice, prior to virus clearance from the cornea, the infection may set off angiogenesis and a proinflammatory cytokine/chemokine milieu resulting in the invasion of $CD4^{+}$T-cells which maybe antigen specific and further cause bystander activation of $CD4^{+}$T-cells of memory/effector phenotype.

Summary

Viruses may act as triggers, accelerators or as regulators of AID. Many animal models support the involvement of viruses in lesion development, although any such evidence for incriminating viruses in human AID is still not forthcoming. However, it is likely that virus infections play a substantial role in a nurturing or triggering activated autoreactive lymphocytes rather than breaking the tolerance of silent autoreactive lymphocytes. Mechanisms involved could include the bystander activation mechanism by proinflammatory viruses possibly combined in some cases with molecular mimicry. Additionally, viruses may serve to interfere with the immune regulatory mechanisms. Accordingly, understanding the role of the virus in triggering or accelerating AID may give insights into mechanisms for the development of AID and their therapeutic strategies.

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