Available online at www.sciencedirect.com
SCIENCE DIRECT®
Molecular Immunology 40 (2004) 1113–1120
Molecular Immunology
www.elsevier.com/locate/molimm

Induction, acceleration or prevention of autoimmunity by molecular mimicry

Urs Christen*, Matthias G. von Herrath

Department of Developmental Immunology, La Jolla Institute for Allergy and Immunology, 10355 Science Center Dr, San Diego, CA 92121, USA

Abstract

The hypothesis that cross-reactivity between microbial and self determinants recognized by the adaptive immune system could induce autoimmune diseases is very intriguing. However, definite proof in humans is very difficult to achieve and evidence is frequently circumstantial. Therefore, animal models are instrumental for understanding, how and when mimicry could be involved in the pathogenesis of autoimmunity. In this article, we will discuss experimental scenarios, where mimicry between foreign and self determinants does not cause disease per se, but rather aggravates a pre-existing yet sub-clinical autoimmune condition. We would like to propose that molecular mimicry is more likely to impact on an already existing autoimmune process rather than precipitate novel disease by breaking of tolerance from the beginning. Already activated autoreactive cells might be easier re-activated and primed for effector functions by cross-reactive ligands than naive lymphocytes.

Keywords: Virus; Diabetes; Fertile field; Pichinde; LCMV; Halothane hepatitis; Cross-reactivity; Autoimmune disease; Repertoire

1. Introduction

A complex series of DNA rearrangement and other genetic modifications generates a large diversity of both B- and T-cell receptors. Thus, the repertoire of the immune system seems almost indefinitely large or at least large enough to adapt to every possible antigenic component in the realm of foreign and self. However, many individual receptors are degenerate. It is now well known that such cross-reactive receptors have the potential to interact with several ligands that share a certain degree of similarity. The concept of molecular mimicry is based on this finding and requires that two or more components (foreign or self) are structurally so similar that an individual B-cell (antibody) or T-cell cannot distinguish between them. In a classical manuscript, Srinivasappa et al. screened over 600 monoclonal antibodies to 11 different viruses, analyzed their reactivity to 14 different organs of normal uninfected mice and found 21 (3.5%) monoclonal antibodies that (cross-)reacted to specific cells of the human body. (Srinivasappa et al., 1986). Instinctively, one would propose that such cross-reactivities between foreign and self-components might be one of the factors responsible for the occurrence of autoimmunity. Indeed, in the last decades cross-reactive T-cells or antibodies have been found in situations, where associations between infectious agents and autoimmune disorders have been known, such as ankylosing spondylitis (Schwimmbeck and Oldstone, 1989), multiple sclerosis (Kurtzke, 1993; Panitch, 1994), and type 1 diabetes (Gamble, 1980; Notkins and Yoon, 1984). For example, sera from patients with akylosis spondylitis frequently react with proteins from *Krebsiella pneumoniae* (Schwimmbeck and Oldstone, 1989). Cross-reactivity of these sera was to peptides of *K. pneumoniae* pulD secretion protein (DRDE) and pulA (pullulanase) with the host proteins HLA-B27 and type I, III and IV collagen, respectively (Fielder et al., 1995). A large majority of patients suffering from myasthenia gravis (MG) carry antibody to the acetylcholine receptor which shares a cross-reactive epitope with herpes simplex virus (HSV) glycoprotein D (Schwimmbeck et al., 1989). Type 1 diabetes has been associated with several viral infections including coxsackie B virus (Gamble, 1980; Notkins and Yoon, 1984; Yoon et al., 1979). Interestingly, Honeyman et al. have found that the high frequency of rotavirus infection in young children with type 1 diabetes cannot be explained by pure coincidence (Honeyman et al., 2000). A more thorough compilation of diseases with a possibly associated with or caused by molecular mimicry is available in recent reviews by Oldstone (Oldstone, 1998) and by Rose and Mackay (Rose and Mackay, 2000). However,

* Corresponding author. Tel.: +1-858-558-3578; fax: +1-858-558-3579.
E-mail addresses: christen@liai.org (U. Christen), matthias@liai.org (M.G. von Herrath).

0161-5890/$ – see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.molimm.2003.11.014

despite all the indications for molecular mimicry as a mechanism to be involved in the etiology of autoimmune disease ranging from epidemiological observations to sequence homology data, no direct evidence for molecular mimicry as an initiator or accelerator of autoimmunity in humans could be demonstrated to date. One major reason for such a lack of direct proof is the complexity of the molecular mimicry hypothesis. The existence of similar target epitopes for degenerate T-cells or antibodies does not necessarily mean that recognition of those mimicking epitopes results in a similar immune response. Mimic epitopes for T-cells can be agonists, antagonist or altered peptide ligands (APLs) that, based on observations made in many different laboratories, can activate, cancel, or modulate effector functions (Kersh and Allen, 1996). Different avidities of the actual target (host) epitope and the (viral/bacterial) mimicking epitope may be another key factor that plays a role in autoimmunity. Lower avidity of a mimicking epitope might require an additional local inflammatory event in order to successfully activate a cross-reactive T-cell and subsequently cause clinical disease.

2. Molecular mimicry in type 1 diabetes

Many experimental systems propose the involvement of molecular mimicry as a basis to study autoimmune diseases in animal models. One of the best examples is the herpes virus-induced keratitis model that is based on a true molecular mimicry between an HSV-1 epitope and an ocular protein (Zhao et al., 1998). Another experimental system uses a genetically engineered Theiler's virus (TEMV) recombinant that expresses a modified myelin component from the central nervous system to induce acceleration of demyelination and autoimmunity (Katz-Levy et al., 1999). For type 1 diabetes the concept of molecular mimicry of self-components by an infective agent was considered and the following scenario for the pathogenesis of type 1 diabetes was hypothesized: first, restricted but low level expression of a self or viral antigen occurs or is pre-existing in β-cells of the islets of Langerhans. This event does not cause disease, since the host is unresponsive (T-cells do not become activated), ignorant (T-cells do not react) or tolerant (no auto-reactive T-cells are present) to the antigen. Later on, a triggering event may occur, which is exposure to an environmental factor or pathogen with cross-reacting antigenic determinants (von Herrath et al., 1994). The result would be an immune response to the virus that at the same time attacks the β-cells and over time leads to progression to T1D after a lag period. A basis for testing this scenario was experimentally established in the late 1980s by the laboratories of Oldstone (Oldstone et al., 1991) and Zinkernagel (Ohashi et al., 1991). Both groups used a rat insulin promoter (RIP) to create separate lines of transgenic mice whose pancreatic β-cells expressed either the nucleoprotein (NP) or the glycoprotein (GP) of the lymphocytic choriomeningitis virus (LCMV) as defined target antigen. The expression of the target-antigen did not lead to β-cell dysfunction, islet cell infiltration, hyperglycemia, or spontaneous activation of autoreactive (anti-LCMV) lymphocytes (von Herrath et al., 1994). However, infection with LCMV results in autoimmune diabetes in >95% of RIP-LCMV mice. In contrast, non-transgenic littermates never develop diabetes or insulitis after LCMV challenge (von Herrath et al., 1994). Obviously, antigenic identity but not mimicry is responsible for this high incidence of T1D in this experimental model (LCMV viral protein is identical to transgene).

Just as proposed for human T1D, the onset of diabetes in RIP-LCMV mice depends on the action of both, autoreactive CD4 and CD8 lymphocytes and correlates with the numbers of auto-aggressive lymphocytes generated (Sevilla et al., 2000; von Herrath et al., 1994). In accordance, the incidence of disease varied between the individual transgenic lines ranging from 2 weeks (RIP-GP lines) to 1–6 months (RIP-NP lines). Further studies revealed the mechanism involved in the rapid compared to the slow progressive diabetes. Transgenic lines expressing the LCMV-GP transgene exclusively in the β-cells of the islets manifested rapid-onset T1D (10–14 days after viral challenge) (von Herrath et al., 1994). In these lines the high systemic numbers of auto-aggressive CD8 lymphocytes were sufficient to induce diabetes and did not require help from CD4 cells. In contrast, in lines expressing the LCMV-NP transgene in both the β-cells and in the thymus, T1D took longer to occur after subsequent LCMV challenge. Several lines of evidence indicated that the anti-self (viral) CTL were of lower affinity and that CD4 lymphocytes were essential to generate anti-self (viral) CD8 lymphocyte-mediated T1D of adult transgenic mice (von Herrath et al., 1994).

In addition, mouse models in which transgene-encoded 'target-antigens' are expressed in the pancreatic β-cells, such as the RIP-LCMV (Ohashi et al., 1991; Oldstone et al., 1991) and the INS-HA (Lo et al., 1992; Lo et al., 1993) mouse, have demonstrated that the presence of auto-aggressive T-cells alone is not enough to precipitate disease. Their precise effector functions and the inflammatory environment are critical additional determinants. For example, when RIP-LCMV mice were crossed with mice expressing an inactive mutated form of IFNγR the diabetes incidence was drastically reduced (Seewaldt et al., 2000) and blockage of TNFα with a neutralizing TNFR55-IgG1 fusion protein at an early stage after LCMV-infection abrogated disease (Christen et al., 2001). In addition, neutralization of the CXCR3 chemokine IP-10 (CXCL10) with a monoclonal antibody dramatically decreased diabetes incidence by blocking the expansion and subsequent migration of auto-aggressive CD8 T-cells into the pancreatic target organ (Christen et al., 2003). Mice expressing the hemaglutinin (HA) of the influenza virus under control of the insulin promoter (INS-HA) as a target antigen and a transgenic anti-HA TcR suffer either from insulitis only, or from insulitis as well as diabetes (Degermann et al., 1994; Scott et al.,

1994). Interestingly, IFNγ transcription levels were significantly higher in islets from diabetic mice, while TNFα was expressed at a higher level in non-diabetic mice (Sarukhan et al., 1998). These results indicate that unspecific 'bystander factors', such as cytokines and chemokines generated during the acute LCMV infection, might provide an inflammatory situation required to drive the auto-aggressive response (β-cell destruction) in 'antigen-specific' models for T1D.

3. Acceleration of autoimmunity by molecular mimicry

In contrast to the Theiler's virus autoimmune encephalomyelitis model that utilizes a modified myelin component to induce demyelination and disease acceleration (Katz-Levy et al., 1999), the RIP-LCMV model uses molecular identity rather than molecular mimicry to induce autoimmunity and requires the presence of the immunodominant LCMV epitopes, such as GP_{33-41} and $GP_{276-284}$ (RIP-GP line), and $NP_{396-404}$ (RIP-NP line). Infection of RIP-LCMV mice with CTL escape variants of LCMV that bear point mutations in the corresponding immunodominant epitopes fails to induce disease (Lewicki et al., 1995; Oldstone et al., 1995). Despite of their close similarity and sequence homology, the CTL escape variant epitopes in the GP_{33-41} sequence (from aa KAVYNFATC to aa KAVYN**L**ATC) and the $NP_{396-404}$ sequence (from aa FQPQNGQFI to aa FQPQNGQ**L**I) (Table 1) do not represent a real molecular mimic of the original epitopes from the immunological point of view, since the point mutation affects critical anchor residues required for proper presentation of the peptide by H-$2D^b$ (Oldstone et al., 1995). However, the failure of these escape variants to induce type 1 diabetes points towards a minimum requirement for recognition to induce autoimmune disease in the RIP-LCMV system. Thus, the question arises, which effect a true mimic that allows for detectable crossreactivity would have on induction or modulation of the autoimmune process in RIP-LCMV mice. Interestingly, infection with Pichinde virus (PV) that bears an epitope that is cross-reactive with the subdominant LCMV-NP epitope $NP_{205-212}$ does not induce diabetes in RIP-NP mice (Fig. 1) (Christen et al., 2004). This naturally occurring molecular mimicry between LCMV-$NP_{205-212}$ and PV-$NP_{205-212}$ manifests itself on the level of subdominant epitopes that play only minor role during the immune response mounted after single infections with LCMV or PV, respectively. Infection of regular C57BL/6 mice with LCMV results in the generation of ∼3–4% of LCMV-$NP_{205-212}$-specific CD8 cells during the acute phase of the immune response and its mimic PV-$NP_{205-212}$ activates ∼1% of CD8 T cells after acute PV infection (Brehm et al., 2002). In addition, nearly no PV-$NP_{205-212}$-specific CD8 T cells can be detected in LCMV-immune mice and no reactivity for LCMV-$NP_{205-212}$ was found in PV-immune mice (Brehm et al., 2002). Thus, a true mimic of a subdominant autoreactive epitope appears unable to induce disease in an immunologically naïve animal, because cross-reactive cell numbers are too low. However, these numbers dramatically change after heterologous infections of the same mouse with both viruses. It was demonstrated in the labs of Welsh and Selin that infections with heterologous viruses radically influence the CD8 T cell memory repertoire (Selin et al., 1999). Secondary infection of LCMV-infected mice with PV, vaccinia virus (VV), and/or murine cytomegalovirus (MCMV) reduced the percentage of CD8 T cells specific for the three major immunodominant LCMV-peptides (GP_{33-41}, $GP_{276-284}$, and $NP_{396-404}$) by more than fivefold (Selin et al., 1999). In contrast to a decrease of CD8 T-cell memory to those epitopes that are not shared among the heterologous viruses, the frequency of CD8 T cells specific for cross-reactive epitopes present during both infections increased massively. Namely, the frequency of LCMV-$NP_{205-212}$-specific CD8 T cells in LCMV-immune mice increases from ∼3–4% (acute phase; single LCMV infection) to ∼30% after secondary infection with PV. Similarly, secondary infection of PV-immune mice with LCMV increases the frequency of both PV- and LCMV-$NP_{205-212}$-specific CD8 T-cells by more than 10-fold (Brehm et al., 2002).

How does this shift in immunodominance after sequential infection with two heterologous viruses that share a mimicking epitope influence the course of autoimmunity? As mentioned above, PV alone fails to induce autoimmunity in the RIP-LCMV-NP model for type 1 diabetes, indicating the molecular mimicry on the level of subdominant epitopes is not sufficient to break tolerance in an naïve animal. However, secondary infection with PV at week 4 post-LCMV infection results in a significant acceleration of disease. At week 5 post-LCMV infection, a time where none of the single infected RIP-NP mice developed T1D, the majority of RIP-NP mice that received a secondary infection with PV were diabetic (Fig. 1) (Christen et al., 2004). In contrast, LCMV-immune RIP-NP mice that received an additional dose of LCMV instead of PV showed no acceleration of disease and PV-immune RIP-NP mice did never develop diabetes, even after a secondary challenge with PV (Fig. 1) (Christen et al., 2004). Interestingly, molecular mimicry was able to accelerate disease, if LCMV-immune mice were challenged with PV, but not vice versa, indicating that tolerance to the LCMV-NP transgene had to be broken prior to a possible acceleration of

Table 1
Immunodominant and subdominant LCMV-NP epitopes

Immunodominant NP epitopes		
LCMV (Armstrong)–NP396-404	FQPQNGQFI	H-$2D^b$
LCMV (Pasteur)–NP396-404	FQPQNGQFI	H-$2D^b$
LCMV (Armstrong–variant) NP396-404	FQPQNGQLI	–
Subdominant NP epitopes		
LCMV (Armstrong)–NP205-212	YTVKYPNL	H-$2K^b$
Pichinde virus–NP205-212 mimic	YTVKFPNM	H-$2K^b$

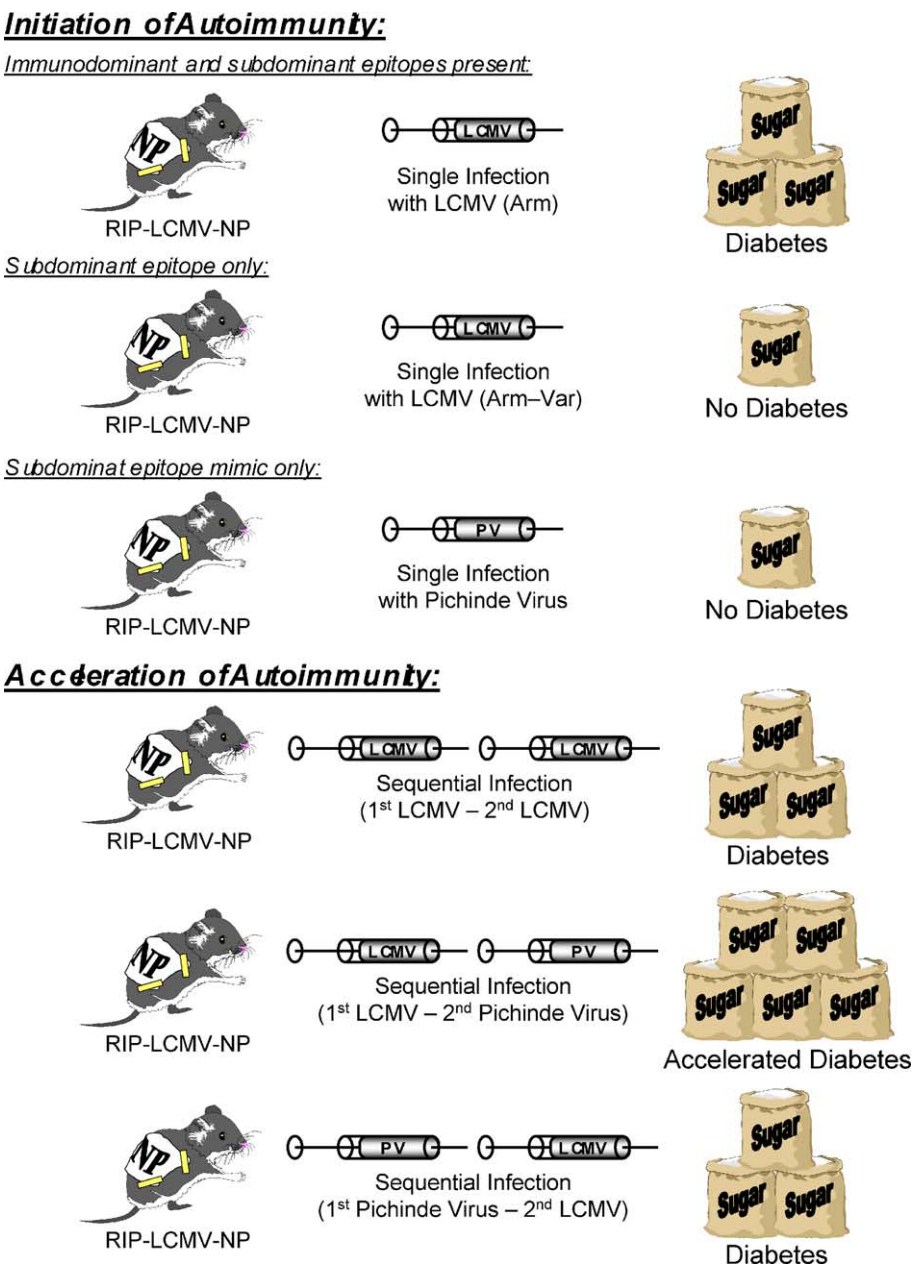

Fig. 1. Initiation vs. acceleration of autoimmunity by virus infections—the RIP-LCMV-NP model for type 1 diabetes uses the identical LCMV-NP-antigen (including all of its epitopes) for triggering the disease that was initially used for the generation of the transgenic mouse line. Autoimmunity can only be initiated if the proper immunodominant epitopes are present on the infecting virus (LCMV-Arm). In contrast, infection with a variant LCMV strain (Arm–Var) expressing a modified immunodominant epitope that cannot be presented by H-2^b, or with a virus that contains a mimic of a subdominant LCMV-epitope (Pichinde virus; PV) fails to induce T1D. However, infection at a later stage when the autoimmune process has been initiated (by infection with the proper virus) a sequential infection with Pichinde virus can accelerate T1D. Thus, even though molecular mimicry between two viruses is not sufficient to initiate the autoimmune process as observed in the RIP-LCMV model for T1D by itself, it can have a considerable impact on the progress of autoimmunity.

autoimmunity by molecular mimicry (Fig. 1). Mechanistically, it may be important to note that secondary infection with PV results in enhanced cytolytic function but not in an increased frequency of IFNγ-producing LCMV-$NP_{205\text{-}212}$ and PV-$NP_{205\text{-}212}$-specific CD8 T cells (Christen et al., 2004) indicating that a mimicking low-affinity epitope can reactivate resting, antigen-experienced CD8 T cells rather than de novo activating native T cells. These findings support the before-mentioned concept that pre-existing cellular activation and/or inflammation might have to be present for 'molecular mimicry to operate. In support of this notion, the massive inflammation that follows LCMV-infection of the pancreatic target organ of RIP-NP mice appears to set the stage for the subsequent development of autoimmunity.

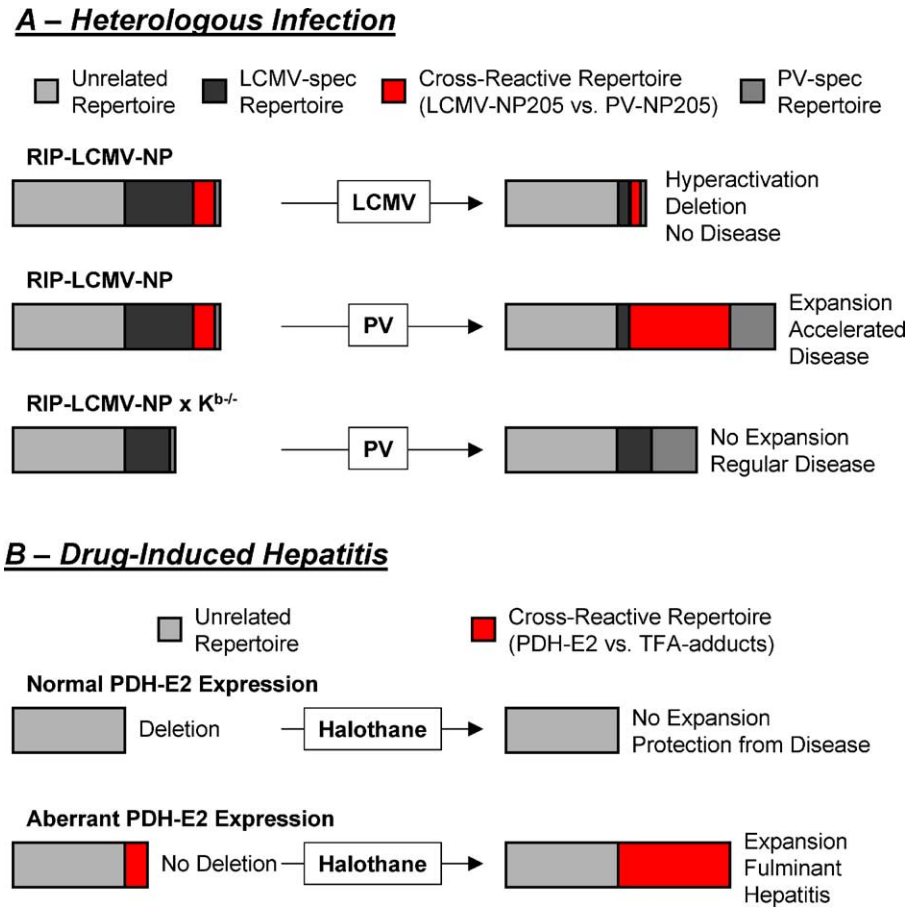

Fig. 2. Expansion of a cross-reactive repertoire. (A) Sequential virus infections can have different impacts on the outcome of disease depending on the expansion level of critical (cross-reactive) T-cells. (1) Signal too strong: reinfection of LCMV-immune mice (left panel) with LCMV results in hyperactivation, deletion of auto-aggressive T-cells and subsequently abrogates disease. (2) Signal just right: in contrast, heterologous infection with PV expands a cross-reactive T-cell repertoire that accelerates the disease process. (3) Signal too weak: in Kb−/− this cross-reactive T-cells are not activated because of the lack of proper presentation of the mimicking epitope(s) and heterologous infection seems to have no impact on the outcome of disease. (B) Presence of a self epitope (PDH-E2) that mimics covalent protein modifications (TFA-adducts) resulting from drug metabolism (Halothane) deletes/silences a TFA-adduct specific repertoire and thus protects from drug-induced autoimmune disease (Halothane hepatitis). Aberrant expression of PDH-E2 prevents the inactivation of such a cross-reactive repertoire. Exposure to Halothane expands the cross-reactive repertoire and subsequently induces fulminant hepatitis.

If critical factors that contribute to the establishment of such a ‘fertile field’, such as chemokines and cytokines, are missing, autoimmunity fails to develop. For example, neutralization of one of the earliest chemokines generated after LCMV-infection, IP-10 (CXCL10) or a traditional pro-inflammatory cytokine, TNFα, abrogates the development of type 1 diabetes in the RIP-LCMV system (Christen et al., 2003, 2001). Thus, infection with LCMV fulfills both requirements for initiating an autoimmune process: First, the provided foreign epitopes are perfect (molecular identity) and of high avidity and second, LCMV causes massive inflammation of the pancreas. In contrast, PV-infection lacks both prerequisites for a successful initiation of autoimmunity: first, the foreign epitope is imperfect (molecular mimicry) and of low avidity and second, PV infection causes only mild inflammation of the pancreas. However, the example of secondary infection with PV suggests that once the autoimmune process is initiated and a sufficient number of host-epitope-specific T cells are present, infection with an imperfect, low-avidity foreign epitope (molecular mimicry) can successfully accelerate an ongoing autoimmune process to a clinically relevant level (Fig. 2A).

4. Protection from autoimmunity by molecular mimicry

Considering the epidemiological data for a possible association of virus/bacterial infection with autoimmune diseases as well as many experimental systems that utilize the concept of molecular mimicry, one is tempted to believe that cross-reactivity between self and foreign components always acts as a trigger or an accelerator of autoimmunity. However, one should consider a protective consequence of

molecular mimicry as well. The presence of an endogenous component may induce immunological tolerance to foreign components against which it is of benefit for the host not to react via an aggressive immune response. An example is drug-induced autoimmunity. Many drugs are metabolized in the liver and can be converted to highly reactive compounds that can form neoantigens in the form of protein-adducts (Hinson and Roberts, 1992; Park and Kitteringham, 1990). These protein adducts might confer molecular mimicry to other self-components. The metabolism of the anesthetic agent Halothane gives raise to trifluoroacetylated proteins (TFA-proteins) in all individuals or experimental animals that are exposed to Halothane, however, only very few individuals (1/3000) develop Halothane hepatitis, an often fatal autoimmune disorder (Gut et al., 1993; Kenna, 1997). Only patients suffering from Halothane hepatitis do not tolerate the presence of TFA-proteins and generate cross-reactive antibodies that recognize both TFA-proteins and components of the pyruvate dehydrogenase complex (PDC) (Christen et al., 1994). Molecular mimicry was pinpointed to the TFA-lysine moiety in TFA-proteins that mimics the lipoic acid prosthetic group of the E2 subunit of PDC (Christen et al., 1991, 1993). Interestingly, patients with Halothane hepatitis were found to have an aberrant expression of the cross-reactive self-component (E2 of PDC) (Christen et al., 1994). Therefore, in this situation, molecular mimicry appears to have a protective rather then detrimental effect by deleting cross-reactive specificities (Fig. 2B). These findings suggest that proper display of the self-component (PDC) can induce immunological tolerance to 'self' and all foreign antigens that look similar enough, such as TFA-proteins that are accidentally generated during Halothane metabolism (Gut et al., 1995).

Interestingly, the host protein pyruvate dehydrogenase complex that confers molecular mimicry to TFA-proteins, is also major autoantigen in primary biliary cirrhosis (PBC), a severe autoimmune disorder of the liver that results in the progressive destruction of bile ducts (Gershwin et al., 2000; Van de Water et al., 1993). Thus theoretically, the generation of TFA-proteins by the metabolism of Halothane might accelerate an underlying PBC that could not be diagnosed at its current stage of development. Since TFA-proteins are ubiquitously formed throughout the liver, the resulting immunopathogenesis might not necessarily resemble the one observed in "spontaneous" PBC. However, there are no epidemiological data available that would support a correlation of PBC with frequent anesthesia with Halothane.

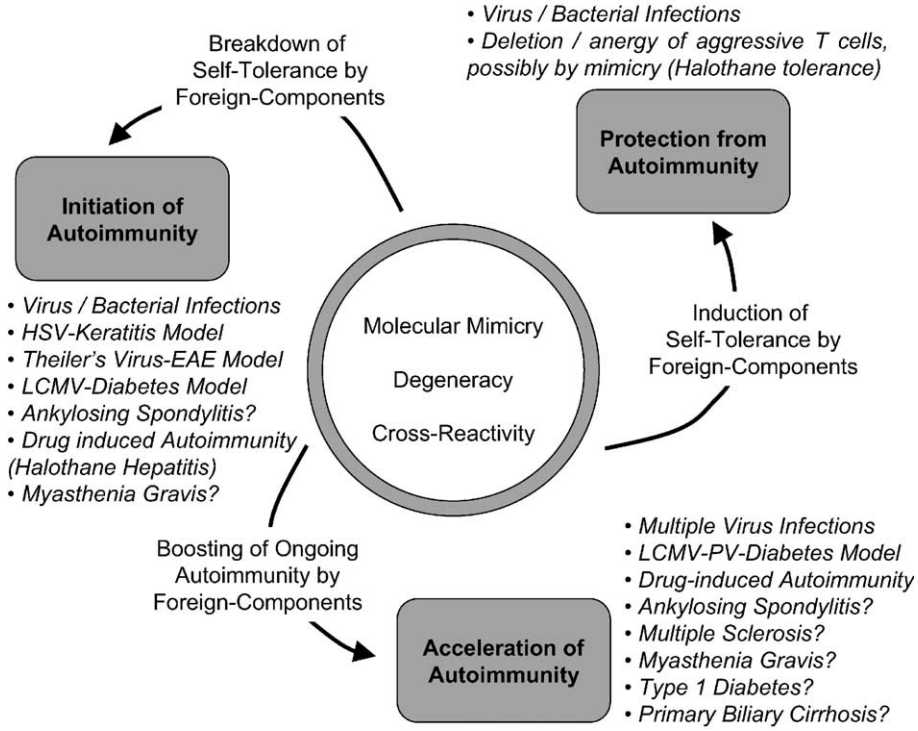

Fig. 3. Possible impact of molecular mimicry on autoimmune diseases—most experimental systems that are based on the concept of molecular mimicry directly trigger the auto-destructive process by delivery of foreign components that confer molecular mimicry of molecular identity to self-components. Thus, the role of molecular mimicry in breaking self-tolerance and subsequent induction of experimental disease in these animal models is unquestioned. In contrast, the situation is much more complex in human autoimmune diseases since foreign components with a potential for molecular mimicry of host molecules, such as viruses, may be long gone at the time of disease diagnosis ('hit-and-run' effect). Therefore, the role of molecular mimicry in autoimmune disorders for which a strong epidemiological association with certain virus infections and the presence of cross-reactive immunity to foreign- and self-components has been demonstrated can be twofold. Either molecular mimicry directly triggers the autoimmune process similar to some experimental animal models or, alternatively, it accelerates a pre-conditioning towards autoimmunity that was initially caused by another mechanism.

5. Conclusions

In this review we highlighted potentially different roles for molecular mimicry in autoimmunity (Fig. 3). Molecular mimicry is an attractive concept and epidemiological evidence suggests an involvement in a broad variety of human autoimmune disorders. However, since viral and bacterial infections are 'hit-and-run' events that often do not leave any clear indicators behind, a direct proof for molecular mimicry as an initiator or accelerator of autoimmunity will remain difficult to find in humans. In contrast, many experimental systems that study possible etiologies of autoimmune diseases or unveil mechanisms of the autoimmune destruction involved, have contributed to our current understanding of molecular mimicry. Here we presented three examples that demonstrate the complexity and diversity in which molecular mimicry might affect us (Fig. 3). First, in the RIP-LCMV model for type 1 diabetes molecular identity can induce autoimmunity if the proper activation conditions are met. Second, sequential infection with viruses that share a closely related epitope (molecular mimicry) can enhance an ongoing autoimmune process, but not break tolerance in naïve animals. Last, the presence of an endogenous mimicking epitope can tolerize the host towards neo-antigen epitopes generated after drug metabolism in the liver and therefore prevent a detrimental immune response against 'neo-self'. We would like to recommend for future clinical investigations that the inflammatory proteome following an acute viral infection has to be tracked and quantitated in individuals at risk to develop autoimmune disease and a temporal association has to be established. Based on such evidence, a direct search for crossreactive T or B cell responses could be initiated that might unveil appearance of mimicry during a temporally limited window following the triggering infection.

References

Brehm, M.A., Pinto, A.K., Daniels, K.A., Schneck, J.P., Welsh, R.M., Selin, L.K., 2002. T cell immunodominance and maintenance of memory regulated by unexpectedly cross-reactive pathogens. Nat. Immunol. 3, 627–634.

Christen, U., Bürgin, M., Gut, J., 1991. Halothane metabolism: immunochemical evidence for molecular mimicry of trifluoroacetylated liver protein adducts by constitutive polypeptides. Mol. Pharmacol. 40, 390–400.

Christen, U., Edelmann, K., Wolfe, T., Rodrigo, E., Coon, B., Oldstone, M.B.A., von Herrath, M.G., 2004. Acceleration of primed autoimmunity but not de novo induction of auto-aggressive lymphocytes by molecular mimicry, submitted for publication.

Christen, U., Jenö, P., Gut, J., 1993. Halothane metabolism: the dihydrolipoamide acetyltransferase subunit of the pyruvate dehydrogenase complex molecularly mimics trifluoroacetyl-protein adducts. Biochemistry 32, 1492–1499.

Christen, U., McGavern, D., Luster, A.D., von Herrath, M.G., Oldstone, M.B.A., 2003. Among CXCR3 chemokines, IP-10 (CXCL10) but not Mig (CXCL9) imprints a pattern for the subsequent development of autoimmune disease J. Immunol. 171, in press.

Christen, U., Quinn, J., Yeaman, S.J., Kenna, J.G., Clarke, J.B., Gandolfi, A.J., Gut, J., 1994. Identification of the dihydrolipoamide acetyltransferase subunit of the human pyruvate dehydrogenase complex as an autoantigen in halothane hepatitis: molecular mimicry of CF3CO-lysine by lipoic acid. Eur. J. Biochem. 223, 1035–1047.

Christen, U., Wolfe, T., Mohrle, U., Hughes, A.C., Rodrigo, E., Green, E.A., Flavell, R.A., von Herrath, M.G., 2001. A dual role for TNF-alpha in type 1 diabetes: islet-specific expression abrogates the ongoing autoimmune process when induced late but not early during pathogenesis. J. Immunol. 166, 7023–7032.

Degermann, S., Reilly, C., Scott, B., Ogata, L., von Boehmer, H., Lo, D., 1994. On the various manifestations of spontaneous autoimmune diabetes in rodent models. Eur. J. Immunol. 24, 3155–3160.

Fielder, M., Pirt, S.J., Tarpey, I., Wilson, C., Cunningham, P., Ettelaie, C., Binder, A., Bansal, S., Ebringer, A., 1995. Molecular mimicry and ankylosing spondylitis: possible role of a novel sequence in pullulanase of *Klebsiella pneumoniae*. FEBS Lett. 369, 243–248.

Gamble, D.R., 1980. The epidemiology of insulin dependent diabetes with particular reference to the relationship of virus infection to its etiology. Epidemiol. Rev. 2, 49–70.

Gershwin, M.E., Ansari, A.A., Mackay, I.R., Nakanuma, Y., Nishio, A., Rowley, M.J., Coppel, R.L., 2000. Primary biliary cirrhosis: an orchestrated immune response against epithelial cells. Immunol. Rev. 174, 210–225.

Gut, J., Christen, U., Frey, N., Koch, V., Stoffler, D., 1995. Molecular mimicry in halothane hepatitis. Toxicology (Section Immunotoxicology) 97, 199–224.

Gut, J., Christen, U., Huwyler, J., 1993. Mechanisms of halothane toxicity: novel insights. Pharmacol. Ther. 58, 133–155.

Hinson, J.A., Roberts, D.W., 1992. Role of covalent and noncovalent interactions in cell toxicity: effects on proteins. Annu. Rev. Pharmacol. Toxicol. 32, 471–510.

Honeyman, M.C., Coulson, B.S., Stone, N.L., Gellert, S.A., Goldwater, P.N., Steele, C.E., Couper, J.J., Tait, B.D., Colman, P.G., Harrison, L.C., 2000. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. Diabetes 49, 1319–1324.

Katz-Levy, Y., Neville, K.L., Girvin, A.M., Vanderlugt, C.L., Pope, J.G., Tan, L.J., Miller, S.D., 1999. Endogenous presentation of self myelin epitopes by CNS-resident APCs in Theiler's virus-infected mice [see comments]. J. Clin. Invest. 104, 599–610.

Kenna, J.G., 1997. Immunoallergic drug-induced hepatitis: lessons from halothane. J. Hepatol. 26, 5–12.

Kersh, G.J., Allen, P.M., 1996. Essential flexibility in the T-cell recognition of antigen. Nature 380, 495–498.

Kurtzke, J.F., 1993. Epidemiologic evidence for multiple sclerosis as an infection. Clin. Microbiol. Rev. 6, 382–427.

Lewicki, H., Tishon, A., Borrow, P., Evans, C.F., Gairin, J.E., Hahn, K.M., Jewell, D.A., Wilson, I.A., Oldstone, M.B., 1995. CTL escape viral variants. I. Generation and molecular characterization. Virology 210, 29–40.

Lo, D., Freedman, J., Hesse, S., Palmiter, R.D., Brinster, R.L., Sherman, L.A., 1992. Peripheral tolerance to an islet cell-specific hemagglutinin transgene affects both CD4+ and CD8+ T cells. Eur. J. Immunol. 22, 1013–1022.

Lo, D., Reilly, C.R., Scott, B., Liblau, R., McDevitt, H.O., Burkly, L.C., 1993. Antigen-presenting cells in adoptively transferred and spontaneous autoimmune diabetes. Eur. J. Immunol. 23, 1693–1698.

Notkins, A.L., Yoon, J.-W., 1984. Virus-induced diabetes mellitus. In: Notkins, A.L., Oldstone, M.B.A. (Eds.), Concepts in Viral Pathogenesis. Springer-Verlag, New York, pp. 241–247.

Ohashi, P., Oehen, S., Buerki, K., Pircher, H., Ohashi, C., Odermatt, B., Malissen, B., Zinkernagel, R., Hengartner, H., 1991. Ablation of tolerance and induction of diabetes by virus infection in viral antigen transgenic mice. Cell 65, 305–317.

Oldstone, M.B., 1998. Molecular mimicry and immune-mediated diseases. FASEB. J. 12, 1255–1265.

Oldstone, M.B., Lewicki, H., Borrow, P., Hudrisier, D., Gairin, J.E., 1995. Discriminated selection among viral peptides with the appropriate anchor residues: implications for the size of the cytotoxic T-lymphocyte repertoire and control of viral infection. J. Virol. 69, 7423–7429.

Oldstone, M.B.A., Nerenberg, M., Southern, P., Price, J., Lewicki, H., 1991. Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. Cell 65, 319–331.

Panitch, H.S., 1994. Influence of infection on exacerbations of multiple sclerosis. Ann. Neurol. 36, S25–S28.

Park, B.K., Kitteringham, N.R., 1990. Drug-protein conjugation and its immunological consequences. Drug Metabol. Rev. 22, 87–144.

Rose, N.R., Mackay, I.R., 2000. Molecular mimicry: a critical look at exemplary instances in human diseases. Cell. Mol. Life Sci. 57, 542–551.

Sarukhan, A., Lanoue, A., Franzke, A., Brousse, N., Buer, J., von Boehmer, H., 1998. Changes in function of antigen-specific lymphocytes correlating with progression towards diabetes in a transgenic model. EMBO J. 17, 71–80.

Schwimmbeck, P.L., Dyrberg, T., Drachman, D.B., Oldstone, M.B., 1989. Molecular mimicry and myasthenia gravis. An autoantigenic site of the acetylcholine receptor alpha-subunit that has biologic activity and reacts immunochemically with herpes simplex virus. J. Clin. Invest. 84, 1174–1180.

Schwimmbeck, P.L., Oldstone, M.B., 1989. *Klebsiella pneumoniae* and HLA B27-associated diseases of Reiter's syndrome and ankylosing spondylitis. Curr. Top. Microbiol. Immunol. 145, 45–56.

Scott, B., Liblau, R., Degermann, S., Marconi, L.A., Ogata, L., Caton, A.J., McDevitt, H.O., Lo, D., 1994. A role for non-MHC genetic polymorphism in susceptibility to spontaneous autoimmunity. Immunity 1, 73–83.

Seewaldt, S., Thomas, H., Ejrnaes, M., Christen, U., Wolfe, T., Rodrigo, E., Coon, B., Michelsen, B., Kay, T., von Herrath, M.G., 2000. Virus-induced autoimune diabetes: most b-cells die through inflammatory cytokines and not perforin from autoreactive (anti-viral) CTL. Diabetes 49, 1801–1809.

Selin, L.K., Lin, M.Y., Kraemer, K.A., Pardoll, D.M., Schneck, J.P., Varga, S.M., Santolucito, P.A., Pinto, A.K., Welsh, R.M., 1999. Attrition of T cell memory: selective loss of LCMV epitope-specific memory CD8 T cells following infections with heterologous viruses. Immunity 11, 733–742.

Sevilla, N., Homann, D., von Herrath, M., Rodriguez, F., Harkins, S., Whitton, J.L., Oldstone, M.B., 2000. Virus-induced diabetes in a transgenic model: role of cross-reacting viruses and quantitation of effector T cells needed to cause disease. J. Virol. 74, 3284–3292.

Srinivasappa, J., Saegusa, J., Prabhakar, B.S., Gentry, M.K., Buchmeier, M.J., Wiktor, T.J., Koprowski, H., Oldstone, M.B.A., Notkins, A.L., 1986. Molecular mimicry: frequency of reactivity of monoclonal antiviral antibodies with normal tissues. J. Virology 1986, 397–401.

Van de Water, J., Turchany, J., Leung, P.S.C., Lake, J., Munoz, S., Surh, C.D., Coppel, R., Ansari, A., Nakanuma, Y., Gershwin, M.E., 1993. Molecular mimicry in primary biliary cirrhosis: evidence for biliary epithelial expression of a molecule cross-reactive with pyruvate dehydrogenase complex-E2. J. Clin. Invest. 91, 2653–2664.

von Herrath, M.G., Dockter, J., Oldstone, M.B.A., 1994. How virus induces a rapid or slow onset insulin-dependent diabetes mellitus in a transgenic model. Immunity 1, 231–242.

Yoon, J.-W., Austin, M., Onodera, T., Notkins, A.L., 1979. Virus-induced diabetes mellitus: isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N. Engl. J. Med. 300, 1173–1179.

Zhao, Z.S., Granucci, F., Yeh, L., Schaffer, P.A., Cantor, H., 1998. Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection [see comments]. Science 279, 1344–1347.