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Introduction: Epitope mimicry as a component cause of autoimmune disease

J. M. Davies*

Department of Biochemistry and Molecular Biology, Monash University, Wellington Road, Clayton, Victoria 3168 (Australia)

Introduction

The causes of autoimmune diseases have yet to be fully elucidated. Autoantibodies, autoreactive T cell responses, the presence of a predisposing major histocompatibility complex (MHC) haplotype and responsiveness to corticosteroids are features, and some are possibly contributory causes of autoimmune disease. The most challenging question is how autoimmune diseases are triggered. Molecular mimicry of host cell determinants by epitopes of infectious agents with ensuing cross-reactivity is one of the most popular yet still controversial theories for the initiation of autoimmune diseases [1]. Throughout the 1990s, hundreds of research articles focusing to various extents on epitope mimicry, as it is more accurately described in an immunological context, were published annually. Many of these articles presented data that were consistent with the hypothesis of mimicry but that did not actually prove the theory. Other equally convincing reports indicated that epitope mimicry was not the cause of the autoimmune disease despite sequence similarity between molecules of infectious agents and the host.

Some 20 years ago, Rothman [2] proposed a model for disease causation and I have used this as a framework to examine the role of epitope mimicry in the development of autoimmune disease. The thesis of Rothman's model is that an effect, in this instance autoimmune disease, arises as a result of a cause. In most cases, multiple-component causes contribute synergistically to yield the effect, and each of these components alone is insufficient as a cause. Logically, some component causes, such as the presence of a particular autoimmune response, are also necessary causes.

Epitope mimicry

Epitope mimicry may be a component cause of autoimmune disease. The hypothesis states that similar epitopes present in infectious agents prime autoaggressive immune responses against self epitopes. These autoimmune responses spread progressively to incorporate other intrinsic (self) antigens as their targets of attack; the instigating extrinsic (mimicking) antigen derived from the infectious agent may or may not be detectable at the time of clinical presentation of the autoimmune disease. The hypothesis of epitope mimicry is captivating since it incorporates each of the known components into a plausible mechanism for disease induction. Thus the theory has been experimentally illustrated: cross-reactivity has been demonstrated at the B and now T cell level and circumstantial evidence is available in some cases of disease in humans. Guillian-Barré syndrome, for which the pathogenic microbe can be isolated from subjects with the disease, and Chagas disease are two of the most convincing examples of human disease in which mimicry is a likely component cause [1, 3].

The theory of epitope mimicry was first developed from the observation of mimicry by a parasite evading host responses and prey mimicking its environment to evade predation [4]. Mimicry is logical in an evolutionary sense, since a pathogen could best survive selective pressures if it evolved to mimic its host and so evade immune attack; but the unfortunate consequence in some instances is that cross-reactive autoimmune responses ensue. The development of an autoimmune disease would be unlikely to exert any selective pressure against a pathogen during evolution since the time lag to the onset of autoimmune disease far exceeds the time necessary for a pathogen to complete its life cycle.

* Present address: J. M. Davies, Department of Allergy, Asthma and Clinical Immunology, The Alfred Hospital and Monash University Medical School, Commercial Road, Prahran, Victoria 3181 (Australia), Fax + 61 3 9903 0783, e-mail: Janet.Davies@med.monash.edu.au

Not surprisingly, the evolution of organisms has occurred in a selectively efficient manner such that common genes, or domains thereof, that perform similar functions in different organisms are conserved with minor mutations. At a submolecular level, certain peptides that form particular structural units are repeatedly reused in different molecules if they meet the structural needs of that molecule. Evidence of such evolutionary efficiency is present in the protein and genomic databases. Homologues with high degrees of similarity and identity are conserved throughout various levels of the evolutionary tree and certain di-, tri-, quadra-, and penta-peptides are more frequently found, indicating their preferential use as submolecular units [5]. It is not surprising that sequence similarity is a relatively common event or that cross-reactivity does in fact occur at times during infections. Cross-reactivity then could be coincidental or causative of autoimmune disease.

Difficulties in determining the cause of autoimmune diseases

Deciphering the relative contributions of any one of multiple component causes of an autoimmune disease is challenging. First, because for many autoimmune diseases, examples being systemic lupus erythematosus and rheumatoid arthritis, definitive diagnosis can be uncertain since clinical features overlap with those of various other diseases. Second, the development of an autoimmune disease may be gradually progressive such that disease onset is difficult to discern. For this reason, the impact of epitope mimicry on the causation of autoimmune disease has been difficult to evaluate.

Genetic predisposition and autoimmunity per se are insufficient causes of autoimmune disease

Both autoimmune reactivities, particularly T cell responses, and certain genetic traits are component causes of autoimmune disease. Autoreactive T cells can adoptively transfer autoimmune disease to naïve laboratory animals thus proving their causative effect. However, the presence of autoimmune responses themselves cannot be sufficient cause in humans since an autoimmune disease can occur in the absence of its hallmark autoantibody, and so-called natural autoantibodies and autoreactive T cells can occur in normal individuals. Likewise, epidemiological data on genetic associations with autoimmunity indicate that the presence of certain genetic traits, for example a permissive HLA haplotype, are insufficient cause of autoimmune disease.

Environmental agents as component causes of disease

Modulatory effects of the environment on autoimmunity are strongly suggested by observations that infection reduces the incidence of diabetes in non-obese mice, the incidence of autoimmune diseases in identical twins is discordant, and that there are geographical gradients, mostly in latitude, in the incidence of autoimmune diseases. Other non-infectious environmental factors including the presence of iodine in water supplies, which increases the risk of thyroiditis, are likewise modulators of autoimmune diseases [6]. However, we are primarily interested here in infectious agents and what remains unclear are the mechanisms of action they exert on the immune system that may trigger autoimmune diseases. Viruses often incorporate homologues of cellular genes involved in immune regulation, such as cytokines, chemokines and components of complement, that can directly alter the local milieu in favour of the virus and at the same time affect the outcome of any autoimmune response present [7]. An inflammatory or adjuvant effect of infection may tip the balance against a negative response and towards a positive response so as to activate the autoimmune cascade that can lead to disease. This is exemplified by Theiler's murine encephalomyelitis virus that causes encephalitis in mice due to spreading of reactivity to self epitopes following infection [8], and by Coxsackie B virus triggering bystander activation of naturally present GAD-reactive T cells against pancreatic islets [9]. Besides epitope mimicry, bystander activation of autoreactive lymphocytes during infection is another likely and favoured mechanism by which infection modulates autoimmunity.

Epitope mimicry as a component cause of autoimmunity

There are several engaging new findings that support the theory of epitope mimicry. One with profound implications is the degree of plasticity in the recognition of peptides in the context of MHC class II by T cell receptors. Cross-reactivity of autoimmune T cells with peptides derived from bacteria and viruses questions the dogma of monospecificity of clonal T cells [10]. Cross-reactivity at the T cell level is a most significant finding since the driving force behind the pathogenesis of autoimmune diseases is essentially the T cell response. The second important finding is the demonstration that exogenous antigen that mimics endogenous antigen can be processed and presented by B cells such that autoimmune T cells are primed against the endogenous antigen [11]. Linked with this is the demonstration of epitope spreading of immune responses to new epitopes of a target antigen (intramolecular spreading) or determinants of another antigen (intermolecular spreading)

[8]. Epitope spreading provides a mechanism by which an autoimmune response triggered by a mimicking exogenous antigen progresses to a truly autoimmune response against the mimicked self antigen and also other antigens. However, the epitope-spreading model of Farris et al. [12] described in this issue, states that spreading occurs because the target antigens are physically linked intracellularly as members of a complex. One wonders whether antigen processing and subsequent epitope spreading would occur naturally if the mimicking exogenous antigen were a constituent of a virus and not complexed with the mimicked host antigen. A fourth important effect is that of epitope regression, demonstrated by the loss of ability to detect an immune response to an epitope with which a proliferative T cell response was previously observed [13]. This could explain the inability to detect the relevant reactivity in subjects in whom an infectious agent might have caused an autoimmune disease via a mimicry event earlier on. This scenario of epitope regression fits with the hit-and-run hypothesis of Dyrberg and Oldstone [14].

As a consequence of the recent findings outlined above and throughout the series of informative reviews in this issue, we may reassess the way we think about mimicry. Progression to autoimmune disease could proceed by different routes, each with individual sets of component causes. We now know that multiple viral and bacterial peptides are capable of stimulating proliferation of naturally present anti-myelin T cell clones from subjects with multiple sclerosis [10]. It is therefore feasible that different infectious agents might provide the antigenic stimulus for cross-reactive autoimmune T cells in different individuals. Alternatively, different pathogens successively encountered by the same individual may provide multiple priming events for cross-reactive autoimmune T cells to provide cumulative assault that lead to autoimmune disease.

Arguments for and against epitope mimicry from animal models

One effective way to investigate the immunopathogenic potential of epitope mimicry is to utilise natural and experimental animal models. As outlined by Lawson [15] and Rose and Mackay [16] in this issue, there are cases both for and against epitope mimicry. Whereas addition of myelin epitopes to the vaccinia virus failed to induce encephalitis in mice [17], in a different model, introduction of a viral antigen to oligodendrocytes led to chronic central nervous system inflammation following viral challenge in the periphery [18]. Furthermore, the deletion of a cross-reactive epitope of a herpes simplex virus abrogated the ability of the virus to cause autoimmune stromal keratitis in the eye [19], which suggests that the presence of the mimicking determinant was in this case a necessary cause of the disease.

In this review on epitope mimicry

This special issue of *Cellular and Molecular Life Sciences* is dedicated to epitope mimicry. The aim is to review current data that impact upon the theory of epitope mimicry and to analyse its mechanisms. Yuki [3] examines Guillian Barré syndrome, which is traditionally thought of as a post-infectious syndrome of *Campylobacter jejuni* that manifests in some individuals, but which appears to be mediated by autoantibodies, and for which instances of the disease have been induced by injection of antigen alone. Kukreja and Maclaren [20] review mimicry in diabetes. Over the last 10 years, mimicry in type 1 diabetes has evoked immense interest and controversy due to the association of Coxsackie B4 infection in mothers of children with type 1 diabetes, and the presence of sequence similarity between a key target antigen of the pancreatic β cell, GAD, and the Coxsackie viral protein P2-C, which both contain the PEVKEK motif. Lawson [15] reviews animal models of mimicry and evidence for immunological cross-reactivity with particular emphasis on myocarditis following murine cytomegalovirus infection, in which the autoimmune phase of disease persists in the absence of detectable viral antigen. Rose and Mackay [16] examine classical examples in which mimicry has been proposed as a factor in the pathogenesis of human autoimmune diseases and critically assess the data in support of mimicry as a component cause of autoimmunity.

The next section focuses on the mechanisms of mimicry. Liang and Mamula [11] review the capacity of B cells primed with foreign antigen to activate autoreactive T cells to respond to similar endogenous antigen. Farris and colleagues [12] review the role of determinant spreading in the progression to autoimmune disease and provide a description of the pathways to autoimmunity, for which mimicry may well be a component.

Conclusions

The most significant recent evidence in support of the mimicry hypothesis for causation of autoimmune disease includes (i) the cross-reactivity of autoreactive T cells from subjects with autoimmune disease, (ii) the demonstration that B cells can present autoantigens to naturally present naïve autoreactive T cells and (iii) the ability of immune responses to spread to new determinants of multideterminant antigens. Together, these illustrate the principal factors that would be necessary for epitope mimicry to contribute to the immunopathogenesis of autoimmune disease. Given the extensive list

of examples of cross-reactivity that have been demonstrated over the years, epitope mimicry is highly likely to occur naturally in vivo. Epitope mimicry is likely to synergise with a genetic predisposition and autoimmunity per se to become sufficient cause of autoimmune disease.

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