Biomedical Science

Molecular Mimicry—Hypothesis or Reality?

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A number of observations support molecular mimicry as a possible pathogenetic mechanism in diseases such as acute rheumatic fever, reactive arthritis after enteric infection or associated with Reiter's syndrome, myasthenia gravis, or even in rheumatoid arthritis. Molecular mimicry can be defined as a sharing of epitopes in linear or 3-dimensional presentation on disparate proteins from entirely different sources—for instance, group A streptococcal membranes and human cardiac myosin. How exposure to or infection with organisms sharing molecular similarity with antigens of the human host can evade tolerance and actually induce a self-reacting humoral or cellular immune response is still not clear; however, a large body of evidence has now been accumulated that documents apparent molecular mimicry mechanisms in these disorders. In some diseases, the molecular mimicry appears to involve human target organs and specific components of the infectious organism, whereas in others the host HLA cell surface molecules appear to share antigens with presumed bacterial or viral initiators of disease.

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Burnet's original hypothesis that forbidden clones resurrected themselves periodically to initiate an autoimmune response represented one of the first attempts to explain the occurrence of autoimmune disease.[1] Although initially attractive as a rational way of explaining the vexing enigma of autoimmune mechanisms, the clonal selection theory with its implied episodic emergence of forbidden clones has not held up well against much subsequent empiric data. Other possible mechanisms whereby the self becomes its own target are now being considered and actively pursued to attempt to explain the occurrence of autoimmune phenomena and the actual genesis of diseases such as systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, reactive arthritis, and myasthenia gravis. In this analysis we review the clinical and laboratory observations that have prompted the concept of molecular mimicry as an underlying mechanism that could initiate an autoimmune reaction. Moreover, we will also attempt to examine strong supporting evidence and other aspects that may constitute important reservations for accepting molecular mimicry as the major avenue for inducing autoimmune phenomena.

Acute Rheumatic Fever

Clearly the most compelling example of molecular mimicry can be found in the case of acute rheumatic fever. A number of clinical observations and laboratory phenomena appear to support an underlying mechanism of molecular mimicry as being a major initiator of the acute symptoms and subsequent chronic manifestations of the disease. Previously thought to be uncommon and dying out in the United States and Canada, rheumatic fever has re-emerged as a major health problem, with sizable epidemics occurring recently in Utah[2] and several portions of the Midwest, Tennessee, and Pennsylvania.[3-6]

Virtually all of the clinical manifestations of acute rheumatic fever, including chorea, acute migratory polyarthritis, and acute carditis and valvulitis, can be explained on the basis of molecular mimicry mechanisms. This is related to the astonishing number of epitopes that appear to be shared between various human tissues and components of β-hemolytic group A streptococci. Perhaps no single group of bacteria has been as exhaustively studied for molecular mimicry as β-hemolytic group A streptococci. After the initial recognition of cross-reactivity between group A streptococcal components and human myocardium by Kaplan and co-workers,[7-9] the immunochemical basis for this cross-reactivity was extensively refined by Zabriskie and Freimer[10] and later by Van de Rijn and associates.[11] Through direct immunologic observations, human valvular glycoproteins were found to cross-react with components of group A streptococci.[12,13] Moreover, group A streptococcal antigens have also been shown to cross-react with components of the human cardiac conduction system.[14] Long after the initial rheumatic episode, levels of streptococcal group A carbohydrate antibodies were found to be markedly elevated in serum from patients with rheumatic heart disease and previous acute rheumatic fever.[15] Moreover, when such patients later underwent cardiac valve resection and artificial valve replacement, levels of anti-group A carbohydrate antibody often declined precipitously.[16] These observations appeared to indicate that an immune response to autologous tissues had been induced based on the previous repeated, intense antigenic exposures in early childhood to group A streptococcal carbohydrate during clinical or possibly subclinical rheumatic fever episodes. Thus, the removal of the diseased cardiac valves at an operative procedure such as mitral valve resection and the insertion of an artificial heart valve were followed by a rapid decline in levels of anti-group A-specific anticarbohydrate

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ABBREVIATIONS USED IN TEXT

HSV = herpes simplex virus
Ig = immunoglobulin

antibody. The presence of large quantities of group A-cross-reactive glycoprotein in the patients' diseased heart valves apparently stimulated an antigenic response sufficient to maintain high levels of group A carbohydrate-specific antibody within the circulation. Thus, in some way the long-standing hyperreactivity of such patients to group A carbohydrate epitopes was being enhanced and continued through cardiac valvular autoantigen reinforcement.

On many occasions, we and others, using immunofluorescence or immunoperoxidase and highly specific polyclonal or monoclonal antibodies to various streptococcal components,[17] have examined heart valves surgically removed because of chronic rheumatic heart disease for residual traces of streptococcal antigens. In all cases, no direct evidence for the retention of streptococcal antigens within macrophages or other phagocytes was obtained. The failure to find streptococcal antigenic material in such phagocytes years after the last acute episode of rheumatic fever does not rule out continued low levels of messenger RNA capable of providing the original antigenic message induced by the group A streptococcal epitopes in question. Precisely how such fundamental questions relating to the mechanisms driving autoimmune processes in the body can be approached experimentally remains to be determined.

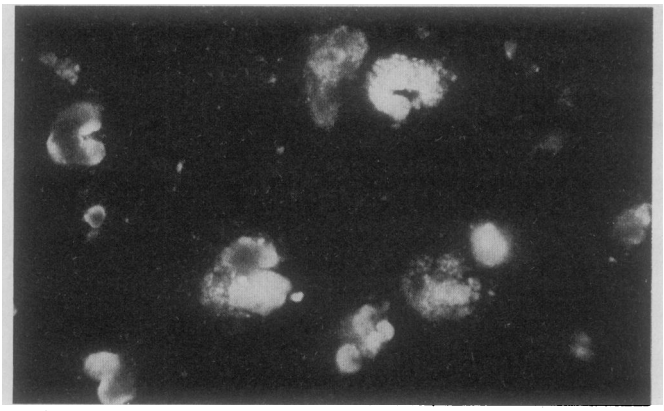

Figure 1.—Antineuronal antibody from the serum of a child with acute rheumatic fever stains neuronal cytoplasm in a frozen section of normal human brain through the caudate nucleus. Bright cytoplasmic immunofluorescence is seen in a number of positively staining neurons (original magnification x 350).

For years acute or subacute chorea has been accepted as a major manifestation of acute rheumatic fever. Indeed, when Bland examined a large number of patients who had had chorea years previously as the major manifestation of a rheumatic episode, roughly a quarter showed clinical evidence for rheumatic valvular lesions—predominantly mitral insufficiency or mitral stenosis.[18] The connection between the brain and the heart became clearer when it was found that many patients with acute rheumatic fever and such choreiform episodes show immunoglobulin (Ig) G antibodies in their serum that cross-react with neuronal cytoplasmic antigens of nerve cells situated in the various anatomic locations of the brain. These nerve cells—subthalamic and caudate nucleus neurons—are probably involved in the generation of choreiform movements.[19] An example of this remarkable molecular mimicry is shown in Figure 1. The antineuronal antibodies present in the serum of children with Sydenham's chorea can be completely absorbed using purified preparations of group A streptococcal membranes.

The arthritis that is often characteristic of an acute attack of rheumatic fever has been called migratory because it often will affect a number of joints in succession. Never does the migratory arthritis of acute rheumatic fever affect a single joint for more than a few days or a week. This transient and evanescent quality distinguishes the joint manifestations of acute rheumatic fever from other conditions affecting children, such as juvenile rheumatoid arthritis, systemic lupus erythematosus, or septic arthritis. Recently the joint manifestations of acute rheumatic fever have also been ascribed to molecular mimicry.[20] Direct cross-reactivity has been demonstrated between components of streptococcal M protein and joint structures such as cartilage glycoproteins and other components of synovial tissues. Cross-reactive antibodies that were capable of complement activation were demonstrated in these patients' serum with arthritis as a clinical manifestation of their acute rheumatic fever syndrome. Previous studies of rheumatic fever synovial fluids had documented complement component profiles consistent with activation of the complement cascade.[21] It thus appeared that the acute arthritis associated with rheumatic fever could be due to antistreptococcal antibodies directly cross-reacting with joint glycoprotein components and activating the complement cascade to induce an intense local inflammatory reaction in the joints.

Thus the carditis, valvular lesions, chorea, and arthritis of acute rheumatic fever have now all been shown to involve cross-reacting epitopes between the components of group A β-hemolytic streptococci and human cardiac and joint tissue, and the central nervous system. Moreover, some evidence for cell-mediated immune responsiveness in the case of rheumatic carditis and particulate streptococcal products has also been presented.[22-24] A partial catalogue of the extent of the remarkable molecular mimicry that has now been documented between the group A streptococcus and various sites and tissues involved in acute rheumatic fever is presented in Table 1.

Ankylosing Spondylitis and Reactive Arthritis

Molecular mimicry has also been implicated in the genesis of ankylosing spondylitis and the spondyloarthropathy associated with reactive arthritis.[28-31] A number of previous observations appeared to support molecular mimicry. Thus levels of anti-*Klebsiella pneumoniae* antibodies were reported to be higher in patients with ankylosing spondylitis than in controls.[32] Direct cross-reactions were reported between polyclonal and monoclonal antibodies to various products and the HLA-B27.5 gene product.[30,31] This latter seemed important because more than 95% of patients with ankylosing spondylitis and 70% to 80% of patients with reactive arthritis such as Reiter's syndrome were positive for HLA-B27. Schwimmbeck and co-workers analyzed the protein sequence data base and found a remarkable six amino acid homology (QTDRED) between the HLA-B27.5 sequence and that of the *K pneumoniae* nitrogenase reductase (Table 2).[33] It was estimated at the time that the chances of this exact sequence homology occurring were less than 1 in 20 million! They found elevated levels of antibodies to peptides containing the homologous QTDRED sequence in

TABLE 1.—*Molecular Mimicry Between Epitopes Within the Group A β-Hemolytic Streptococcus and Human Tissues Involved in the Acute Inflammatory Disorder of Acute Rheumatic Fever*

Group A Streptococcal Component	*Human Cross-Reacting Tissue Elements*	*Reference Source*
Membranes	Myocardial sarcolemmal membrane	Zabriskie and Freimer, 1966[10]; Van de Rijn et al, 1977[11]
Cell walls	Myocardial cells	Kaplan, 1963[7]
Glycoproteins	Heart valve glycoproteins	Goldstein et al, 1967[12]
Membranes	Caudate and subthalamic nuclei neuronal cytoplasm	Husby et al, 1976[19]
Antigens	Cardiac conduction system	Kasp-Grouchowska and Kingston, 1977[14]
Protein	Cardiac sarcolemmal membrane	Dale and Beachey, 1985[25]; Kraus et al, 1990[26]
Carbohydrate	Cardiac valvular structures	Dudding and Ayoub, 1968[15]
Membranes	Cardiac myosin	Krisher and Cunningham, 1985[27]
M protein	Articular cartilage and synovium	Baird et al, 1991[20]

HLA-B27-positive patients with ankylosing spondylitis and in HLA-B27-positive patients with Reiter's syndrome and reactive arthritis.[33]

Implied with these findings was a direct mechanism of molecular mimicry between autologous HLA-B27.5 antigenic epitopes and those present on *K pneumoniae* nitrogenase. When Husby and associates used rat antiserum to several HLA-B27.5 peptides in conjunction with similar antiserum to *K pneumoniae* nitrogenase peptides to actually stain synovial tissues of patients with ankylosing spondylitis or reactive arthritis, strong cross-reactivity was repeatedly demonstrated.[34] Thus, the part of the class I HLA-B27.5 antigens encompassing the homologous QTDRED sequence was strongly expressed on both synovial membrane lining cells and vascular endothelium of vessels in inflamed synovium of patients with ankylosing spondylitis. Similar staining patterns of synovial lining cells and vascular endothelium were also found using rat antiserum to homologous *K pneumoniae* peptides, confirming the impression of direct molecular mimicry at the actual tissue level. Subsequent attempts, however, to confirm the presence of humoral antibody to both *K pneumoniae* peptides and HLA-B27 peptides were only clearly positive for antibody to HLA-B27.5 peptides.[35,36] No notably elevated levels of humoral antibody to *K pneumoniae* peptides were found in the large ankylosing spondylitis or reactive arthritis-Reiter's disease populations examined. Moreover, the *K pneumoniae* peptide did not seem to cross-react with patients' anti-B27 peptide antibodies.

Subsequently, a plasmid called pHS-2, derived from the arthritogenic strains of *Shigella flexneri*, was also found to encode a sequence containing a homologous stretch of amino acids (Table 2).[37] We found that affinity-purified anti-B27.5 peptide antibodies significantly cross-reacted with the peptide derived from pHS-2.[36] Using peptides containing point substitution of amino acids, it was clearly shown that leucine common in HLA-B27.5 and pHS-2 but not in *K pneumoniae* nitrogenase was critical for the cross-reactivity. Surprisingly, another homologous sequence was found in *Yersinia enterocolitica*, also associated with reactive arthritis (Table 2).[38] Substantially higher proportions of patients with ankylosing spondylitis showed elevated levels of antibody against the homologous sequence, although the cross-reactivity with the HLA-B27.5 sequence was not clearly observed.[38] Such common occurrence of homologous sequences among Enterobacteriaceae might confer uniqueness to HLA-B27, which could possibly be associated with autoimmunity or an inability to clear microorganisms because of cross-tolerance. Thus, direct mechanisms of molecular mimicry may contribute to the understanding of the underlying pathogenic mechanisms that may be occurring in reactive arthritis or the spondyloarthropathies.

An experimental approach to the puzzle of precisely how the presence of class I HLA-B27.5 may predispose persons to the development of ankylosing spondylitis or reactive arthritis was reported by Hammer and colleagues in 1990.[39] These workers produced Lewis rats transgenic for HLA-B27.5 plus

TABLE 2.—*Sequence Homology Between Proteins of Possible Relevance to Autoimmune Disease*

Protein	*Amino Acid Sequence*
HLA-B27.5	A Q T D R E D L R T L
Klebsiella pneumoniae nitrogenase	R Q T D R E D E L I I
pHS-2	A Q T D R H S L S C I
YOP1	S K T D R E N S V S I
Acetylcholine receptor α chain	P E S D Q P D L
Herpes simplex virus type 1 gD	P N A T Q P E L
Mycobacterial hsp65	T F G L Q L E L T
Proteoglycan link protein	T A V V A L E L Q
Epstein-Barr virus gp110	E Q N Q E Q K R A A Q R A A
HLA-DR4, Dw4	K D L L E Q K R A A V D T Y

β_2-microglobulin and found that such animals spontaneously developed a disease similar in many respects to ankylosing spondylitis. Moreover, the disease seemed to develop in direct proportion to the actual transgene dose effect—that is, transgenic animals with multiple copies of the HLA-B27 transgene seemed much more likely to have the disease than did transgenic rats with low numbers of transgenes expressed. Our own studies of serum specimens from these same transgenic animals (provided by J. D. Taurog, MD) indicated that a low proportion (15%) of the rats studied also produced humoral antibody to the HLA-B27.5 peptide AKAQTDREDLRTLLRY and CAQTDRHSLSY, a peptide representing the potential cross-reacting epitope in the pHS-2 plasmid. The levels and distribution of the anti-B27 or anti-pHS-2 peptide antibodies, however, did not correlate directly

with the presence of the experimental disease in the rats (unpublished data, May 1992). This observation appeared to represent a strong caveat against accepting direct molecular mimicry as a major factor in at least the experimental model of ankylosing spondylitis and reactive arthritis in transgenic Lewis rats. Whether a process of molecular mimicry occurs as a basic driving event in the spondyloarthritides still remains to be determined.

An important additional reservation as to how molecular mimicry might be involved in diseases such as ankylosing spondylitis or reactive arthritis is that some element of cell-mediated immunoreactivity against shared class I HLA-B27 and bacterial antigens would be expected. We, however, were unable to demonstrate T-cell hyperreactivity against peptides such as those representing a class I B27.5 epitope reacting with autologous patients' IgG antibody when a large number of both B27-positive and B27-negative patients with ankylosing spondylitis were examined using a sensitive migration inhibition factor assay.[35] Thus, although high levels of antibody reacting with the B27.5 peptide could be demonstrated, no evidence for T cell-mediated immune reactivity could be found in the same patients. Much still needs to be learned concerning T cell-mediated immune reactivity and presumed autoimmune reactions that may be involved in disorders such as ankylosing spondylitis or Reiter's syndrome.

Myasthenia Gravis

Myasthenia gravis has been classified for some time as an autoimmune disease. Even before anti-acetylcholine receptor antibodies were perceived to be part of the pathogenetic mechanisms of the disease, patients with myasthenia were being treated by total thymectomy on the rather marginal evidence that T cells and T-cell control might play a fundamental role in fostering the disease.[40,41] When the immunogenicity of the acetylcholine receptor began to be recognized and the various structural and antigenic components of the receptor identified, a large body of experimental evidence began to accumulate that indicated that a combined humoral and cellular immune response to immunodominant epitopes of the acetylcholine receptor appeared to be the major mechanism of pathogenesis of the myasthenia gravis disease process.[42-44] No clear insight into how vital neuromuscular transmitters such as acetylcholine receptors actually become autoantigenic has yet emerged. A natural alternative or explanation that could fit with the clinical and experimental evidence might be that an exogenous stimulus was introduced or became available in affected persons in whom myasthenia then develops on the basis of a profound immune reaction that they mount against antigenic epitopes of the acetylcholine receptor. The key question here is, what actually initiates the immune reactivity against self-acetylcholine receptors? Again, Schwimmbeck and co-workers have produced a body of experimental observations that support a possible molecular mimicry mechanism in myasthenia gravis.[45] Data-bank searches have elicited evidence that certain exposed or hydrophilic residues of herpes simplex virus type 1 (HSV-1) contain homologies with sequences in the acetylcholine receptor (Table 2).[45] Patients with myasthenia show humoral antibodies that react with linear peptide sequences present in HSV-1 glycoprotein D.[45] During the course of this work, no evidence was forthcoming concerning cell-mediated or T-cell immune responses to the linear HSV-1 epitopes in patients with myasthenia.

This work on presumed molecular mimicry and an etiopathologic initiating event in myasthenia gravis provides the essence of the problem discussed here. From a clinical standpoint, there is little evidence that would support the notion that the disease is induced by HSV-1 infection. Moreover, various epidemiologic studies suggest that 60% to 90% of the population in developed western countries—the United States, Canada, Europe—have had an original HSV-1 infection at some time during their childhood or early adulthood. Clearly many persons who have had a primary or even secondary HSV-1 infection must be at risk of having antibodies to HSV-1 that could then cross-react with the acetylcholine receptor and eventually result in myasthenia gravis. The wide prevalence of HSV-1 infection and the rarity of myasthenia gravis are difficult to reconcile when the facts available are considered.

Rheumatoid Arthritis

Three lines of evidence suggest the possible involvement of molecular mimicry mechanisms in several aspects of rheumatoid arthritis.

Mycobacterial 65-Kilodalton (kd) Heat Shock Protein (hsp65)

Initial information concerning the relevance of mycobacterial antigen came from an adjuvant arthritis model. Arthritis resembling human rheumatoid arthritis or Reiter's disease could be induced by a single injection of complete Freund's adjuvant, a mixture of mycobacterial antigen and mineral oil. Holoshitz and associates isolated a $CD4^+$ T-cell clone, A2b, that was capable of inducing adjuvant arthritis when transferred to another susceptible rat strain.[46] Of interest, A2b was shown to proliferate, recognizing not only mycobacterial antigen but also cartilage proteoglycan, strongly suggesting a molecular mimicry mechanism in adjuvant arthritis.

The epitope for A2b was subsequently mapped as the peptide (180 to 188) of the mycobacterial 65-kd heat shock protein using deletion mutants of the recombinant protein.[47] The possibility of mimicry between hsp65 and proteoglycan seemed to be strengthened when partial amino acid sequence homology was found between this epitope and a proteoglycan link protein (Table 2).[48] Subsequent studies using the overlapping peptides, however, clearly showed that A2b was fully stimulated by the peptide TFGLQLE (180 to 186), and each single substitution of amino acid by alanine virtually abolished the reactivity.[49] Thus, the possibility of the direct cross-reactivity of hsp65 and proteoglycan link protein seems to be unlikely because only three residues of the seven amino acids are shared.

In human rheumatoid arthritis, a synovial fluid lymphocyte response against mycobacterial antigens[50-54] as well as the presence of IgG antibody to mycobacterial hsp65[55,56] has been reported. Several possible interpretations have been proposed, especially with respect to the role of hsp65 in human disease. Given the extensive homology (about 40% to 50% at the amino acid level) between the mycobacterial and human homologues, it was thought entirely likely that the human hsp65 homologue was the actual target of activated synovial T cells. Although this possibility was theoretically validated by the occurrence of immunologic cross-reactivity between mycobacterial and mammalian hsp65,[57-59] some recent reports do not support this hypothesis. Gaston and colleagues showed that T-cell clones recognizing mycobacterial

hsp65 did not cross-react with the human homologue.[60] Mycobacterial hsp65-reactive synovial T cells were not shown to be the dominant fraction of synovial T cells, especially at the chronic stage of rheumatoid arthritis.[52,54,61]

Alternatively, there could be an hsp65 cross-reacting host antigen other than human heat shock protein in the synovial tissue, for instance, proteoglycan. Primary sequence homology between *Escherichia coli* 40-kd hsp (dnaJ) and HLA-DR4 has been reported, as discussed later. Finally, it may be that the mycobacterial antigen, for some reason persisting in the synovial tissue, is the actual target of activated lymphocytes because the persistence of *Y enterocolitica* antigen in the joints of patients with reactive arthritis has now been clearly documented.[62] If this is the case, rheumatoid arthritis might be caused by *Mycobacterium* species by a mechanism similar to that for reactive arthritis. The fact that IgG is particularly low in glycosylated residues in both rheumatoid arthritis and tuberculosis[63] might affirm the causal relationship between these two diseases.

Bacterial or Viral Fc Binding Proteins and Rheumatoid Factors

Some bacteria possess proteins that bind to the human IgG Fc fragment. As information concerning the fine IgG specificity of these Fc binding proteins became available, interesting relationships between them and rheumatoid factors were apparent. Thus, Fc binding proteins such as staphylococcal protein A, streptococcal protein G, and T15 bind to the C_H2-C_H3 interface region of IgG, where most of the polyclonal rheumatoid factors derived from patients with rheumatoid arthritis react.[64-68] Protein A was also shown to stimulate rheumatoid factor production when cultured with human lymphocytes.[69]

An explanation for the relationship between rheumatoid factor and protein A (or other bacterial Fc binding proteins) may be that rheumatoid factors could be the anti-idiotypic antibody against autologous antibacterial Fc binding protein.[70,71] This mechanism could be referred to as "idiotypic mimicry" because the internal image of anti-Fc binding protein antibody should mimic the autologous IgG Fc region. Supporting this possibility, Oppliger and associates demonstrated that human rheumatoid factors bound to the Fab portion of chicken anti-protein A antibody.[72]

Herpesviruses also bind Fc binding proteins to the similar C_H2-C_H3 interface region of human IgG.[73-75] We have shown that human rheumatoid factors bind to Fab fragments of several monoclonal antibodies to the Fc binding protein of HSV-1 and HSV-2.[76,77] Subsequent epitope mapping using overlapping synthetic peptides confirmed that the epitopes for the monoclonal antibodies on the HSV Fc binding protein significantly overlap with the IgG binding site (R.C.W. and co-workers, unpublished data, May 1992). Other members of the herpesvirus family such as cytomegalovirus and Epstein-Barr virus have been more heavily implicated in the pathogenesis of rheumatoid arthritis. These viruses have also been known to possess Fc binding proteins.[78,79] The hypothesis that rheumatoid factor may be the anti-idiotypic antibody against anti-viral Fc binding protein requires further study.

Primary Sequence Homology Between HLA-DR4 Antigen and Infectious Agents

The susceptibility to rheumatoid arthritis is linked to HLA-DR4 and DR1 antigens. Primary sequence analysis revealed that these associated class II subtypes shared QRRAA or QKRAA at positions 70 to 74 within the third hypervariable region of the DRβ1 chain.[80] This region may be critical in the presentation of a hypothetical disease-associated peptide to T cells. An alternative possibility was proposed by Roudier and colleagues.[81] By computer analysis, these workers found a QKRAA sequence in gp110 of Epstein-Barr virus (Table 2)[82] and a 40-kd hsp of *E coli*, dnaJ.[83] They showed that a 15-mer peptide encompassing the QKRAA sequence derived from the DRβ1 chain or gp110 could be immunogenic for persons who did not possess this sequence, and remarkably the immune response was actually cross-reactive at both the T-cell and B-cell levels.[81] Whether immunization with the gp110 sequence could induce autoimmunity to an autologous DR molecule in DR4-positive persons remains to be established.

Conclusions

Molecular mimicry remains an attractive hypothesis to explain how disease-susceptible persons get disease by triggering events. Indeed, apparently meaningful primary sequence homology between autologous host tissues and various other extrinsic bacterial or viral antigens was found for many disorders, as discussed earlier. Much of this evidence still seems to be inconclusive, however, and such sequence homology could be merely a coincidence without any pathologic significance. In future studies, conformational similarity should be demonstrated rather than just a primary sequence homology for B-cell epitope mimicry. For T-cell cross-reactivity, the way in which the diseases involved must break T-cell anergy needs to be addressed. Much additional work is needed to determine whether molecular mimicry is actually pathogenetic or only an interesting hypothesis.

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