Review Article

Molecular Mimicry in Human Diseases- Phenomena or Epiphenomena ?

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Abstract

Molecular mimicry is one mechanism by which infectious agents (or other exogenous substances) trigger an immune response against the host antigens. When a susceptible host acquires an infection with an organism that has antigens immunologically similar to the host antigens but differ sufficiently, to induce, an immune response when presented to T cells, results in loss of tolerance to host antigens. Further more there is development of a pathogen-specific immune response that cross-reacts with host structures to cause tissue damage and disease. Till date the advances in the research in molecular biology has documented evidence to suggest that molecular mimicry plays in important role in pathogenesis of a number of diseases. This review is a brief overview of some of these disorders.

Introduction

Autoimmune disease is the consequence of an immune response against self-antigens that results in the damage and eventual dysfunction of target organs. Although the triggering event in most autoimmune diseases is unknown, an infectious cause has long been postulated to explain the development of autoimmunity in certain cases through molecular mimicry.

The Basic Immunology of Molecular Mimicry

The response of a T cell, whether it is productive expansion, tolerance, or death, lies in the recognition by the T-cell antigen receptor of an antigenic peptide bound to a major-histocompatibility-complex (MHC) molecule on the surface of an antigen-presenting cell. This recognition event is very flexible; giving T cells the potential to recognize a broad range of foreign antigens. However, this range of specificities also makes it possible for T-cell antigen receptors to cross-react with selfantigens. Protection against autoimmunity is provided by immunological tolerance, a state in which the individual is incapable of developing an immunologic response to a self antigen.[1,2] This self tolerance is of 2 broad types,

1. Central tolerance
2. Peripheral tolerance

Central tolerance refers to clonal deletion of self reactive T cells during their maturation in the thymus. T lymphocytes that bear receptors for self antigens undergo apoptosis within the thymus. The developing T cells that express high affinity receptors for such self antigens are negatively selected or deleted so that the peripheral T cell pool is lacking in self reactive cells.[3]

Peripheral tolerance refers to the deletion of those self reactive T cells which have escaped the central intrathymic deletion.[4] In the thymus and in the periphery, the fate of a T cell is determined by the avidity of its antigen receptor for the peptide–MHC complex. It appears that the affinity of the receptor for the complex and the number of complexes act in concert to direct the outcome of the reaction between the peptide–MHC complex and the T-cell receptor.[5,6] However, some T cells are not deleted in the thymus or rendered tolerant to autoantigens or deleted peripherally, possibly because they are inaccessible to antigen or because the level of antigen is too low to activate them. Since these T cells do not recognize their cognate antigens, they are called "ignorant" T cells, and the antigens for which they are specific are referred to as "cryptic."[7]

Infections may provide the stimulus for the breakdown of tolerance through several nonspecific mechanisms unrelated to molecular mimicry. Molecular mimicry however is one of the most important pathophysiological events that can directly involve the specificity of the immune response in an unintended way to result in the breakdown of tolerance.[8]

According to the theory of molecular mimicry (Fig-1), an autoimmune response can ensue after an infection if the immune response against the pathogen cross-reacts with host antigens. Molecular mimicry depends on demonstrating that T cells can be activated by antigenic determinants of an infectious agent that are similar to the determinants present in the host. The development of peptide-sequence data bases has resulted in the identification of many linear sequences of amino acids shared by organisms and humans, but many of these sequences lack any clinical correlation. Furthermore, it has been calculated that, on the basis of chance alone, up to 10 perfect matches can be found in protein-sequence data bases for a sequence of 5 amino acids.[9] Therefore, antigenic mimicry is probably more complex than simple amino acid–sequence homology alone and many new studies underscore the fact that linear-sequence homology is not critical for mimicry.[10] The next level of evidence that molecular mimicry is a mechanism underlying autoimmune disease would be the demonstration that quiescent, autoreactive T cells could be activated by infection with an infectious agent bearing an antigen homologous to one in the host.

Some Critical Concepts

There are difficulties inherent in proving that infection is the cause of autoimmune disease.

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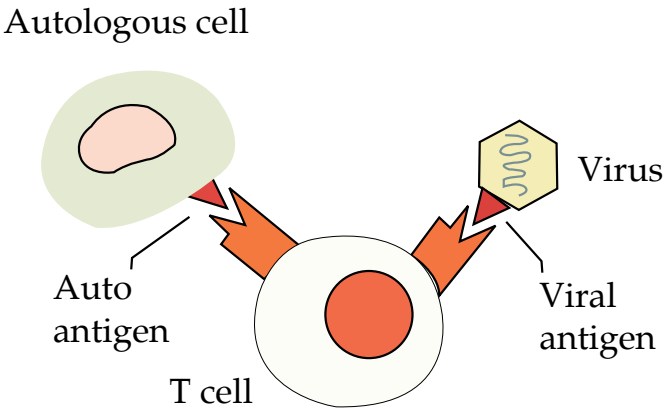

Fig. 1 : Diagram showing Molecular Mimicry Hypothesis. The molecular mimicry hypothesis suggest that a certain antigen (Viral / Bacterial) has a great degree of similarity with endogenous structures. Mistaken identity triggers the host immune system (autoantibodies) to attack the foreign as well as endogenous targets when infected with organism.

1. The infectious process may have resolved long before the disease becomes clinically evident, making it difficult to establish a reliable temporal association between a particular organism and a particular disease.
2. The infection may itself be occult. So perhaps, it is difficult to exclude the possibility that a particular autoimmune disease is the result of an immune response against persistent viable or even nonviable infectious agents, with mimicry occurring as an epiphenomenon.
3. Mimicry might also arise as a secondary phenomenon caused by an alteration of host antigenic determinants through tissue injury and the creation of neoepitopes. Tissue injury also contributes to the development of self-reactive T cells by uncovering previously cryptic epitopes. These mechanisms lead to an expanded T-cell response over time, known as "epitope spreading."

Considering the above concepts, it becomes imperative to address and recognize several important principles;

1. Antigenic mimicry alone may not be sufficient for pathologic tissue cross-reactivity.
2. Neither antigen homology nor T-cell proliferation in response to complexes of MHC molecules and peptides can alone be considered a specific indicator of pathogenic mimicry.
3. The demonstration of a tissue-specific antibody response is likewise not, in itself, a specific indicator of pathogenic mimicry and may be due to tissue injury.
4. Antigenic mimicry may elicit tolerance of the host immune response rather than autoimmunity.[11]

Molecular Mimicry and Human Diseases

Molecular mimicry has been linked to the pathogenesis of several important conditions, a few important conditions will be discussed in this article.

Multiple Sclerosis

Most experts believe that multiple sclerosis is an autoimmune disease in which T cells recognize and attack components of the axonal myelin sheath and other features of the central

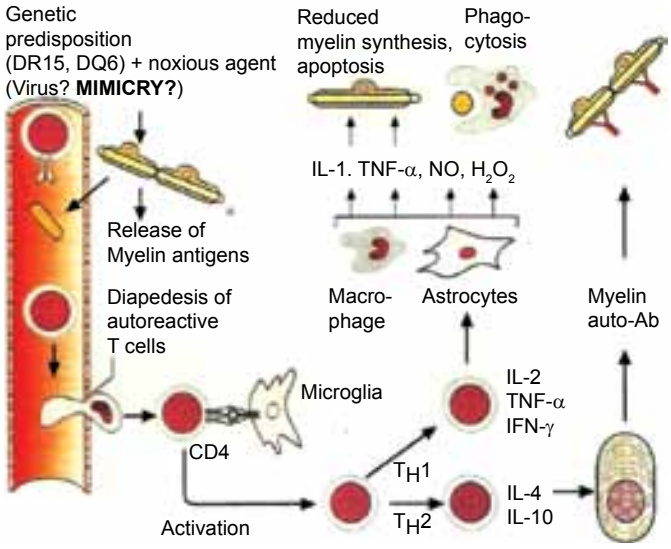

Fig. 2 : Diagram showing Molecular Mimicry in Multiple Sclerosis. Genetic predisposition along with molecular mimicry leads to migration of autoreactive T cells through blood brain barrier into the CNS. Microglial cells than present the myelin peptides to activated T cells T_H2 cells induced B cell activation and formation of myelin reactive autoantibodies leads to demyelination.

nervous system, destroying myelin and the underlying axon (Fig. 2). Although self-reactive T cells are present in the immune system of people with multiple sclerosis, they are also found in a quiescent state in perfectly healthy people. Recent work by Lang and colleagues focused on molecular mimicry, one of the presumed triggers of autoimmunity.[12]

Lang and co-workers investigated the antigen-specific T-cell receptor of a particular T-cell clone (Hy.2E11), originally isolated from the blood of a patient with multiple sclerosis. The clone was selected for its reactivity to a self antigen i.e, the myelin basic protein (MBP). But it was later found to cross-react with a peptide analogous to part of a viral antigen, the polymerase of the Epstein–Barr virus (EBV).[13] Structural similarity between viral T cell epitopes and self-peptides could lead to the induction of an auto aggressive T cell response. Based on the structural requirements for both MHC class II binding and TCR recognition of an immunodominant myelin basic protein (MBP) peptide, criteria for a data base search were developed in which the degeneracy of amino acid side chains required for MHC class II binding and the conservation of those required for T cell activation were considered. A panel of 129 peptides that matched the molecular mimicry motif was tested on seven MBP-specific T cell clones from multiple sclerosis patients. Seven viral and one bacterial peptide efficiently activated three of these clones. Only one peptide could have been identified as a molecular mimic by sequence alignment. The observation that a single T cell receptor can recognize quite distinct but structurally related peptides from multiple pathogens has important implications for understanding the pathogenesis of autoimmunity.

Guillain-Barre Syndrome

All forms of Guillain-Barré syndrome probably result from postinfectious molecular mimicry (Fig. 3), in which nerve antigens are attacked by the immune system because they resemble antigens presented by microbes, in particular, C. jejuni. For example, the HS/0:19 serotype of C. jejuni is common in northern Chinese patients with Guillain-Barré syndrome and has also been isolated from such patients in Ireland and the United

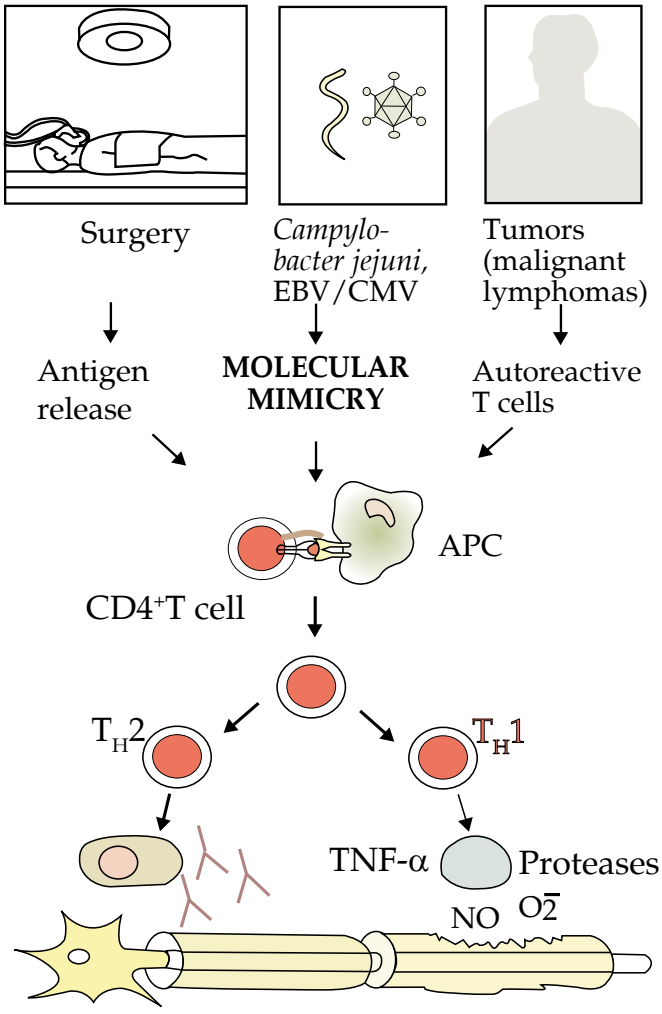

Fig. 3 : Diagram showing Molecular Mimicry in GBS. Along with other mechanisms, C. jejuni / EBV / CMV induced molecular mimicry activate the autoantigens (myelin, ganglioside antigents). Antigen presenting cells (APC) present this autoantigens to T cells and TH2 from antibodies against the organisms as well as myelin causing demyelination.

States. Assays with antiganglioside antibodies, bacterial toxins, and lectins have characterized potential immunogenic regions of diarrhea-associated C. jejuni strains, though no definitive antigen or antibody has been identified as being responsible for Guillain-Barré syndrome.[14]

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In chronic inflammatory demyelinating polyneuropathy, self-tolerance breaks down, and auto reactive T cells and B cells, which are part of the normal immune repertoire, become activated, causing the organ-specific damage characteristic of autoimmune disease. The concept of molecular mimicry may hold special relevance to the breakdown in tolerance associated with autoimmune neuropathies. However, in chronic inflammatory demyelinating polyneuropathy, specific targets for such a response have been convincingly identified only in rare instances.

Although chronic inflammatory demyelinating polyneuropathy occurs rarely in the context of cancer, an association with melanoma is of great interest, since both

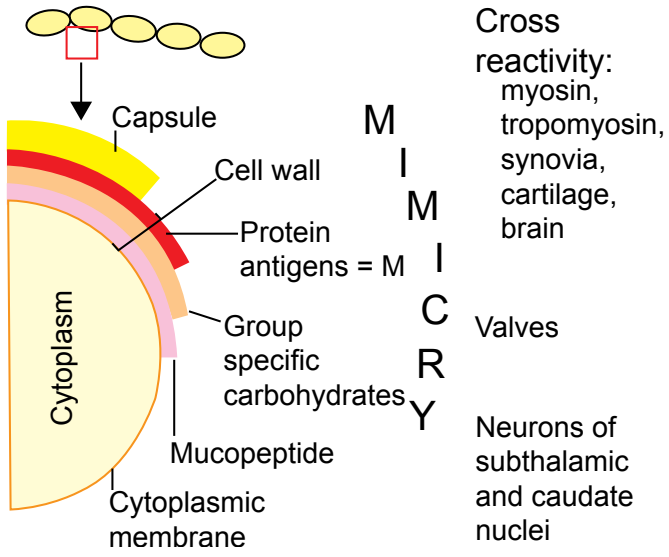

Fig. 4 : Diagram showing Molecular Mimicry in Acute Rheumatic Fever. Similarity between streptococcal cell wall antigens with endogenous antigens in cardiac tissue, synovium, cartilage and brain leads to immunologic attack by the host antibodies and manifestations of acute rheumatic fever.

melanoma and Schwann cells are derivatives of neural crest tissues and share antigens. Several cases of chronic inflammatory demyelinating polyneuropathy have been reported in association with melanoma; several carbohydrate epitopes shared by the myelin sheath and the tumor have been implicated as target antigens. On the basis of current data, chronic inflammatory demyelinating polyneuropathy appears to be an organ-specific, immune-mediated disorder emerging from a synergistic interaction of cell-mediated and humoral immune responses directed against incompletely characterized peripheral nerve antigens.[15]

Acute Rheumatic Fever

The classic clinical paradigm for molecular mimicry (Fig. 4), has been acute rheumatic fever after infection with group A ß-hemolytic streptococci. Serum from patients with acute rheumatic fever contains antibodies to an antigen in the membrane of the organism, the type 5 streptococcal M protein, which cross-reacts with myocardial tissue.[16,17]

Epitopes present in the cell wall, cell membrane, and the A, B, and C repeat regions of the streptococcal M protein are immunologically similar to molecules in human myosin, tropomyosin, keratin, actin, laminin, vimentin, and N-acetylglucosamine. This molecular mimicry is the basis for the autoimmune response that leads to ARF. It has been hypothesized that human molecules—particularly epitopes in cardiac myosin—result in T cell sensitization. These T cells are then recalled following subsequent exposure to group A streptococci bearing immunologically similar epitopes.[18]

PANDAS

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) is defined as rapid, episodic onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms after a group A β-hemolytic streptococcal infection (GABHS).[19] The current hypothesis for the pathology PANDAS is that a streptococcal infection occurring

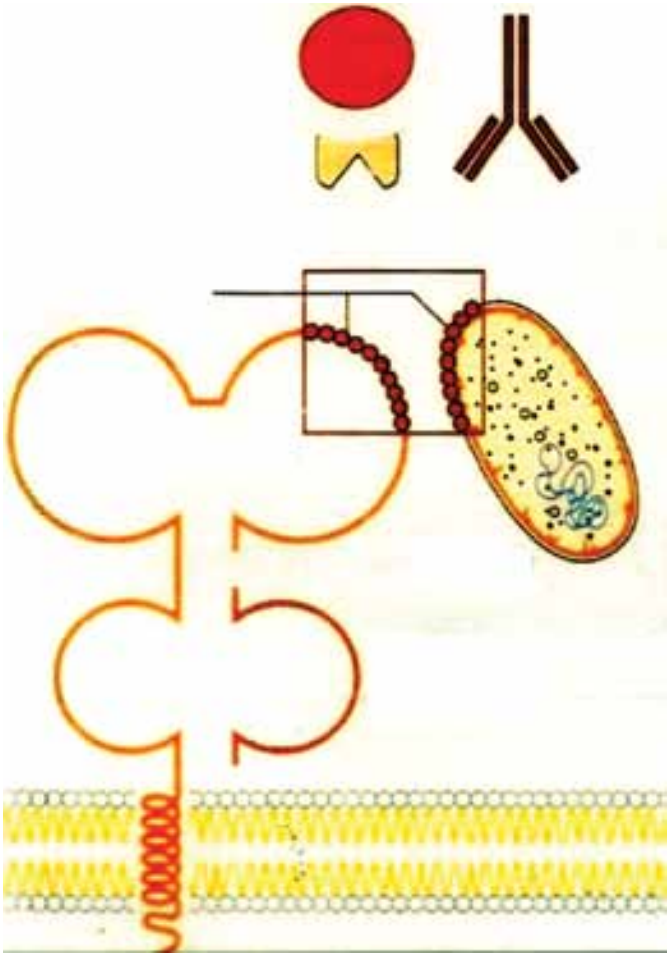

Fig. 5 : Diagram showing Molecular Mimicry in Spondyloarthropathies. Structural similarity between the polymorphic regions of HLA-B27 and microbial antigens leads to induction of host immune response against microbes as well as endogenous HLA-B27 antigens, triggering a still unknown cascade leading to manifestations of spondyloarthropathies.

in a vulnerable host causes antibody production and these antibodies cross-react with the cellular components of the basal ganglia. This process, known as molecular mimicry, is believed to be the process that causes the OCD and tic disorder symptoms in the PANDAS subgroup of patients. There is controversy in the medical field over the reality of this disease, as studies have failed to prove or disprove its existence.[20,21] PANDAS became popular in the late 1990s and continues to be a highly researched and controversial topic in the field of paediatric neuroscience.

The central nervous system diseases that are hypothesized to being linked with a streptococcal infection are,

- Sydenham's chorea
- Tourette syndrome
- Dystonia
- Myoclonus
- Parkinsonism
- Paroxysmal Dystonic Choreoathetosis
- Motor Stereotypes
- Encephalitis lethargica

Further studies on the link between GABHS antibodies and the potential for molecular mimicry to cause the neuropsychiatric symptoms of PANDAS are currently underway.

Lyme Arthritis

In some patients infected with the spirochete Borrelia burgdorferi, Lyme arthritis develops as a late sequela. In about 10 percent of these patients, the arthritis is resistant to antibiotic therapy and becomes chronic. There is usually no detectable spirochetal DNA in the affected joints. Human leukocyte-function–associated antigen 1 (LFA-1, CD11a/CD18, or integrin $\alpha_L ß_2$) has been proposed as an autoantigen in these patients because it contains a peptide sequence that is homologous to one in the outer-surface protein A (OspA) of B. burgdorferi.[22]The link between this autoreactivity against LFA-1 and the synovitis of B. burgdorferi infection awaits further clarification.

Spondyloarthropathies

In the spondyloarthropathies, particularly Reiter's syndrome and reactive arthritis, there is a clear temporal relation between arthritis and antecedent bacterial infection, combined with a strong host genetic susceptibility (HLA-B27). Studies provide support for the concept of microbial mimicry of B27 (Fig. 5), based on monoclonal-antibody cross-reactivity[23] and sequence homologies.[24] A systematic search of a sequence data base showed that B27, to a greater degree than other B alleles, shares an unexpected number of hexapeptides and pentapeptides with gram-negative bacterial proteins.[25] In a study of B27-transgenic mice immunized with a shared peptide of B27 and Klebsiella, the B27 genotype, instead of predisposing the mice to arthritis, actually rendered them tolerant to this shared peptide.[26,27] This finding supports the idea that antigenic mimicry may induce tolerance rather than autoimmunity. It has also been argued that B27 is distinctive in its propensity to misfold in the endoplasmic reticulum, which may induce a pro-inflammatory cascade called the unfolded protein response. Furthermore, B27 may have a distinct tendency to form heavy chain homodimers at the cell surface, and the possible consequences of this change for the immune response are under investigation. In B27 transgenic rats, the spontaneous development of pathology strikingly similar to human SpAs has supported the notion that B27 itself is the critical genetic factor in disease pathogenesis. These animals demonstrate pathology similar to that of Crohn's disease in the GI tract, spondylitis, peripheral arthritis, uveitis, and psoriasiform skin and nail changes. Of interest, if such animals are raised in a germ-free environment, there is a marked reduction in joint and gut disease, thus implying a dynamic interrelationship between microbial triggers and background host genes that seems to recapitulate the situation seen clinically.

Type 1 Diabetes Mellitus

In patients with type 1 diabetes mellitus, mimicry related to viral infection has been proposed on the basis of sequence homology between glutamate decarboxylase (GAD65), an enzyme concentrated in pancreatic beta cells,[28] and coxsackievirus P2-C, an enzyme involved in the replication of coxsackievirus B.[29] Although cross-reactivity between coxsackievirus P2-C and GAD65 has been demonstrated in mice, and an immune response to the homologous peptides is generated by immunization of mice with full-length proteins, cross-reactivity between GAD and coxsackievirus P2-C has not been consistently found in studies of T cells or serum antibodies from patients with diabetes. Furthermore, a search of data bases identified 17 viruses with some homology to various fragments of GAD65, indicating that

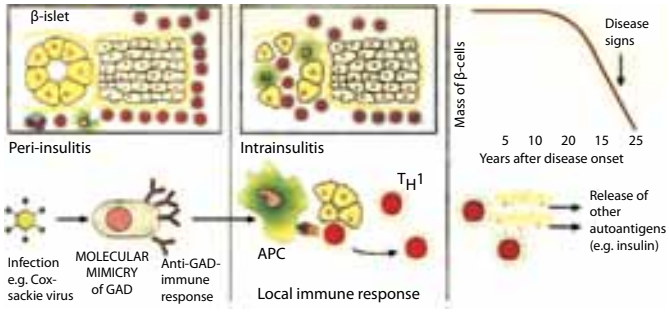

Fig. 6 : Diagram showing Molecular Mimicry in Diabetes Mellitus. Glutamate decarboxylase 65 (GAD 65) is an important islet cell autoantigen. Coxakievirus proteins have great degree of homology with the GAD 65. Infection initiates cross reactive antibodies against GAD 65 leading to peri insulitis which results in activation of Antigen Presenting Cells (APCs) and subsequent intra insulitis. Gradual distruction of beta cells then leads to overt diabetes mellitus after several years.

cross-reactivity between GAD65 and coxsackieviruses is not unique. Moreover, peripheral-blood mononuclear cells from patients with diabetes mellitus can be stimulated to proliferate by insulin and several islet-cell antigens as well as GAD65. In view of this reactivity to several antigens, which could represent epitope spreading, caution is warranted in drawing conclusions about the role of cross-reactivity between GAD65 and coxsackievirus peptides specifically, and that of molecular mimicry (Fig. 6), in general, in the pathogenesis of diabetes mellitus.[30]

Autoimmune Polyglandular Syndrome (APS)

APS develops as a result of multiple genetic defects which occur simultaneously or due to a molecular mimicry mediated immune response against antigens expressed by different endocrine organs (Fig. 7).

Type 1 is most common in teenagers and is characterized by, adrenocortical insufficiency (immune response to 21-hydroxylase), hypoparathyroidism (autoantibodies to parathyroid calcium sensors) and recurrent mucocutaneous candidiasis. Hypogonadism sometimes occur due to autoantibodies to p450 side chain cleavage enzyme.

Age dependent type II APS is characterized by, co-occurence of adrenocortical insufficiency and autoimmune thyroid disease. This subtype is associated with IDDM in 50% of cases.

Type III APS is characterized by thyroid and other autoimmune diseases in the absence of adrenocortical insufficiency.

Primary Biliary Cirrhosis

Autoimmunity in the peripheral Molecular mimicry is the most widely proposed mechanism for the initiation of autoimmunity in primary biliary cirrhosis.[31] Several candidates have been suggested as causative agents, including bacteria, viruses, and chemicals in the environment. Escherichia coli, have attracted the most attention because of the reported elevated incidence of urinary tract infections in patients with primary biliary cirrhosis and the highly conserved nature of the mitochondrial autoantigens. Antibodies against the human pyruvate dehydrogenase complex react well against the E. coli pyruvate dehydrogenase complex. However, antibodies to the E. coli pyruvate dehydrogenase complex are often lower in titer

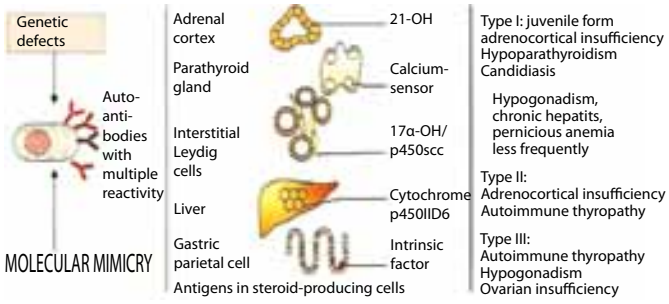

Fig. 7 : Diagram showing Molecular Mimicry in Autoimmune Polyendocrinopathy Syndrome (APS). APS develops as a result of multiple genetic defects or molecular mimicry mediated immune response against antigens expressed by different endocrine organs.

and are more frequent in patients in later stages of primary biliary cirrhosis than in patients in earlier stages.

Figures 1 through 7 depicts, schematic representation of molecular mimicry in causation of some human diseases.[32]

Conclusion

For the researchers in the field of molecular mimicry challenges will always be there, so as to prove that molecular mimicry is the key pathogenic mechanism in autoimmune disorders. The frequency of shared peptide sequences and the flexibility inherent in immune recognition suggest that mimicry may be ubiquitous in biologic systems. From the clinical perspective, work in this area has not led to any treatments with proven efficacy. Rather, in some studies it has been demonstrated that, in some disorders, instead of having the deleterious role, mimicry may actually contribute to a successful host defense and healing.

If molecular mimicry is a biologically important phenomenon, it has important implications for vaccination. Possibly vaccination against infectious diseases activates pathways of molecular mimicry in genetically susceptible hosts, and this may be the basis of adverse reactions to vaccines. And by the same law, the concept of molecular mimicry suggests that nonresponsiveness to vaccines could be a function of tolerance.

Molecular mimicry has remained an attractive explanation for autoimmune diseases for a considerable time, mainly on the basis of circumstantial evidence. But still, molecular mimicry retains an intrinsic importance, because it links current concepts of immune defense with concepts of autoimmunity.

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