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Molecular Mimicry and Auto-Immunity

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Abstract

The term "molecular mimicry" was coined by R. Damian in 1964, who was first to suggest that antigenic determinants of micro-organisms may resemble antigenic determinants of their host. Damian suggested that this similarity served as a defense mechanism of a microorganism from the host's immune system and prevented the development of immune response to the micro-organism, thereby protecting it from host defense. Years later, the term "molecular mimicry" was attributed a different meaning—namely, antigenic determinants of microorganisms might elicit an auto-immune response that harms the host. The concept of molecular mimicry is based on a structural similarity between a pathogen or metabolite and self-structures. The similarity could be expressed as shared amino acid sequences (linear or mimotope) or similar conformational structure between a pathogen and self-antigen.

"Molecular mimicry" has become a very popular explanation for the frequent association of infection with auto-immune disease.

Index Entries

Molecular-mimicry; autoAbs; infection; autoimmunity; rheumatic fever; Chagas disease; systemic lupus erythematosus; Guillain-Barré syndrome.

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Introduction

Crossreactivity between pathogens and self-structures were analyzed by screening more than 600 monoclonal antibodies (Abs) directed to diverse viral components for recognition of 14 different organs *(1–5)*. Twenty-one monoclonal Abs from a human source (3.5%) were found to be specific to a certain virus and crossreacted with specific human cells. Several of these were multiple-organ-reactive Abs and were recognized antigens in more than one organ. Such crossreactivity might be a result of the Ab binding either the same molecule present in more than one organ or similar epitopes on different molecules in multiple organs *(6)*. Researchers have concluded that the reactivity of monoclonal antiviral Abs with normal tissues is a common phenomenon and could be a basis for provoking an auto-immune response in certain conditions. B-lymphocytes that make antiviral Abs that crossreact with normal host cell antigens may continue to be stimulated by those host antigens long after the viral infection has disappeared. If this is the case, molecular mimicry may partly account for the enigma of persistent immunity in the absence of continued viral exposure. Pender *(7)* proposed that human chronic auto-immune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis, Sjögren's syndrome, rheumatoid arthritis, auto-immune thyroiditis, auto-immune hepatitis, cryptogenic fibrosing alveolitis, and pure red cell, are based on infection of autoreactive B-lymphocytes by Epstein–Barr virus (EBV). Latently EBV-infected autoreactive memory B-cells may lodge in organs where their target antigen is expressed and act as antigen-presenting cells. When $CD4^+$ T-cells that recognize antigens within the target organ are activated in lymphoid organs by cross-reactivity with infectious agents, they migrate to the target organ but fail to undergo activation-induced apoptosis because they receive a costimulatory survival signal from the infected B-cells. The autoreactive T-cells proliferate and produce cytokines, which recruit other inflammatory cells, with resultant target organ damage and chronic auto-immune disease *(7)*.

Over the last decades, T-cells or antibodies with crossreactive capabilities were found in human sera in association with a wide spectrum of auto-immune diseases (Table 1 summarizes key examples). Notably, not every crossreaction or homology in amino acid sequences between a self-infecting and infecting agent has a biological function *(23)*. Furthermore, epitopical imitation of T-cells may be agonistic or antagonistic or may alter a peptide's binding capability to its ligand and, therefore, may induce, revoke, or regulate T-cell activity *(24)*. A different avidity between a target epitope and the imitating agent (virus/bacteria) may be another cause that plays a roll in auto-immunity, because weak avidity to a target epitope may require a second hit (e.g., a local infection) to stimulate and induce T-cells with crossreactive abilities, thereby causing a disease.

Molecular Mimicry in Rheumatic Fever

Rheumatic fever is a classic example for molecular mimicry between an infecting agent—*Streptococcus pyogenes* (group A streptococcus) and an auto-immune disease in humans *(10–12)*. The disease is characterized by damage to the heart, joints, and the central nervous system (Sydenham's chorea). The activity of the host's immune system against the streptococcus generates a cross-recognition to human tissue components, thus causing an auto-immune reaction. Heart damage is the most serious consequence resulting from such a cascade, is present in 30 to 45% of the cases, and presents damage to the heart valves, often causing heart failure and the need for interventional valve replacement. The molecular mimicry in this case activates T-cells, which recognize various sequences of the M protein in the bacteria's cell wall, and supports B-cells with auto-immune capabilities. Therefore, in rheumatic fever, both

Table 1
Main Examples of Molecular Mimicry Between a Pathogen and Auto-Immune Disease

Disease	Host antigens	Pathogens	References
Chagas' cardiomyopathy	Ribosomal protein 23 kD, myosin, B13 protein, Cha-peptide.	*Trypanosoma cruzi*	*3,4,8,9*
Rheumatic fever	Cardiac myosin, tropomyosin laminin, vimentin, actin, keratin, *N*-acetyl-glucosamine	*Streptoccocus pyogenes*	*10–12*
Myasthenia gravis	Acetylcholine receptor, neurofilaments	Herpes virus, *Hemophilus influenzae*	*3,13,14*
Multiple sclerosis	Myelin basic protein	Corona, measles, mumps, EBV, herpes	*4,15–17*
Guillain-Barré	Gangliosides, lipo-oligosaccharide	*Campylobacter jejuni*	*18,19*
Type 1 diabetes mellitus	Islet antigens:GAD 65, proinsulin carboxypeptidase H	Coxsackievirus B, Rotaviruses, Herpes, hepatitis C, rhino-, hanta retroviral	*18,19*
Ankylosing spondylitis	HLA-B27, type I, II, IV collagen	*Klebsiella pneumoniae*, chlamydia	*4,22,23*
Antiphospholipid syndrome	β_2-glycoprotein-I	*Hemophilus influenza*, *Neisseria gonorea*, Tetanus toxin, CMV	*24,25*
Systemic lupus erythematosus	Ro 60 kD, NMDA, dsDNA	EBVpneumococcal polysaccharide	*26–29*

cellular and humoral immunity participate in the auto-immune reaction.

The main occurrences leading to heart damage include:

1. An infection of the upper respiratory airways by *S. pyogenes*, which allows presentation of the infector's antigens by macrophages or dendritic cells in compatibility with major histocompatibility complex (MHC) class II for $CD4^+$ T-cells, causing the initial activation of B-cells and specific $CD4^+$ T-cells and consequently initiating the cellular and humoral reaction against the bacteria's antigens.
2. Some of the Abs created are crossreactive with heart proteins, such as actin, myosin, tropomyosin, laminin, elastin, vimentin and keratin; they hurt heart tissues and allow CD4 T-cells to penetrate. The autoreacting cells that penetrate recognize heart tissue proteins by use of molecular mimicry, and in the presence of pro-inflammatory cytokines (such as interleukin [IL]-1 or IL-2), they hurt the heart tissue or heart valve tissue. Additionally, binding of crossreactive Abs increases the expression of vascular cell adhesion molecule-1 that react with very late antigen-4, which is expressed on the surface of T cells, thereby increasing cellular permeability into different tissues. The pro-inflammatory cytokines interferon (IFN)-γ and tumor necrosis factor-α support the development of heart valve damage. This model was built and based on the following studies *(2–4,10,11)*:
   a. $CD4^+$ T-cell lines obtained from peripheral blood of patients with rheumatic fever reacted with M protein and its peptide derivatives, both originating from *S. pyogenes*.
   b. Studies proving the contribution of pro-inflammatory cytokines to activation and proliferation of $CD4^+$ T-cells specific for M protein.
   c. Human leukocyte antigen class II alleles are genetic markers for the disease and contribute to the presentation of the *Staphylococcus* pro-

teins as well as self-antigens for T-cell receptors.
d. $CD4^+$ T-cells isolated from an indignant heart valve of a patient with rheumatic fever showed specificity to myosin.
e. Abs purified from sera of patients with rheumatic fever react with different components of heart, joint, brain, and skin tissues.
f. The M protein and its derivatives, in addition to myosin protein extracted from heart tissue, may induce a rheumatic disease in mouse and rat hearts.

Additionally, in rheumatic fever, researchers have demonstrated molecular mimicry between the sugar product *N*-acetyl-β-D-glucosamine carbohydrate (GlcNAc), which is a part of the envelope surrounding *S. pyogenes,* and a part of the human nerve cell membrane (ganglioside) *(12)*. Monoclonal Abs, derived from human B-cells obtained from a patient with rheumatic fever with evidence of nerve damage (Sydenham's chorea), reacted with GlcNAc from the bacteria and nerve cell membranes. Furthermore, these Abs induced signal transduction activities by calcium/calmodulin-dependent protein kinase IIin nerve cells, implying the involvement of these Abs in the pathogenesis of damage to the nervous system in rheumatic fever *(12)*.

Molecular Mimicry in Chagas Disease

This disease affects approx 30% of the 20 million people infected by the unicellular parasite *Trypanosoma cruzi* in South America. Evidence of the presence of inflammatory cell infiltration within the heart despite absence of evidence of the presence of the parasite evoked the assumption that the *Trypanosoma* induced the auto-immune state *(3–5,8,9)*. Indeed, Abs purified from sera of patients with Chagas disease reacted with the parasite and self-components such as ribosomal protein 23 KD (which is a functional protein on the β_1-adrenergic receptor present in tissues of the heart and the brain shell), the Myosin protein, protein B13, and Cha-peptide (a peptide of human origin that carries an epitope common for both B- and T-cells). Immunization with the proteins or the Cha peptide, or passive infusion of autoreactive T-cells, induces an animal model in mice imitating the human Chagas disease. Additionally, infection of mice with *T. cruzi* causes a cellular and humoral immune reaction accompanied by heart damage similar to that observed in Chagas disease *(9)*.

Molecular Mimicry in Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an example of damage to the peripheral nervous system mediated by an immune reaction and is characterized by paralysis of the extremities and additional motor damage. Clinical manifestations often appear 1 to 3 wk after infection with the bacteria *Campyllobacter jejuni* or a viral infection such as EBV, cytomegalovirus (CMV), or *Mycoplasma pneumoniae*. Four conditions were determined to establish the assumption that GBS results from molecular mimicry between an infecting agent and a self-component *(18,19)*.

1. Epidemiologically, a correlation was shown between the presence of an infecting agent, a reaction to the infection, and, onset of an auto-immune disease.
2. High titers of Abs bond to *C. jejuni* and gangliosides (Galactose-*N*-Acetyl-GD1a-1, GD1a, GMIb, GMI). Moreover, an infection with CMV induces synthesis of Abs that crossreact with GM2, whereas *M. pneumoniae* induces synthesis of Abs that crossreact with galatocerebroside. Characterization of T-cells in GBS showed an increase in $CD4^+$ cells. $CD8^+$ cells expressing receptors for αβ or γ, which showed no reaction against glycopeptides but did react against protein components in *C. jejuni*, were located and isolated from nerves and peripheral blood samples of patients. Monoclonal and polyclonal Abs, specific against gangliosides and obtained from patients with GBS, were

described as having biological activities and complement binding; they create damage, mediated by complement proteins, at the ends of motor nerves. Additionally, these Abs were found to have qualities of ion-gate blocking and damaged the blood–nerve barrier.

3. The common structure between *C. jejuni* and nerve cells was identified. Lipo-oligosaccharide (LOS) of *C. jejuni* imitates the structure on the ganglioside. Abs' obtained from patients with GBS bind to LOS from *C. jejuni*.
4. GBS may be induced in a mouse model by injecting LOS or by an infection of *C. jejuni*. The mice developed high titers of Abs against gangliosides with similar activities as Abs obtained from human patients with GBS. Furthermore, the clinical presentation in mice resembled the clinical presentation of GBS in humans.

Molecular Mimicry in SLE

Various mechanisms have been proposed in attempts to decipher the sources for development of SLE, based primarily on genetic and environmental causes. Upon researching the subclinical conditions of the disease, Abs specific against nuclear antigens such as SmD1, SmB/B', and Ro 60kD were identified in patient sera. These Abs identified and reacted to a peptide derived from a nuclear antigen of EBV (EBNA-1). By doing so, they created a molecular mimicry reaction between a human component and an EBNA-1 particle in EBV *(26,27)*. Rabbits immunized with Ro 60kD or with EBNA-1 developed crossreacting Abs that bonded to both antigens. Simultaneously, the rabbits developed an overt clinical setting resembling SLE in humans, including leukopenia, thrombocytopenia, and renal damage *(27)*.

Furthermore, molecular mimicry was found between other components of EBV, such as latent membrane protein 2A (LMP2A) and a B-cell receptor expressed on B-cells that participates in transmission of viability messages to mature B-cells *(26)*. LMPA2A is a functional homolog of B-cell receptors involved on the one hand in viability signaling to B-cells and on the other hand in regulation of the litic circle.

Diamond et al *(28,29)* provided an additional example of molecular mimicry as a potential aggravator of anti-dsDNA Abs in lupus upon exposure to pneumococcal polysaccharide. The target epitope of these anti-dsDNA/ pneumococcal polysaccharide crossreactive Abs was a pentapeptide Asp/Glu-Trp-Asp/Glu-Tyr-Ser/Gly, as defined by using a peptide phage display library. This sequence is also present in the extracellular domain of murine and human *N*-methyl-D-aspartate receptor subunits NR2a and NR2b. Moreover, anti-dsDNA Abs with this crossreactivity mediate apoptotic death of neurons in vivo and in vitro. Furthermore, when these Abs penetrate brain tissue, they can cause changes not only in cognitive competence but also in emotional behavior *(29)*.

Molecular Mimicry and Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is characterized by recurrent fetal loss, repeated thromboembolic phenomena, thrombocytopenia, and prolonged coagulation time. These diverse clinical pictures are associated with elevated levels of mainly circulating antiphospholipid β-2-glycoprotein-I (β2GPI)-dependent Abs. Employing a peptide phage display library, we identified three hexapeptides that react specifically with the anti-β2GPI monoclonal Abs located on the β2GPI molecule as mimotopes *(30)*. All three peptides specifically inhibit the biological functions of the corresponding anti-β2GPI monoclonal Abs (in vitro endothelial cell activation and induction of experimental APS in vivo). Using the Swiss Protein database revealed high homology between the hexapeptides with different bacteria and viruses. Naive mice were immunized with a panel of pathogen particles *(24)*. All the immunized

mice developed antiphospholipid Abs. However, the most significant levels of mouse anti-β2GPI were detected in the mice immunized with *Haemophilus influenzae* or with *Neisseria gonorrhoeae* and bound β2GPI in a dose-dependent manner. Mouse IgG specific to the relevant peptide (equivalent to β2GPI) was affinity purified from the immunized mice. These specific immunoglobulins were infused intravenously into BALB/c mice, and the development of APS clinical manifestations was studied. Only the mice infused with mouse Abs affinity purified on a TLRVYK-peptide-column originated from mice immunized with *H. influenzae,* tetanus toxoid, or with *N. gonorrhoeae* had the potential to induce clinical manifestations that resembled experimental APS. In this case, we proved that the mechanism of pathogenic anti-β2GPI generation was induced by epitope mimicry with a pathogen *(24)*. Pierangeli et al. *(25)* demonstrated that immunization of mice with shared peptide between CMV and β2GPI could induce generation of mouse anti-β2GPI Abs and ex vivo models of thrombosis as well as fetal loss. Finally, molecular mimicry between a pathogen and β2GPI molecule was proposed to be one of the main explanations for the origin of APS *(31)*.

Molecular Mimicry Between a Drug and a Self-Component As an Inducer or Protector of an Auto-Immune State

We have discussed molecular mimicry between infecting agents to self-antigens as a cause for development of auto-immune diseases. Many drugs are dismantled endogenously by the liver. Consequently, new foreign antigens termed neo-antigens may be created in the form of protein adducts. These new antigens may resemble self-antigens. The metabolism of the anesthetic halothane elevates levels of trifluoroacetylated (TFA) proteins in humans or in mouse models. Only 1 of 3000 people develop hepatic injury (halothane hepatitis) *(32)*. These people cannot tolerate presence of TFA proteins and create crossreacting Abs that identify the TFA proteins and pyruvate dehydrogenase (PDH) *(33)*. The molecular mimicry has been defined as TFA-lysine in TFA proteins that imitate clusters of prostatic lipoic acid of the subunit E2 of PDH *(33)*. Interestingly, patients with halothane hepatitis did not properly express the crossreacting component E2. Therefore, in this instance, molecular mimicry played a protective role by canceling the crossreacting specificity. These findings raise the possibility that proper introduction of self-components (such as PDH) may induce immune tolerance to a self-component and to other foreign antigens that present similar structures—for example, TFA proteins created spontaneously during halothane metabolism.

Another example for a protective state originating from molecular mimicry was presented in *Myesteniae gravis*. A peptide derived from the bacteria *H. influenza*, which shares 50% homology in amino acid sequence with an epitope of the acetylcholine receptor, was found to have protective activities in this disease *(14)*. Rats who received this peptide prior to the induction of the disease developed a weaker illness. The cellular reaction weakened and was expressed in the appearance of low levels of the cytokines IL-2, IL-12, IFN-γ and IL-4. Additionally, levels of Abs directed against acetylcholine were decreased compared with rats that were not treated.

In conclusion, we have presented several main examples in which molecular mimicry between micro-organisms and a self-component may induce or accelerate an auto-immune disease such as rheumatic fever, GBS, Chagas disease, SLE, or APS (summarized in Fig. 1). Molecular mimicry may also serve a role in protection against an auto-immune disease (e.g., halothane). In other circumstances, where the avidity between the common component and the target site is weak, there is a need for a second hit to induce the disease.

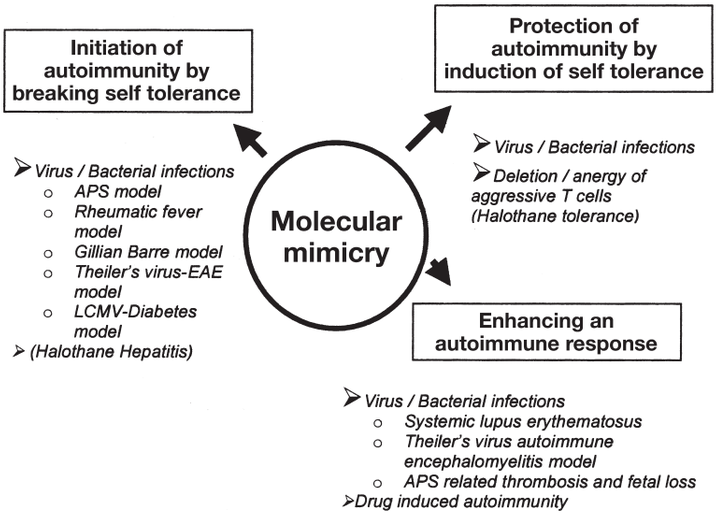

Fig. 1. Reciprocal relations between molecular mimicry and auto-immunity.

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