

Hypothesis

Molecular mimicry may contribute to pathogenesis of ulcerative colitis

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Abstract Ulcerative colitis (UC) is a chronic inflammatory bowel disease with mucosal inflammation and ulceration of the colon. There seems to be no single etiological factor responsible for the onset of the disease. Autoimmunity has been emphasized in the pathogenesis of UC. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are common in UC, and recently two major species of proteins immunoreactive to pANCA were detected in bacteria from the anaerobic libraries. This implicates colonic bacterial protein as a possible trigger for the disease-associated immune response. Autoantibodies and T-cell response against human tropomyosin isoform 5 (hTM5), an isoform predominantly expressed in colon epithelial cells, were demonstrated in patients with UC but not in Crohn's colitis. We identified two bacterial protein sequences in NCBI database that have regions of significant sequence homology with hTM5. Our hypothesis is that molecular mimicry may be responsible for the pathogenesis of UC.

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1. Introduction

Autoimmune diseases are a challenge not only to the patients suffering but also to the researchers trying to understand their etiology and biology. When the answers for the cause of autoimmune diseases are being sought, the microbial kingdom seems to be the place to look for 'trouble makers'. The observation that infection can precipitate an autoimmune disease dates back to more than a century [1]. Paroxysmal cold hemoglobinuria, and rheumatic fever are a couple of important examples in support of this notion. It is well established that autoreactive T and B cells exist in the blood of healthy individuals and these cells can potentially induce autoimmunity if activated beyond certain thresholds [2]. In fighting the infection, the immune system must discriminate between self and a pathogen to destroy pathogen without destroying its host. Discrimination between self and non-self is critical for the

maintenance of fine balance of human immune system. An error in judgment could lead to self-destruction of host cells. Infection with certain parasites, bacteria, viruses, mycobacteria, and yeast can potentially induce autoimmunity [2].

The concept of molecular mimicry states that antigenic determinants of infectious microorganisms resemble structures in the tissue of the host but differ enough to be recognized as foreign by the host immune system [1]. The initial support for the suggestion that molecular mimicry might play a role in autoimmune disease was found in 1983 when the antibody against the phosphoprotein of measles virus and Herpes simplex type I cross-reacted with an intermediated filament protein, vimentin, of human cells [3].

2. Infectious etiology of autoimmune diseases

It is known that autoreactive T and B cells exist in the blood of healthy individuals [4,5], but why only in certain individuals these cells cause autoimmunity? Infectious agents are recognized to be likely candidates in altering the balance in immunoregulatory processes which could break self-tolerance. Some of the autoimmune diseases that are linked to bacterial pathogens are rheumatoid arthritis [6–8], Graves' disease [9,10], ankylosing spondylitis [11,12], systemic lupus erythematosus [13–15] and insulin dependent diabetes mellitus [16,17].

Do the bacteria/viral infections initiate/cause autoimmune diseases or they are the proverbial last straw that tilt the balance from tolerance to defense? Or, is it an attack that is a natural mechanism of self-preservation devised by the body? The answers may be specific to the individual diseases. It has been generally believed that microbial pathogens could be initiators and propagators of a number of autoimmune diseases. For example, in Chagas' disease, the presence of cardiac inflammatory infiltrate in apparent absence of *Trypanosoma cruzi* parasite suggests that the trypanosome initiates an autoimmune response [18].

The autoimmune diseases could be viewed as cases of mistaken identity. In the era of genomics and proteomics and in the realm of molecular and structural basis of human diseases, it is hard to ignore the role of 'molecular twins' or 'structural dupes' that could play a trick on the unsuspecting host immune system. We may also consider the microbial peptides/proteins as 'molecular con artists'. It is a philosophical issue as to whether the microbes pro-actively attack the immune system or the host immune system 'over reacts' in its efforts to preserve its identity. Nevertheless, the consequence is a chronic

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Abbreviations: UC, ulcerative colitis; TM, tropomyosin; MHC, major histocompatibility complex

autoimmune disease. As modern medicine aims to treat the disease rather than the symptoms, there is a need to identify the factors and facilitators of pathogenesis and to pursue the ultimate goal of suggesting and identifying the targets for drug discovery to cure the disease.

3. Mechanisms of infection-mediated autoimmunity

Infectious agents can participate in any three stages of autoimmune diseases: Initiation, propagation, and tissue destruction. How can infection trigger or exacerbate autoimmunity? There are three attractive hypotheses: the molecular mimicry hypothesis suggests shared epitopes between the host and pathogen that can either elicit autoreactivity or allow the organism to persist in the host by evading immune recognition. The autoreactive memory T-cells can respond to subsequent infection or environmental factors and can induce long-term damage to the host organ having the cross-reactive epitopes. Fig. 1 presents a schematic of the mechanisms of molecular mimicry in infection mediated autoimmune processes. The second hypothesis proposes that the immune response elicited by the infection can cause upregulation of chaperones, heat shock proteins, and major histocompatibility complex (MHC) molecules, resulting in abnormal processing and presentation of sequestered self-antigens. The third hypothesis involves a newly characterized class of bacterial proteins called superantigens which are inducers of inflammatory reactions and potentially cause expansion of autoreactive T cells.

According to the molecular mimicry hypothesis, the presence of shared and/or cross-reactive epitopes between the host and the pathogen may induce autoaggression by evoking autoreactive T and B cells. The response to a dominant microbial epitope may evoke an immune response to a cross-reactive cryptic self-epitope. Alternatively, molecular mimicry may allow the organism to evade immune elimination and survive in the host, causing damage by unknown mechanisms. Molecular mimicry is thought to account for numerous infection-associated autoimmune disorders ([19,20] and Table 1). These include the post-streptococcal autoimmune disease in which epitopes shared between the bacterial M protein as well as

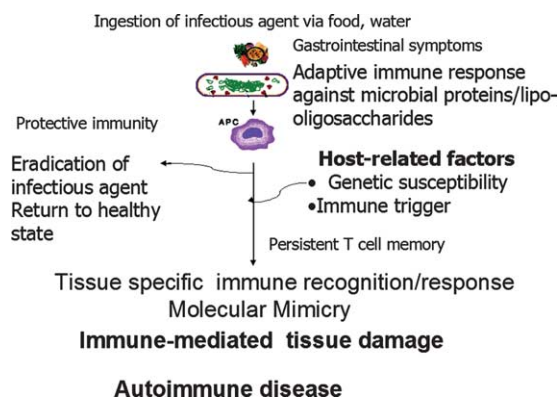


Fig. 1. Role of molecular mimicry in infection mediated autoimmune disease. Food-borne infection with bacteria leads to diarrhea. The host mounts an adaptive immune response towards bacterial antigens. Under the influence of host-related factors, such as polymorphisms in immune response genes and priming of the immune system by previous or concomitant infections, the immune response is diverted and high titer cross-reactive antibodies against bacterial antigens are produced. Abbreviations: APC, antigen presenting cell. (The schematic is adapted from [65].)

other surface proteins and a number of host proteins such as myosin, tropomyosin (TM), vimentin, and laminin have been described [21–24]. The initiation of an autoimmune response requires that the immune system receives two signals – one is antigen specific and the other is non-antigen specific. The antigen may be provided by a virus or a bacterium in molecular mimicry. Human populations that are exposed to high pathogen loads have a much lower incidence of autoimmunity than their ‘pathogen-free’ counterparts probably due to development of tolerance [25].

4. Is amino acid sequence similarity critical to molecular mimicry?

Antigenic mimicry was thought to be primarily limited to epitopes that shared a noticeable degree of chemical similarity; that is if they share significant homology [26]. Arguments for

Table 1
Examples of infectious etiology of some autoimmune diseases

Immune-mediated disease	Microbe/antigen	References
Graves' disease	Thyrotropin receptor	[9,10]
Ankylosing spondylitis	<i>Klebsiella pneumoniae</i> , pulD secretion protein (DRDE)	[11,12]
Systemic lupus erythematosus	Epstein–Barr virus nuclear antigen-1 (EBNA-1), PPPGMRPP	[13–15]
Insulin-dependent diabetes	Coxsackie virus B4, protein P2-c; cytomegalovirus, major DNA-binding protein rotaviruses, islet antigens (GAD 65, proinsulin carboxypeptidase H), α -TM	[16,17]
Behcet's syndrome		[54]
Lyme arthritis	<i>Borrelia burgdorferi</i> , OSP-A	[56]
Acute rheumatic fever	Group A streptococci, M-protein	[57]
Chagas' disease	<i>Trypanosoma cruzi</i> , B13 protein	[16,58]
Multiple sclerosis	Myelin proteins, corona, measles, mumps, EBV, Herpes, Chlamydia, etc.	[16,59–61]
Myocarditis	Coxsackie B3, streptococci, ADP/ATP carrier protein cardiac myosin	[62–66]
Guillain–Barré syndrome	<i>Campylobacter jejuni</i> , peripheral nerve gangliosides	[56,67–69]
Myasthenia gravis	Herpes, acetylcholine receptor	[70–72]
Celiac	Adenoviruses, enteric microbes, gliadin	[73,74]
Autoimmune uveitis	Viruses, S-antigen	[75]
Peptic ulcer/gastric CA	<i>H. pylori</i> , self-antigens on gastric mucosa	[76]
Primary biliary cirrhosis	Pyruvate dehydrogenase complex Anti-mitochondrial response HLA DR	[77]
Rasmussen's encephalitis	Microorganisms: <i>E. coli</i> , <i>S. cerevisiae</i> antilglutamate receptor (GLUR3) response	[78]
Rheumatoid arthritis	<i>Proteus mirabilis</i> , ESRRAL peptide	[6–8]

molecular mimicry are based on amino acid homologies identified from databases. There seems to be a view that topological considerations that invoke the classical examples of 'lock and key' mechanism are universal. The notion 'what fits, fits', irrespective of the sequence [27] suggests a possibility that conformational mimicry may be more relevant than antigen mimicry. However, the reality could be somewhere in between. The proposition that peptide sequence bears a signature for immune response and any other peptide that mimics its structure can elicit similar response seems to generate a debate much the same way as the suggestion by Anfinsen [28], when he suggested that the amino acid sequence of a protein dictates its three dimensional structure. In an interesting report, Jones et al. [29] catalogued human heat shock proteins that have similarity to known autoantigens suggesting that sequence similarity may be necessary but not a sufficient criteria.

It is a common fact that the sequence is critical for the functional three-dimensional structure of proteins, and chaperones aid the process of folding into functionally active structures. Similarly, it seems likely that while the amino acid sequence of peptide is important for immune response, the adjuvant, the immunological equivalents of chaperones, play crucial role in shaping the antigens to be immunogenic. The fact that microbial peptides with limited sequence homology with myelin basic protein can activate T cell response seems to suggest a possibility that molecular mimicry could include conformational mimicry as well [27]. On the other hand, significant sequence similarity could qualify a peptide/protein to be a better 'molecular mimic or a conformational mimic'. Two types of signals are important for the generation of immune response: (1) antigen specific recognition through T-cell and B cell receptors, and (2) a number of non-antigen specific non-clonal signals. It is possible that an infectious agent may provide the specific signals by molecular/conformational mimicry or release endogenous antigen. The microbial agents seems to trigger autoimmune response by providing adjuvant milieu in the form of upregulation of co-stimulatory molecules and other factors related to inflammation. For example, activation of antigen presenting cells during microbial infection upregulates co-stimulatory molecules and results in secretion of inflammatory cytokines.

5. Is ulcerative colitis an autoimmune disease?

The answer seems to be equivocal with suggestions and evidence on both sides. However, what seems to be unequivocal is that there may not be one single etiological factor responsible for the onset and perpetuation of the disease [30–32]. The fact that UC patients are prone to flare-ups suggest a possible role for bacteria in the disease process. Furthermore, as UC is a chronic disease as opposed to infectious colitis, it is tantalizing to postulate that the host immune system initiates a panic reaction due to signals emanating from bacteria because of 'shared molecular identity'. Are bacteria responsible for the pathogenesis of UC or do they take advantage of vulnerable immune system to initiate the disease process and generate symptoms. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are common in UC [33,34] and pANCA is recently shown to detect a protein epitope expressed by colonic bacteria and thus implicates colonic bacterial proteins as a target of the disease-associated immune response [35].

A destructive inflammatory response directed toward a self-antigen such as mucin, goblet cells, colonocytes and other cells has been proposed as the underlying basis of UC [36]. The role of mucosal dysfunction and environmental factors, including ubiquitous enteric bacteria in acute and chronic intestinal inflammation have been shown by transgenic and knock out rodent models [37–40]. The mechanisms by which microbes may play their role in the pathogenesis of UC, includes release of inflammatory mediators influencing critical cytokine responses [41,42] and possibly by mimicry related to autoimmunity [43]. The presence of anti-neutrophil cytoplasmic antibodies in about two thirds of the patients with UC as well as primary sclerosis cholangitis (PSC), supports autoimmunity in UC [44,45].

An important contribution in favor of the concept of autoimmune basis of UC is the observation that human TM isoform 5 (hTM5), a cytoplasmic protein which is predominantly expressed in the colon epithelial cells, is a potential autoantigen associated with UC [46–52]. However, its precise role in the pathogenesis of UC is yet to be established. If indeed, it is responsible for the pathogenesis of UC, is it responsible for the initiation of the disease and/or for its perpetuation or chronicity?

How do the host effector immune cells see it as an antigen? While these are some questions that need to be addressed, we ask if molecular mimicry involving bacterial sequences that resemble hTM5, is associated with any stage of UC.

6. Homologous peptides of hTM5 in bacteria

In pursuit of answers for this question, we looked for sequences in bacterial genomes that are homologous to hTM5. When we searched the NCBI database, we found two bacterial proteins that have regions of significant sequence homology with hTM5. One of them is a sensor protein, from *Bacillus cereus* [Accession No. NP_834548]. The other one is a hypothetical protein found in cyanobacteria *Nostoc punctiforme* [Direct submission to NCBI, Accession No. ZP_00112434]. While the sensor protein has a similarity with the C-terminal part of hTM5, the other protein resembles N-terminal part of hTM5 (Fig. 2). Interestingly, only the N-terminal and C-terminal peptides of hTM5 are found to have significant homology with these bacterial proteins. More interestingly, the sensor protein from *B. cereus* is identical to VanS sensor protein anthracis [53].

7. Does this sequence homology suggest any role for these bacteria in the disease process of UC?

Given the significant homology in the sequence of peptides from hTM5 with *Nostoc punctiforme* and *B. cereus*, it is



Fig. 2. Alignment of amino acid sequences of peptides from hTM5 with the uncharacterized protein from *Nostoc punctiforme* (A), and a sensor protein VanS from *Bacillus cereus* (B).

reasonable to postulate a role for molecular mimicry in UC. *B. cereus* is an opportunistic pathogen causing food poisoning manifested by diarrhoeal or emetic syndromes. It is closely related to the animal and human pathogen *Bacillus anthracis*. In addition to this, there is a suggestion that α -TM acts as an autoantigen in Bechet's syndrome in in vitro experiments and in animal models [54]. A structural analysis of 109 autoantigens involved in various autoimmune diseases showed that majority of them have significantly charged coiled-coiled helices. Interestingly, α -TM has the highest probability of forming coiled coil conformation and thus has a potential for autoantigenicity [55]. These considerations clearly suggest that hTM5 has the necessary sequence and structure to be potential molecular mimic in UC. However, sequence similarity may not be a sufficient condition to qualify TM5 as an initiator of UC. Therefore, we postulate that, perhaps, hTM5 may be associated with UC after the initiation stage caused by bacterial infection. As shown in Fig. 2B, the C-terminal part of hTM5 located between amino acids 188–213 is similar to the peptide region 120–145 amino acids of sensor protein from *B. cereus* and *B. anthracis*. In addition, to this, the N-terminal part of hTM5, spanning the amino acids 6–31, is similar to the peptide region 201–226 of a protein from *Nostoc punctiforme* (Fig. 2A). The shared epitopes in hTM5 and bacterial proteins described in the preceding text may therefore be involved in molecular mimicry. This is a provocative and testable hypothesis. We realize that our hypothesis is based on sequence similarity between hTM5 and bacterial proteins found in the NCBI database only and therefore, our results from the search for potential molecular mimics of hTM5, based on amino acid homology, represent a preliminary observation. An experimental verification of our hypothesis by studies focusing on specific immune responses in UC against these two peptides would be needed and are critical to establish molecular mimicry associated with hTM5 in UC.

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