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EDITORIAL

# Molecular mimicry in cutaneous autoimmune diseases

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## Abstract

The emulation of characteristics of a different organism to gain biological advantage is a common phenomenon in nature, described and defined with the term "mimicry" in the second half of the 19th century. In the last decades, mimicry at molecular level has been evidenced as a method used by several pathogen microrganisms to control metabolic functions of infected cells and elude host's immune system. Because of molecular mimicry, immune reactions against microbial molecules can turn against the mimicked self-molecules in predisposed subjects, leading to autoimmunity. This pathogenic mechanism, which gives a possible explanation for the specific epidemiological and chronological association between some infections and some autoimmune diseases, is well known and verified in many fields of medicine, but not adequately studied in dermatology: experimental data are available only for leprosy, atopic dermatitis, Behçet's disease, Vogt-Koyanagi-Harada syndrome and systemic erythematous lupus, while for few other diseases its role is hypothetical or suggested on the basis of single, small experiments or anecdotal reports. An overview of available data and hypotheses about the role of molecular mimicry in autoimmune cutaneous diseases is presented here, together with the perspectives offered by the use of bioinformatics and the personal experience of the author in this field.



**Key words:** Molecular mimicry; Dermatology; Autoimmunity; Bioinformatics; Amino acid sequence homology

**Core tip:** Molecular mimicry between microbial and human proteins is often used by pathogens to control biosynthetic/regulatory pathways of infected cells and elude immune reaction of host. In predisposed subjects, immune response against non-self molecules can, because of molecular mimicry, turn against self antigens and trigger autoimmune diseases. This mechanism, which explains the specific epidemiological link between some infections and some autoimmune diseases, is known and experimentally confirmed in several disciplines, but much less studied in dermatology. Bioinformatics can greatly help and boost research by quickly and almost inexpensively identifying molecules most probably involved in triggering autoimmunity *via* molecular mimicry.

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## MIMICRY IN NATURE

The first use of the term "mimicry" in biology dates back to 1862, when Henry Walter Bates[1] published the results of his studies on some species of the order *Lepidoptera* living in the Amazon valley. He reported that some species, belonging to different families, show unexpected similarities of the appearance of wings, and suggested a possible correlation between this phenomenon and natural selection. Indeed, some color patterns of wings allow predators to visually distinguish edible

from not edible preys. Based on this mechanism, Bates suggested that an edible prey showing the color pattern of a not edible species can significantly reduce the probabilities of being attacked, thus increasing the chances of survival.

The development of similar morphological characteristics in different organisms had been already noticed about one century earlier by Carl Nilsson Linnaeus, during his complex work of classification of known living species, and had been explained as a consequence of physical or biochemical interactions with the surrounding environment. The revolutionary element introduced by Bates was the demonstration that some prey-predator interactions occur exclusively through transmission of visual information, and that survival strategies of an organism can include transmission of deliberately false information about its identity or characteristics (the term used by Bates was actually "deception"). Subsequent studies have shown also the existence of acoustic, olfactory and behavioral mimicry in nature.

The so-called "Batesian mimicry" was only the beginning of a fascinating journey that led scientist to better understand the complexity of the interactions between living beings. Soon after his first discoveries, Bates found that some unrelated species, equally not edible for predators, also shared the same color pattern. This apparent contradiction was explained in 1878 by Müller[2] (hence, this kind of mimicry was defined "Mullerian mimicry"). Müller pointed out that predators learn that a prey is not edible by trial and error, and suggested that, in this case, mimicry is useful to equally split over many species, instead of only one, the number of individuals sacrificed for such learning process[2]. In 1968 Wolfang Wickler, concluding a work started by previous researchers, reported another type of mimicry, defined as "emsleyan" (in honor of M. G. Emsley[3], who first proposed it) or "mertensian" (in honor to R. Mertens)[4]. Mimicry is not used only for defensive purposes: some predators can mimic features of different species to deceive preys and capture them more easily ("aggressive mimicry")[5]. A particular type of Batesian mimicry has been defined as "automimicry": in this case, an individual shows characteristics of different individuals of the same species which are more often avoided by predators (a typical example is that of many bees and wasps, whose males, devoid of defensive systems, take the color pattern of females, which are dangerous for predators because of their sting)[6].

## MOLECULAR MIMICRY

Relatively recently, the progress of biology and laboratory techniques allowed to discover that mimicry is present in living organisms also at a molecular level, probably even more than at a macroscopic level. Circumscribing discussion only to human diseases, it must be pointed out that molecular mimicry has several peculiarities, because of the intrinsic complexity of host-pathogen interactions. During an infection, a pathogen is at the same time a "predator" of its host, but also a "prey" of the host's immune system; consequently, molecular mimicry between pathogens and hosts could be classified as aggressive mimicry (although atypical, because the mimicked model is also the prey) and, at the same time, as Batesian mimicry. Moreover, pathogens use hosts' resources to live and replicate, and molecular mimicry is used to control such resources rather than just killing the host.

Typically, microrganisms are able to synthesize proteins similar to those that are involved, in humans, in the regulation of fundamental processes such as apoptosis, cell proliferation, inflammation and immune response. In this way, they can "hijack" and modulate these mechanisms to their advantage.

In the dermatologic field, one of the most studied examples is that of HHV8 (human herpesvirus 8), which is notoriously linked to Kaposi's sarcoma. This virus extensively exploits molecular mimicry and can interact with cells at multiple levels. The viral genetic loci ORFK12 and ORFK72 produce v-FLIP and v-cyc-D, viral homologs of the human proteins FLIP and cyclin D, respectively. FLIP (FLICE Inhibiting Protein) prevents cell apoptosis mediated by tumor necrosis factor α and Fas-ligand, by inhibiting FLICE (Fas-associated death domain-like interleukin 1 beta-converting enzyme), while cyclin D activates kinases cdk4 and cdk6, thus inducing phosphorilation and inactivation of pRb, a protein which is able to stop the G1 phase of the cell cycle in case of DNA damage[7,8]. Additionally, HHV8 produces a homolog of human Bcl-2 (a protein which inhibits Bax-induced apoptosis) and human IRF (Interferon Regulating Factor), and can also switch immune response from Th1 to Th2 type through homologs of human interleukin 6 and macrophage inhibiting protein Ⅰ, Ⅱ and Ⅲ[8].

## MOLECULAR MIMICRY AND AUTOIMMUNITY

The frequent and specific epidemiological association between some infections and some autoimmune diseases was already highlighted several decades ago: the most famous examples are probably diabetes, autoimmune thyroiditis, multiple sclerosis and, in dermatology, systemic erythematous lupus, vitiligo, scleroderma, lichen sclerosus, chronic atrophic acrodermatitis[9]. The hypothesis that similarities between molecules of different nature could be a cause of autoimmunity was proposed in 1976 by Shapiro *et al*[10], who also created and introduced, in the same paper, the term "molecular mimicry". With rare exceptions, technical limits prevented almost completely experimental tests on this theory for about 20 years. Starting from mid-1990s, thanks to the simultaneous "coming of age" of new laboratory techniques for production and analysis of biomolecules, high-power and low-cost computers and worldwide informatic networks, a significant increase of research on molecular mimicry has become possible, and produced several

confirmations of the hypothesis proposed by Shapiro and colleagues, explaining its pathogenic mechanism.

It is well known that mounting a specific immune response requires antigen presentation by APCs (Antigen Presenting Cells) to T cells. More in detail, an antigen fragment is presented in the context of an MHC (Major Histocompatibility Complex) molecule present on APC surface, and the MHC-antigen fragment complex is recognized by a TCR (T-Cell Receptor) molecule on T cell surface. Physical and biochemical complementarity of the above three components (MHC, antigen fragment, TCR) is necessary for immune activation, and this guarantees the specificity of the response. However, the number of possible antigen fragments is between $10^{12}$ and $10^{15}$, while the size of the human T cell repertoire is around $10^{8}$. Thus, the antigen recognition mechanism has a certain degree of flexibility: a T cell clone can recognize several antigens which share some characteristics. This makes the system efficient even in case of many possible mutations of microbial antigens, and allows response not only against a single pathogen, but against all pathogens which possess similar antigens[11].

On the other hand, the flexibility of the antigen recognition system is the basis for possible development of autoimmunity *via* molecular mimicry. When a sufficiently high degree of similarity exists between a microbial and a human protein, the immune system of certain subjects can be unable to distinguish them, and an immune response mounted against the microbial antigen for defensive purposes can turn against the self antigen, and persist indefinitely even after resolution of the initial infectious process.

The frequency of autoimmune diseases in epidemiological studies is much lower than that expected on the basis of the aforementioned figures, suggesting the existence of control systems which decrease the risk of autoimmune reactions. Deletion of autoreactive T cell clones has been considered for a long time the main control mechanism, but modern studies suggest that its importance is limited: only the most dangerous clones are actually deleted, leaving many potential autoreactive ones in the available T cell repertoire. Other, quantitatively more important mechanisms are peripheral induction of T cell apoptosis, induction of anergy, action of regulatory T cells. Immunological cross-reactivity between two molecules is clearly not sufficient for the induction of autoimmune diseases: a simultaneous dysregulation of control mechanisms is necessary. This can occur because of complex and not yet completely understood combinations of genetic and environmental factors, including the immune system alterations induced by infectious microrganisms (directly and/or, again, *via* molecular mimicry).

## MOLECULAR MIMICRY IN DERMATOLOGY

Commonly accepted as a trigger of autoimmunity in many fields of medicine[12-30], molecular mimicry is less known in dermatology, and only few experimental studies on its role in autoimmune cutaneous diseases are available. Indeed, when mentioned, molecular mimicry is often only postulated as a possible explanation for the onset of autoimmunity after some infections, without any *in vivo*, *in vitro*, computational or even theoretical data about the molecules possibly involved.

In a search on the PubMed database (http://www.pubmed.gov), the first paper of dermatological interest on molecular mimicry dates back to 1992, when Muryoi *et al*[31] studying anti-topoisomerase I antibodies from scleroderma patients, demonstrated homology between the human autoantigen and the UL70 protein of cytomegalovirus and suggested in their conclusions that "activation of autoreactive B cell clones by molecular mimicry is possible". After that paper, attention was focused on several skin diseases, but often anecdotally and with contrasting results.

### Leprosy

Experimental data of "molecular mimicry reactions between cytoskeletal proteins, host stress proteins and *Mycobacterium leprae* antigens or stress proteins" were presented by Kroumpouzos *et al*[32] about 20 years ago. More recently, Singh and collaborators have confirmed those results, and, thanks to the progress in laboratory techniques, have been able to specify the molecules involved, *i.e.*, heat shock protein 65 (hsp65) of *Mycobacterium leprae* and human cytokeratin-10, which share seven epitopes[33]. This may not be the only cross-reactivity relevant for this disease: indeed, Rambukkana *et al*[34], in 1992, identified an epitope common to mycobacterial hsp65 and human cytokeratin 1/2.

### Psoriasis

Mainly because of the striking association of certain forms of the disease with streptococcal infection, many of the dermatological studies on molecular mimicry have focused on psoriasis, but with controversial results. As described in a paper by Noah *et al*[35] the skin basement membrane zone is a depository for at least one circulating streptococcal antigen, which is largely present there in lesional skin and, to a lesser extent, in non lesional skin of psoriatic patients, but absent in the skin of healthy subjects. It is also known that *Streptococcus pyogenes* DNA can be detected in tissues of patients affected by plaque psoriasis[36], and T cells able to recognize determinants common to streptococcal M-protein and keratin can be found in patients' blood[37], but this is not sufficient to explain disease onset in the majority of cases[38,39]. Other microrganisms postulated as possible triggers of psoriasis *via* molecular mimicry are cytomegalovirus and human herpesviruses 6 and 7, but the only experimental study on them, performed on a small sample of 10 patients, did not show sufficient evidence to confirm such hypothesis[40].

### Atopic dermatitis

At the end of 1990s, Valenta *et al*[41] introduced the idea of autoallergy, *i.e.*, IgE-mediated reactivity against self antigens, as a pathogenic factor in atopic dermatitis. Suc-

cessive studies by that and other workgroups not only confirmed the correctness of the original idea, but also showed that in some cases autoallergy can be induced by molecular mimicry between autoallergens and allergens produced by fungal species living on human skin and particularly abundant in atopic subjects[42].

### Urticaria

The discovery of histamine-releasing autoantibodies against Fc epsilon receptor 1 or IgE in a remarkable percentage of patients affected by chronic idiopathic urticaria led some researchers to hypothesize a possible role of molecular mimicry in this condition[43]. Many microrganisms have been suspected as potential triggers, but only anecdotal reports exist to date, and, from an evidence-based viewpoint, arguments in favor of this theory are weak[44]. This does not rule out the possibility of a link, but suggests the need for further studies on this topic.

### Behçet's disease

Multisystem inflammatory disorder which is epidemiologically associated to microbial infections, Behçet's disease appears as an ideal candidate to demonstrate the role of molecular mimicry in the pathogenesis of cutaneous autoimmune diseases. As suggested in a recent review, known potential triggers include *Saccharomyces cerevisiae*, mycobacteria, *Borrelia burgdorferi*, *Helicobacter pylori*, *Escherichia coli*, *Staphylococcus aureus*, *Mycoplasma fermentans*, *Streptococcus sanguinis*, herpes simplex virus-1, hepatitis C virus, parvovirus B19, cytomegalovirus, Epstein-Barr virus and varicella zoster virus[45]. However, no experimental evidence of molecular mimicry with human autoantigens is currently available. In 1997, Sakane *et al*[46] postulated that the autoantigen targeted by autoreactive T-cells cross-reacting with microbial antigens could be heat shock protein 60 (hsp60). Recently, Ghasemi *et al*[47] showed that human hsp60 shares significant homology, in particular for which concerns some segments known as epitopes, with hsp60 proteins produced by many bacteria epidemiologically associated to Behçet's disease: this provides a theoretical basis for the above hypothesis and suggests a path for future *in vitro* and *in vivo* research.

### Systemic lupus erythematosus

The involvement of molecular mimicry in the pathogenesis of this systemic disease with cutaneous manifestations is experimentally and clinically well studied. As outlined in a 2008 review by Doria *et al*[48], "molecular mimicry, especially between Sm or Ro autoantigens and EBV Nuclear Antigen-1 response, as well as the overexpression of type 1 INF genes are among the major contributors to SLE development".

### Other autoimmune cutaneous diseases

Some experimental data show the involvement of molecular mimicry in Vogt-Koyanagi-Harada syndrome, graft-versus-host disease and pemphigus. As discovered by Sugita, T cells specific for tyrosinase can also recognize the cytomegalovirus envelope glycoprotein H, and this can explain the reported association between cytomegalovirus infection and Vogt-Koyanagi-Harada syndrome[49]. Another product of the same virus, namely the protein UL94, is cross-reactive with the cell surface tetraspanin transmembrane 4 superfamily member 7 (TM4SF7 or NAG-2) human molecule and can constitute the trigger for the onset of scleroderma-like skin lesions in chronic graft-versus-host disease in allogeneic stem-cell transplant patients[50]. The case of pemphigus is rather peculiar, because the molecular homology found by Gilbert *et al*[51] is not between a self and a non-self antigen, but between the human monoclonal antibody F12 and the adhesion molecules desmoglein 1 and bullous pemphigoid antigen 2.

Molecular mimicry has also been postulated as a possible cause of herpes simplex virus-associated erythema multiforme, by Aurelian *et al*[52], sarcoidosis, by Tchernev *et al*[53], and -on the basis of single case reports- alopecia areata associated with gastric *Helicobacter pylori* infection[54], and vitiligo developing around nodular lesions of Kaposi's sarcoma in a patient with acquired immunodeficiency syndrome[55].

## BIOINFORMATICS AND MOLECULAR MIMICRY

As previously mentioned in this article, the remarkable progress in research on molecular mimicry is the result of the simultaneous development and the interaction between two disciplines traditionally considered "distant", such as biology and informatics. After many years of pilot studies, bioinformatics has finally become an integral part of the modern set of research tools, particularly in some fields.

The high level of complexity of living organisms, determined by multiple, multifactorial and only partially known concurring events, can not be currently emulated or represented by any software or mathematical model; consequently, *in vivo* and/or *in vitro* experiments are still the essential part of research in any field of biology. However, when studying molecular mimicry, bioinformatic techniques allow quick and almost inexpensive analysis of a large number of microbial and self antigens, identifying the most probably cross-reactive ones and, in some cases, even the epitopes possibly involved. Such data are useful to better focus time and resources when performing traditional experiments.

One of the first bioinformatic techniques in this field, and still among the most used ones, is the analysis of homologies between amino acid sequences. A complete definition of the statistical methods needed for such analysis was published in 1997 by Altschul *et al*[56], authors of the software BLAST (Basic Local Alignment Search Tool). Originally created for the study of "evolutionary distance" between organisms, BLAST has been successfully used to define the probable function

of newly discovered proteins and to identify potential cross-reactive segments of different proteins.

Less common, but very interesting, are the softwares able to detect the presence, in the sequence of a protein, of amino acid "motifs" that determine the binding of a peptide to a specific MHC (Major Histocompatibility Complex) molecule for presentation to the immune system. When such motifs are contained in homologous segments of microbial and self antigens, higher probability exists that such homology is pathogenically relevant; this could also explain, at least in part, the increased risk for certain autoimmune diseases in subjects who possess specific HLA (Human Leukocyte Antigen) genes.

Last in chronological order of development, but certainly not in importance, are some more sophisticated softwares able to predict secondary and tertiary structure of molecules, as well as their reciprocal interactions. These softwares can improve our understanding of immune phenomena, and, in the field of molecular mimicry, allow identification of cross-reactivity due to non-linear epitopes (epitopes formed by parts of a protein which are distant in the linear sequence, but close to each other in the actual three-dimensional structure). Mainly because of the high computational resources needed, this kind of bioinformatic analysis has been used only by some Centers, but the continuous progress of informatic technology should allow a larger diffusion in relatively short times[11].

Use of bioinformatic tools could be a relatively easy way to boost research on molecular mimicry in dermatology. Studies performed and published by our workgroup in this field concern: (1) the possible correlation of lichen sclerosus, borreliosis and Hashimoto's thyroiditis; (2) autoimmune diseases characterized by anti-Ku autoantibodies; and (3) atopic dermatitis.

The idea of a possible correlation of lichen sclerosus, borreliosis and Hashimoto's thyroiditis originated by our observation of a woman affected by lichen sclerosus and seropositive (IgG and IgM) for *Borrelia burgdorferi*, who developed Hashimoto's thyroiditis three months after the onset of the autoimmune cutaneous disease[57]. Based on that hypothesis, we initially used BLAST to search for amino acid sequence homologies of the four known thyroid autoantigens -thyroid stimulating hormone receptor (TSH-R), thyroid peroxidase (TPO), thyroglobulin (Tg) and sodium-iodide symporter (NIS)- with the 6606 proteins of *Borrelia* known at that time. We found 16 significant homologies, of which 5 for TSH-R, 2 for Tg, 3 for TPO and 6 for NIS; all of them concerned protein sequences known as autoepitopes[29]. Successively, we found that human thyroid autoantigens and proteins of Yersinia and Borrelia share amino acid sequence homology that includes binding motifs to HLA-DR molecules and T-cell receptor[30]. In that occasion, to find HLA binding motifs we developed the first version of our program MotiFinder, which was later improved to become a general purpose pattern search software[58]. In the last phase of our study, we evaluated the similarity between *Borrelia* proteins and the human ECM-1 protein (Extra Cellular Matrix protein 1), which is the autoantigen involved in lichen sclerosus: in this case, 18 bacterial proteins with significant primary sequence homology were identified. We also searched the potentially cross-reactive microbial and human proteins found in all the above researches for the binding motif of MHC molecules encoded by the HLA-DQ7 allele, which is reported in literature as a risk factor for both Hashimoto's thyroiditis and lichen sclerosus: this motif was present in all but one of the proteins examined, thus supporting the idea that, in some genetically predisposed subjects, *Borrelia* infection can be the trigger of Hashimoto's thyroiditis and/or lichen sclerosus[59].

The Ku protein is a heterodimer made of two subunits, p70 and p80, is part of a group of DNA-associated nuclear proteins and plays a key role in fundamental processes like DNA repair, maintaining of chromosomal stability and regulation of transcription and V(D)J recombination, particularly in conditions of cell stress. Anti-Ku autoantibodies are found in some patients with systemic erythematous lupus and related diseases and in about 5% of scleroderma patients; in this latter case, they are strongly suggestive of a systemic sclerosis/polymyositis overlap syndrome[9]. In 1992, Reeves suggested the possible role of molecular mimicry in the etiopathogenesis of anti-Ku autoimmunity[60]. Using *in silico* techniques, we verified the potential cross-reactivity of the two Ku subunits with bacterial ($n$ = 5229868 at the time of our search), viral ($n$ = 629582) and fungal ($n$ = 511126) proteins. The results are an excellent example of the possibilities of bioinformatics: in few minutes of elaboration, we found that only 14 proteins out of the more than 6300000 examined have significant homology with the p70 subunit and 12 with the p80 subunit of Ku. These proteins, all belonging to fungal species which are known as human pathogens, should be considered primary targets of experimental research in this field. Additionally, we found that homologous segments overlapped totally or, in one case, partially, with at least one of the sequences of p70/p80 that contain T-cell autoepitopes[61].

Concerning atopic dermatitis, the role played by molecular mimicry in determining the so-called "autoallergy", *i.e.*, IgE-mediated autoimmunity, has been demonstrated in 2005 by Schmid-Grendelmeier *et al*[42]. These researchers showed that the fungal allergen Mala s 11 of *Malassezia sympodialis*, a common component of the cutaneous flora, can trigger IgE response against the highly similar human protein manganese superoxide dismutase, and a similar response can be induced by allergen Asp f 6 of *Aspergillus fumigatus*. We used bioinformatic tools to verify whether other allergens could play a role similar to that of Mala s 11 and Asp f 6 *via* molecular mimicry. A BLAST analysis allowed us to discover a single allergen, in addition to the aforementioned ones, significantly homologous to human manganese superoxide dismutase,

namely Hev b 10 of *Hevea brasiliensis* (better known as "latex tree")[62]. Indeed, the level of homology to the autoallergen is in this case even higher than that of Mala s 11 and Asp f 6, and a three-dimensional model of the proteins, created with the software SWISS-MODEL[63], confirmed that this is true even for which concerns solvent-exposed residues[62]. Experimental studies are currently in progress to verify whether such homology is pathogenically relevant for atopic dermatitis.

## CONCLUSION

The full understanding of the mechanisms underlying the development of autoimmunity is a fundamental target of basic and clinical research, not only for its scientific relevance, but also for its possible therapeutic applications: indeed, knowledge and control of the key points of the pathway which leads to autoimmune diseases could allow a really "etiological" treatment of such diseases, with significant progress also in the treatment of immunodeficiency syndromes and tumors.

Induction of autoimmunity is a complex and largely unknown process, which requires a precisely synchronized multi-step interaction of several predisposing and environmental factors. In such contest, it would be obviously rather simplistic to think of molecular mimicry as the only cause of all autoimmune diseases: indeed, infections are a trigger in a small number of cases, and possession of specific HLA haplotypes is not a sufficient explanation. However, research in this field is worth to be performed, because it could shed a new light on our understanding of autoimmunity: molecular mimicry certainly plays its role at the initial stages of the pathway(s) leading to autoimmunity, and could be at least one of the key elements/events which break the equilibrium of the immune system, somehow maintained by the organism until a given moment, and, interacting with genetic factors, transform predisposition into actual disease.

Bioinformatic tools can be particularly useful to promote, improve and accelerate research on molecular mimicry, particularly in disciplines like dermatology, where it has not yet been adequately studied: such tools can quickly and almost inexpensively identify molecules worth of further investigation with laboratory and clinical techniques, and, in a next future, could help to design therapeutic and/or preventive strategies aimed to the real causes of autoimmune diseases.

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