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# Disease mimicry—a pathogenetic concept for T cell-mediated autoimmune disorders triggered by molecular mimicry?

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**Abstract**

Molecular mimicry is considered as a mechanism by which infectious pathogens may break immunological tolerance and cause autoimmune disease. It implicates that peptides shared between pathogen and host may induce cross-reactive immune reactions. According to this hypothesis, the resulting autoimmune response actually represents a secondary immune response. It is mediated by cross-reactive T cells that have been educated in a primary immune response against a particular pathogen. Using psoriasis vulgaris as a model, this article discusses the potential functional consequences molecular mimicry should have for the resulting autoimmune disease. It proposes that due to the functional memory of T cells, which is an integral feature of adaptive immunity, the phenotype of an autoimmune disease induced by molecular mimicry should reflect the immune mechanisms raised in the primary immune response. This process might be called 'disease mimicry'.


*Keywords:* Molecular mimicry; Disease mimicry; Psoriasis; Bacterial trigger; Autoimmunity

## 1. Introduction

The development of many T cell-mediated autoimmune disorders has been etiologically linked to infectious agents. A model proposed to account for this link is molecular mimicry [1]. It suggests that pathogen expresses a stretch of protein that shares antigenic structures with host tissue. If this pathogen-encoded epitope is presented by the major histocompatibility complex, it may activate potentially self-reactive T cells. As a consequence, the tolerance to autoantigens breaks down and the pathogen-specific immune response cross-reacts with host structures to cause tissue damage and disease.

This model provides a highly attractive explanation of how infection breaks tolerance, and it has been linked to the pathogenesis of several autoimmune disorders [2]. Molecular mimicry, however, bears another intriguing aspect that so far has not received attention. In addition to providing the trigger for autoimmunity, it should crucially affect the particular type of the subsequent autoimmune tissue reaction. The reason for this is that an autoimmune response resulting from molecular mimicry actually represents a *secondary*

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*immune response*. The autoreactive T cells become activated against self-antigens after having been primed against an infectious agent [3].

Primary immune responses induce differentiation of naive T cells into specialized regulatory or effector T cell subsets [4] that acquire a particular cytokine pattern and perform select functions. Completion of regulatory or effector functions is accompanied by development of memory T cells. Upon reactivation during secondary responses these memory T cells recall their formerly instructed phenotype and display the functional properties they had acquired during the priming process [5]. This functional memory allows rapid and appropriate protective immune responses to antigen re-exposure. Together with antigen specificity, functional memory is considered as a fundamental principle of specific immunity.

## 2. The concept of disease mimicry

Functional T cell memory should have major pathophysiological consequences when a bacterial or viral pathogen activates cross-reactive T cells. Upon reactivation against self-antigens these T cells should display those particular functional properties they had acquired against the causative pathogen. As a consequence an autoimmune disease resulting from molecular mimicry should resemble the immune mechanisms raised during the priming event. For example, if a virus induces a cytotoxic immune response the autoimmune disorder resulting from molecular mimicry should be characterized by self-reactive cytotoxic mechanisms and subsequent tissue destruction. This process might be called disease mimicry. The concept of disease mimicry proposes that when molecular mimicry triggers autoimmunity features of the primary protective anti-pathogen immune response are reflected by the following secondary autoimmune response. It requires that both the mimicking and the autologous peptide act as a full T cell receptor (TCR) agonist [6]. This has been shown for several naturally occurring mimicking peptide ligands from bacterial and viral antigens [7,8]. Crystal structure analysis of mimicking peptides complexed with an MHC-molecule has furthermore provided a structural basis for the role of molecular mimicry in stimulating cross-reactive TCRs [9].

A T cell-mediated autoimmune disorder obeying to the principles of disease mimicry should meet several criteria:

1. Primary manifestation of the autoimmune disorder should be preceded by infection with a defined pathogen.
2. The tissue alterations of the autoimmune disease should resemble the defense mechanisms raised against the infectious pathogen but should occur in its obvious absence.
3. The autoimmune tissue changes should be mediated by T cells.
4. The pathogenic T cell response should be antigen-specific.
5. Proteins of the inducing pathogen and the affected organ should share common epitopes as targets of the cross-reactive T cell response (actually molecular mimicry).

## 3. Psoriasis vulgaris: paradigm of disease mimicry

A disorder, which might serve as paradigm for disease mimicry is psoriasis vulgaris. Psoriasis represents an HLA-associated T cell mediated skin disease that affects 1.5–2% in the Caucasian population. It is often characterized by lifelong relapsing skin inflammation with intense scaling that may be accompanied by arthritis. In the majority of patients, first psoriasis manifestations are induced by streptococcal angina. A conclusive, fully convincing concept of psoriasis pathogenesis is still missing. When applying the above-mentioned criteria of disease mimicry, however, psoriasis becomes easily comprehensible as a sterile antibacterial skin reaction mediated by cross-reactive antibacterial T cells.

### *3.1. Criterion 1. Psoriasis is induced by infection with group A β-hemolytic streptococci*

In the majority of patients first psoriasis manifestation is triggered by tonsillar infection with *Streptococcus pyogenes* (group A β-hemolytic streptococci). Streptococci are gram-positive bacteria that induce a typical suppurative anti-micro-

bial tissue reaction with diffuse or abscess-like accumulation of neutrophilic granulocytes and lympho-histiocytic infiltrates [10]. The incidence of preceding streptococcal infections in psoriasis ranges between ~60 and 97% [11]. The association of streptococcal infection with particular subtypes of psoriasis implies an inherited susceptibility of a distinct immune response pattern to streptococcal antigens as a key to understanding psoriasis pathogenesis [12].

### *3.2. Criterion 2. Psoriasis resembles an anti-microbial tissue reaction*

Fact is that in many patients with a latency of usually two-to-three weeks streptococcal throat infections are followed by a typical, complex and highly characteristic skin inflammation that contains central aspects of an anti-microbial skin reaction. These include: excessive epithelial hyperplasia with intense desquamation which may be considered as an expulsive mechanism of epithelial surfaces to combat microbial invasion [13]; Production of human beta defensins that are anti-bacterial, keratinocyte-derived peptides [14]; Increased numbers of mast cells [15] that hold a pivotal position in anti-bacterial defense reactions [16]; And infiltration of neutrophilic granulocytes that are potent anti-microbial phagocytes. Neutrophils accumulate in the upper epidermal layers, may form intraepithelial microabscesses or macroscopic visible pustules and are considered pathognomonic for psoriasis.

Despite this array of anti-microbial measures, no causative pathogenic bacteria can be detected in psoriatic skin lesions [17]. Furthermore, once triggered the psoriatic skin reaction will become independent of the inducing streptococcal throat infection, and it resists all anti-microbial treatments. Thus, psoriasis can be considered as a sequel to streptococcal throat infection that resembles the anti-microbial tissue reaction against the triggering pathogen but occurs at a timely and local distance from the infection in the absence of the causative bacteria.

### *3.3. Criterion 3. Psoriasis is mediated by T cells*

Psoriatic skin lesions contain a dense mononuclear infiltrate with numerous activated T cells. Several recent observations suggest that these T cells may constitute the link between streptococcal tonsillitis and psoriatic skin manifestations. Immunosuppressive regimens may efficiently improve psoriasis (summarized in [18]). Only activated T cells from psoriasis patients but not healthy controls were capable of inducing alterations typical of psoriasis when injected into human skin samples transplanted on SCID mice [19]. T cell clones established from psoriatic skin lesions had the select capacity of enhancing keratinocyte proliferation in vitro [20]. This effect was mediated by a Th1-like cytokine pattern. It includes cytokines such as IFN-γ, TNF-α, TNF-β, IL-3 and IL-5 in the absence of IL-4 that may also induce other features of psoriasis [21]. Vice versa, therapeutic application of the Th2-cytokines IL-4 or IL-10 that antagonize Th1-cells may improve psoriasis significantly [22,23]. The efficacy of various T cell selective treatment approaches currently under development corroborates the pathogenic relevance of T cells in psoriasis further [18].

### *3.4. Criterion 4. The lesional psoriatic T cell response is antigen-specific*

Recognizing psoriasis as a T cell-mediated skin disease raised the need for clarifying how the T cells become activated within the skin of patients to initiate psoriatic lesions. Molecular analysis of the TCR usage of the inflammatory psoriatic T cell infiltrate has provided strong evidence in favour of an antigen-driven lesional T cell response. Various studies demonstrated that the lesional TCR usage is highly restricted, with repetitive TCR rearrangements being reflected by the presence of clonally expanded T cell populations [24,25]. The same clonal T cell populations and repetitive TCR rearrangements were associated with the lesional psoriatic immune response over prolonged periods of time and in relapsing disease [25,26]. These results emphasize that the psoriatic immune response involves a restricted subset of clonally expanded T cells. It apparently becomes activated by antigens that are continuously present within psoriatic skin, and it shows no signs of epitope spreading [26]. Instead, identification of a conserved T cell receptor β-chain CDR3-motif

within skin lesions from different patients suggested that the psoriatic immune response is not only preserved within individual patients but that a common psoriasis antigen may be driving responses in different patients [27].

### *3.5. Criterion 5. Streptococci share common epitopes with keratinocyte proteins*

Molecular mimicry between proteins from streptococci and keratinocytes may provide a clue for the identification of the yet unknown psoriatic antigens. Common epitopes of streptococcal antigens and keratinocyte proteins were demonstrated by cross-reactive monoclonal antibodies. Database searches identified not only amino acid sequence homologies of streptococcal M proteins and keratin 6, but also other keratins [28]. Peripheral blood T cells of psoriasis patients but not healthy controls responded to several synthetic peptides corresponding to these homologous regions, when tested in vitro [29]. By these homologies not only M-proteins but also other streptococcal antigens might have the capacity to direct a primary anti-streptococcal T cell response occurring in the tonsils towards homologous organ-specific peptides presented in the skin. In support of this hypothesis increased frequencies of streptococci-specific T cells were identified in psoriatic skin lesions [30]. Furthermore, we were able to identify the clonal TCR rearrangements from psoriatic skin lesions within the small fraction of tonsillar T cells that express the skin homing receptor CLA (cutaneous lymphocyte-associated antigen) and are destined to enter the skin [31]. Thus, psoriasis may be considered as a T cell-mediated autoimmune disease resulting from a cross-reactive immune response based on molecular mimicry.

## 4. Psoriasis—a sterile anti-bacterial skin reaction mediated by an autoreactive subset of regulatory T cells?

In order to understand the particular phenotype of psoriasis it is necessary to recall the role of T cells in the host response to bacteria. Protective anti-microbial immunity involves specialized anti-microbial T cells that belong to the Th1 subset [32]. These T cells elicit phagocyte-mediated defense against infections by secreting cytokines such as IFN-γ and TNF-β that promote the ability of macrophages to phagocytose and destroy microbes. They control influx of macrophages and neutrophils in late primary or early secondary mycobacterial infections [33], and they are integrally involved in granuloma formation [34]. In murine leishmania infection Th1 T cells regulate the recruitment of neutrophilic granulocytes and formation of abscesses in the liver [35]. Another T cell-dependent effect in anti-microbial defense is epithelial hyperplasia [36,37]. Thus, anti-microbial T cells are regulatory T cells that may initiate and coordinate other cell populations to perform tissue-specific expulsive, phagocytic and microbicidal effector mechanisms.

According to the hypothesis of molecular mimicry between proteins from *S. pyogenes* and keratinocytes the pathogenic psoriatic T cells were originally primed against streptococcal antigens. During this process they should have acquired the functional properties of antibacterial T cells. When adapting to the principle of immunological memory, reactivation of these T cells in a secondary immune response against homologous self-antigens in the skin should set off their particular functional properties and finally result in a T cell-coordinated anti-bacterial tissue response. Although being self-reactive this type of T cell response would not induce tissue destruction but rather provoke functional tissue alterations. And indeed, despite the lack of causative bacteria the psoriatic skin changes bear central aspects of an anti-microbial defense reaction, with expulsive hyperproliferation of keratinocytes, accumulation of phagocytes and production of β-defensins being induced by T cells. When integrated into the pathogenetic concept of disease mimicry psoriasis might therefore essentially be interpreted as a sterile anti-bacterial skin reaction triggered by molecular mimicry. It seems to be mediated by a particular regulatory subset of cross-reactive anti-bacterial T cells, and the features of the triggering anti-bacterial immune response are fully reflected by the resulting autoimmune disease.

## 5. Conclusions

The concept of disease mimicry as a functional consequence of molecular mimicry is based on the assumption that once having differentiated, T cells retain their functional properties upon reactivation. It could provide a basis to re-evaluate and explain the pathogenesis and phenotype also of other autoimmune disorders such as Reiter's disease, multiple sclerosis or rheumatic fever in which molecular mimicry is a suspected triggering event. To what degree the original immune response is actually reflected by the autoimmune tissue reaction, however, may depend on various aspects such as the mimicking peptide ligand or the capacity of the affected target organ to respond appropriately to the regulatory effects of the self reactive T cells. Furthermore, simultaneous presence of both pathogenic cross-reactive antibodies and T cells might mask a particular type of T cell-mediated tissue reaction. At least for psoriasis, however, disease mimicry would integrate all the different and seemingly unrelated disease features into a conclusive pathogenetic concept.

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**Take-home messages:**

- T cell mediated autoimmune disorders induced by molecular mimicry represent secondary immune responses mediated by cross-reactive autoimmune T cells that have acquired their functional properties in a primary triggering immune response against an infectious pathogen.
- The concept of disease mimicry implies that due to the functional memory of T cells the phenotype of an autoimmune disease induced by molecular mimicry should reflect the immune mechanisms raised in the primary immune response against the triggering infectious pathogen.
- The concept of disease mimicry may explain the particular phenotype of T cell mediated autoimmune disorders such as psoriasis vulgaris, rheumatic fever or Reiter's disease

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## *The World of Autoimmunity; Literature Synopsis*

**Antibodies to L-periaxin and peripheral neuropathy**

L-periaxin is a protein localized to Schwann cells, and also plays a role in stabilization of mature myelin in peripheral nerves. Autoantibodies to L-periaxin were found in the minority of patients with diabetes mellitus-associated neuropathy and IgG monoclonal gammopathy of undetermined significance neuropathy. Intraneural injection of these antibodies into the endoneurium of rat sciatic nerves significantly attenuated sensory-evoked (but not motor-evoked) muscle action potential amplitudes. This effect could not be induced by sera from control subjects. The injected nerves had morphologic features of demyelination and axon enlargement. These results support a pathogenic effect of anti-L-periaxin antibodies in causing peripheral neuropathy in the minority of patients with diabetes mellitus and IgG monoclonal gammopathy of undetermined significance (Lawlor et al. J Neurochem 2002;83:592).