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Review

# Psoriasis and autoimmunity☆

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ABSTRACT

Psoriasis is one of the most common chronic inflammatory human skin diseases. Though clinically well characterized, the exact etiological and pathogenic mechanisms are still not known in detail. Current knowledge indicates distinct overlap to other inflammatory as well as autoimmune disorders. However, the one or more relevant autoantigens could not be characterized so-far. On the other side, several autoimmune diseases were shown to be associated with psoriasis. In addition, serological autoimmune phenomena, namely diverse circulating specific autoantibodies could be demonstrated in the past. A matter of current debate is if psoriasis is a primary autoimmune disease or secondarily evolving into autoimmunity as seen in other chronic inflammatory diseases. Related to this aspect is the concept of autoinflammation versus autoimmunity where psoriasis shares mechanisms of both entities. Though T-cells remain among the most important cellular players in the pathogenesis of psoriasis and current therapeutic strategies successfully target these cells or their products irrespective of these concepts, autoimmunity if relevant will add to the treatment armamentarium by using protective and prophylactic antigen-specific modalities.



**Contents**



## 1. Introduction

Psoriasis is a common chronic inflammatory skin disease with characteristic, sharply demarcated erythematosquamous plaques restricted to distinct sites or disseminated over the skin surface [1]. In addition to the well-appreciated psoriatic arthritis it may be accompanied by a number of diseases to result in the clinical phenomenon of comorbidity which is shared with other chronic inflammatory diseases like rheumatoid arthritis. These diseases comprise the metabolic syndrome and (resulting) cardiovascular diseases as well as depressions causing increased morbidity and mortality among psoriatic patients [2,3]. They seem to result from a specific chronic inflammatory psoriatic process by the action of various mediators like TNFα or may be mediated by shared pathogenic mechanisms [4].

In addition, various autoimmune diseases have been described as associated and psoriasis itself has been suggested an autoimmune disease [5,6]. However, clear-cut relations to other autoimmune disorders as well as the one or more distinct autoantigens are still missing and tissue or organ destruction as seen in other such diseases are absent. In the past, various serological autoimmune phenomena have been addressed by evaluating the presence of both skin- and organ-reactive autoantibodies or antigen-specific T-cell mediated processes. Recently, the dissection of autoimmunity from autoinflammation as well as the obvious involvement of innate immunity via Toll-like

☆ This manuscript is dedicated to Professor Enno Christophers on the occasion of his 80th birthday combining two major topics of our past cooperation.

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receptors (TLR) in the pathogenesis have fueled the discussion on psoriasis as an autoimmune disease [5–7].

## 2. Clinical aspects of psoriasis

With a frequency of 2.5% in the Caucasian population psoriasis is one of the most common chronic inflammatory skin diseases of man [8]. Whereas 80% of patients present with circumscribed or disseminated, sharply demarcated erythematosquamous plaques referred to as plaque psoriasis, 20% will show sterile pustules on erythematous ground with scaling to a varying extent (Table 1). The pustules may be restricted to palms and soles as in pustulosis palmoplantaris, to acral locations of fingers and toes as in acrodermatitis continua suppurativa Hallopeau or disseminated as in generalized psoriatic pustulosis Zumbusch which is found as the most rare form of psoriasis in only 2% of cases [1].

Skin related symptoms including local or generalized itch and pain may result in massively decreased quality of life which is further aggravated by comorbid conditions and psoriasis arthritis. 30% of patients will show a spectrum of musculosceletal manifestations including arthritis of peripheral or spinal joints (spondylarthritis), enthesitis and dactylitis after a median course of ten years of their skin disease. Clear-cut risk factors for developing arthritis could not be defined so-far as pathogenic mechanisms seem both disease-specifically separate and shared. This is partly reflected by the differential response of skin and arthritis to therapeutic anti-psoriatic agents [9].

## 3. Pathogenic aspects of psoriasis

The major histological traits of psoriasis encompass acanthosis and hyperkeratosis of the epidermis, elongation of dermal capillary vessels and a lymphohistiocytic inflammation which are clinically reflected by erythema, infiltration and scaling. Underlying major pathogenic traits have been allocated to a heterogenous (immuno)genetic background with a number of environmental and endogenous factors which result in a cellular and cytokine imbalance [4,5]. Currently, T-lymphocytes are regarded as major cellular players which are activated by the sequential down-stream action of tumor necrosis factor alpha as well as interleukins 23 and 17 [4,10,11]. An antigen-specific autoimmune pathogenesis has so far been only speculated on, as one or more specific autoantigens could not yet be identified. Recently, the role of innate immunity has been pinpointed by showing the involvement of bacterial and viral products (pathogen-associated molecular patterns PAMs) and toll-like receptors (TLR) to result in an activation of chronic inflammation [6,7].

## 4. Clinical aspects of autoimmunity in psoriasis — disease associations

Generally, autoimmune diseases are characterized by associations to other autoimmune diseases, an (immuno)genetic background, both cellular and humoral immunoreactivity, a more or less severe, yet specific organ involvement often resulting in permanent damage, a female preponderance and late onset of disease.

A number of autoimmune diseases have been reported in the context of psoriasis though a clear correlation and epidemiological numbers are hardly available [12–14]. In addition, the clinical and possibly pathogenic heterogeneity of psoriasis has mostly not been addressed in these studies. Psoriasis could be found associated to autoimmune thyroid diseases like Hashimoto's and Graves' disease [15], Crohn's disease [16,17], diabetes mellitus [2], vitiligo [18,19], alopecia areata [14], celiac disease [20,21] and rarely systemic lupus erythematosus [14].

A number of clinical studies and case histories have addressed the association of autoimmune bullous skin diseases, namely bullous pemphigoid (BP) and pemphigus disease (PV) relating psoriasis to shared skin antigens [22–24]. BP is characterized by specific antibodies against proteins of the skin basement membrane zone, especially against collagen XVII (bullous pemphigoid antigen 180 Kd, BP180) which by detachment of the epidermis from the underlying dermis results in tense blisters of both skin and more rarely mucous membranes (10–30% of cases) [25]. BP is a disease of the elderly with a peak manifestation in the seventh and eighth decade of life. It is either related to immune senescence with decreased suppression of autoimmune responses or age-related increased accessibility of skin antigens resulting in autoimmune responses. Whereas only few cases of associated pemphigus and psoriasis have been published, around sixty patients with BP are available in the literature with a median age of 60 years, a male preponderance (2.5:1) and a median interval between first manifestation of psoriasis and BP of ten years. Damage to the basement membrane by psoriasis related chronic inflammatory processes or UV-therapy have been hypothesized as underlying pathogenic mechanisms. Alternatively subclinical BP may be exacerbated by antipsoriatic treatment [22,23].

Conversely, circulating autoantibodies have been studied in psoriasis. In an own study on 107 patients with psoriasis, 5 showed low-titered anti-BP180 antibodies without any clinical signs of BP, 12 patients an epidermal net-like immunofluorescence pattern in indirect immunofluorescence examination on monkey esophagus as diagnostic substrate, yet negative results in specific anti-dsg 1 and 3 ELISAs [24]. In addition, circulating anti-gliadin and anti-transglutaminase antibodies have been studied in psoriasis patients with varying positivity ranging from 5 to 15%. Again, in our own study of 107 psoriasis anti-gliadin IgG and IgA antibodies were found in 2% and anti-transglutaminase antibodies of IgA and IgG isotype in 2 and 6% of patients respectively. None of the patients showed any clinical sign of celiac disease nor relevant gastrointestinal complaints.

An interesting aspect of an autoimmune relation of psoriasis is the induction of lupus erythematosus (LE)-like symptoms in a small subset of TNF-blocker treated patients [26,27]. Indeed, the denomination anti-TNF induced LE (ATIL) has been coined for this mostly mild disease which is more frequent in patients with rheumatoid arthritis and women (5:1). It is prominently found with infliximab where up to 14% of patients develop anti-DNA antibodies mostly of IgM isotype. Still, only 0.6% of them will show clinical symptoms with more frequent skin involvement than in classical drug induced LE (DILE) [26].

## 5. Autoimmunity in psoriasis — possible autoantigens

Many different possible autoantigens have been studied in the last decades both as antibody and T-cell receptor targets (Table 2). As early as 1978, stratum corneum antibodies were demonstrated in psoriasis patients which could, however, not further be characterized at that time [28]. More recently antibodies to squamous cell carcinoma

**Table 1**
Clinical subtypes of psoriasis.

| Plaque Psoriasis | Pustular psoriasis |
|---|---|
| Guttate psoriasis | Pustulosis palmoplantaris |
| Inverse psoriasis | Generalized pustular psoriasis |
| Scalp psoriasis | |
| Nail psoriasis | |
| Psoriatic erythroderma | |

**Table 2**
Selection of autoantigens targeted by T cells and antibodies.

| T-cell targets | Serological targets |
|---|---|
| Type 1 keratins | Type 1 keratins |
| Human papillomavirus 5 | Human papillomavirus 5 |
| ADAMTS-like protein 5 | Collagen XVII |
| | Gliadin |
| | Squamous cell carcinoma antigen |
| | Heat shock proteins |