

Psoriasis – as an autoimmune disease caused by molecular mimicry

Helgi Valdimarsson¹, Ragna H. Thorleifsdottir¹, Sigrun L. Sigurdardottir¹, Johann E. Gudjonsson² and Andrew Johnston²

¹ Department of Immunology, Landspítali University Hospital, Reykjavik, Iceland

² Department of Dermatology, University of Michigan Medical School, Ann Arbor, MI 48109, USA

Psoriasis is strongly associated with streptococcal throat infection, and patients have increased occurrence of such infections. Psoriatic lesional T cells are oligoclonal, and T cells recognizing determinants common to streptococcal M-protein and keratin have been detected in patients' blood. We propose that CD8⁺ T cells in psoriatic epidermis respond mainly to such determinants, whereas CD4⁺ T cells in the dermis preferentially recognize determinants on the streptococcal peptidoglycan that might itself act as an adjuvant. The streptococcal association might reflect the concurrence of superantigen production promoting skin-homing of tonsil T cells, M-protein mimicking keratin determinants, and adjuvant effects of the peptidoglycan. Accordingly, improvement of psoriasis after tonsillectomy should be associated with fewer T cells that recognize keratin and streptococcal determinants.

Introduction

Psoriasis is a common inflammatory skin disease that can be associated with arthritis. It tends to have a fluctuating course that can sometimes be linked to environmental factors. The disease has a strong genetic component, with a 40–70 % concordance in identical twins [1,2]. Several distinct but overlapping clinical phenotypes have been identified, which might be genetically determined to a large extent [1,3]. Psoriatic skin lesions are characterized by a marked keratinocyte hyperproliferation and altered differentiation associated with dermal and epidermal infiltration of leukocytes, and it is now generally accepted that these pathological changes are triggered and maintained by T lymphocytes [4,5]. As shown in Figure 1, the majority of the T cells infiltrating the dermis are of the CD4 phenotype, whereas CD8⁺ T cells predominate in the lesional epidermis [5,6]. Furthermore, the pathological epidermal hyperplasia coincides with epidermal influx of α 1 β 1 integrin positive T cells and can be prevented by specific blocking [5]. In normal human skin basal keratinocytes express keratins K5 and K14, and suprabasal keratinocytes express mostly K1 and K10, whereas K6 and K16 are expressed during wound healing and in psoriatic lesions, and these keratins together with K17 predominate in psoriatic skin [7]. The homology between M-protein and keratins is mostly restricted to K14, K16 and K17. Interestingly, expression of these psoriasis-associated keratins

can be induced *in vitro* by addition of the pro-inflammatory cytokines IL-1 β [8] or IFN- γ [9]. Recent studies indicate that, in addition to Th1 cells, Th17 cells have an important role in psoriasis [10], including IL-17-producing CD8⁺ T cells [6], and that the keratinocyte hyperproliferation might be driven by the Th17 cytokine IL-22 either directly or indirectly [11]. IFN- γ is a powerful inducer of the chemokine CCL20, a ligand for C-C chemokine receptor-6 (CCR6), which is expressed by T cells, including CD8⁺ T cells that can produce IL-17 [6]. Thus, IFN- γ might have a triple role in psoriasis: first, by inducing and maintaining a putative K17-dependent autoimmune loop [9]; second, by stimulating myeloid dendritic cells (DC) to induce T cells to produce IL-17; and third, at the same time, stimulate epidermal production of CCL20, which attracts the IL-17-producing cells to the epidermis [6].

Recent reviews have mostly addressed the clinical, genetic and cytokine aspects of psoriasis, and only one [12] of the approximately 500 review articles that have been published on psoriasis in the past three years has focused on the fundamental question of whether psoriasis is an autoimmune disease.

Others and we have recently reviewed the genetic and pathogenic aspects of psoriasis [13–15]. Notably, over 60% of psoriasis patients carry one or two class I HLA-Cw*0602 alleles compared with a population frequency of 10–15%, and this HLA allele was recently strongly implicated as an important susceptibility allele in psoriasis [16]. On the basis of this and other pathogenic features of the disease, we argued that CD8⁺ T cells are likely to be the ultimate effector cells that recognize auto-epitopes presented by the binding pockets of HLA-Cw6 or other HLA class I molecules on the keratinocyte surface. This pathogenic activity is, of course, generated through a complex interplay between CD4⁺ and CD8⁺ T cells as well as antigen presenting cells (APCs), including cross-presenting DCs [15]. Here, we focus mainly on reports that have addressed the issue of T cell specificity and the nature of the auto-antigen(s) in psoriasis.

Psoriasis, streptococcal infections, and the palatine tonsils

An association between streptococcal throat infection and the acute guttate form of psoriasis (an early onset form) has been demonstrated in many studies, and the reported incidence of streptococcal infections preceding this type of psoriasis ranges between 56% and 97% [reviewed in Ref.

Corresponding author: Valdimarsson, H. (helgiv@landspitali.is).

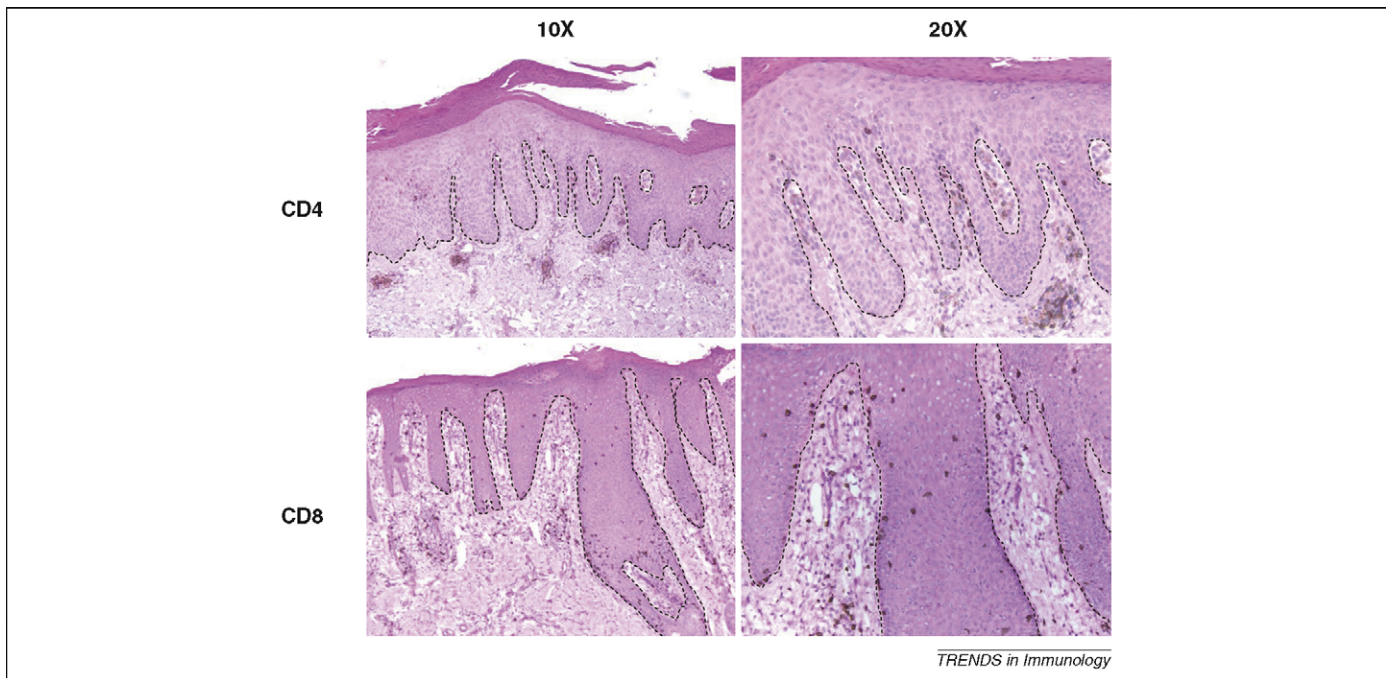


Figure 1. Sections of psoriatic skin lesions counterstained with haematoxylin/eosin for CD4⁺ and CD8⁺ T cells (brown). Note that the dermis is infiltrated mostly by CD4⁺ T cells, whereas most of the CD8⁺ T cells are located in or around the epidermal ridges. The broken line indicates the border between the epidermis and dermis.

17]. Furthermore, we demonstrated in a prospective study that chronic plaque psoriasis is also exacerbated after such infections and that the psoriasis patients had about a ten-fold higher frequency of streptococcal throat infections than age-matched household controls [18]. As has been established for acute guttate psoriasis, worsening of chronic psoriasis was associated only with throat infection by the three groups of β -hemolytic streptococci (A, C and G) that express M-protein on their surface [18]. M-protein, a major virulence factor composed of two polypeptide chains in a complex with an alpha-helical coiled-coil configuration, is anchored in the bacterial cell membrane. In contrast to a very variable N-terminal part of the protein, the C-terminal membrane-anchored half is highly conserved in different bacterial strains and serotypes. No association has been found between psoriasis and particular M serotypes [19].

Non-symptomatic carriage of streptococci in the tonsil crypts is common and these bacteria are efficiently internalized by crypt macrophages and epithelial cells, where they are protected from most commonly used antibiotics. Streptococcal carriage might be associated with increased incidence of symptomatic streptococcal throat infections [20]. There are several reports of partial or complete remission of psoriasis following tonsillectomy, but no controlled prospective trial has been reported. As most psoriasis patients have a fluctuating disease activity and spontaneous remissions are not uncommon, matched patient controls are essential to determine whether tonsillectomy has any beneficial effect.

Reports on oligoclonality of lesional T cells in psoriasis

Since 1994, at least 14 studies reported by nine independent groups have indicated that chronic psoriasis lesions are infiltrated by oligoclonal T cells, and failure to identify oligoclonal lesional T cells has been reported by only one

group that studied patients with the acute guttate form but not chronic plaque psoriasis [21]. These studies, which are summarized briefly in Table 1, involve over 70 patients, including 27 with psoriatic arthritis, and collectively they make a strong case for the notion that the T cells, which mediate chronic psoriasis, are driven by conventional antigen(s). Furthermore, follow-up studies have shown that while minor clones tend to be transient, dominant clones can persist for a long time and even re-appear in lesional skin after drug-induced remission [23,24,29,34]. Moreover, identical T cell clones have been detected in both skin and synovial lesions in patients with psoriatic arthritis (PsA) [31,32]. Notably, in the four studies where CD4⁺ and CD8⁺ T cells in the blood were analyzed separately, oligoclonality was detected among the CD8⁺ but not the CD4⁺ T cells [25,26,33,34].

A study reported by researchers who had previously identified a number of CD4⁺ and CD8⁺ T cell clones in synovial fluid from patients is of special interest [33]. They argued that, as psoriasis usually relapses soon after treatment with methotrexate is discontinued, T cell clones with specificities that are relevant in the very early stages of the inflammatory process should persist during the treatment [34]. Interestingly, most of the expanded clones did not persist and the T cell clones that could be detected during the treatment (about 12% of the clones that were detected in active tissue before the treatment with methotrexate) were of the CD8⁺ T cell lineage, and were found in both joint fluid and blood [34]. These findings highlight the well-known phenomenon that the great majority of lymphocytes that infiltrate active inflammatory sites are polyclonal, and not specific for the antigen(s) that initiated the inflammatory changes [reviewed in Ref. 35]. In autoimmune reactions, some of these polyclonal T cells might, however, recognize and proliferate clonally in response to new auto-antigens exposed or activated by the inflammatory

Table 1. Reports on oligoclonal T cells in psoriatic skin and joint lesions.

Ref.	No. patients	Tissues studied	TCR-V β bias	Methods		Oligoclonality	Comments
				CDR3 sequencing	Spectratyping		
22	7	E	V β 3, 13.1	Yes	No	Yes (7/7)	Study confined to lesional epidermal T cells, oligoclonality of CD8+ T cells detected in blood
23	4	E	V β 3, 13.1	Yes	No	Yes (4/4)	Same patients as in Ref. 22, clonal persistence > 15 months
24	11	E & D	V β 2, 6	Yes	No	Yes (3/3)	Clonal persistence for at least 18 months
25	5	E & D	V β 5.1, 12,16	No	Yes	Yes (4/4)	Oligoclonality among CD8+ T cells in blood
26	10	E & D	Inconsistent	Yes	Yes	Yes (4/6)	Early or expanding lesion, T cell oligoclonality also in blood
27	6	E & D	V β 9, 20	Yes	No	Yes (6/6)	Concordant identical twins with identical lesional clones
28	10	E & D	Inconsistent	No	Yes	Yes (9/10)	Identical clones identified in symmetrical skin lesions
29	2	E & D	V β 2, 3, 6, 13, 17	Yes	No	Yes (2/2)	Dominant clones persist, non-dominant clones transient
30	5	E	Inconsistent	Yes	Yes	Yes (5/5)	Oligoclonality restricted to dominant clones
31	9	E, D, S	Inconsistent	Yes	No	Yes (9/9)	Homologous clones in skin and joint lesions
32	3	E, D, S	Inconsistent	Yes	No	Yes (3/3)	Homologous clones in skin lesions and synovial membrane
33	6	SF	NR	Yes	Yes	Yes (6/6)	Oligoclonality more pronounced in CD8+ T cells and identical CD8+ T cell clones identified in blood
34	9	S & SF	NR	Yes	Yes	Yes (9/9)	Dominant CD8+ T cell clones observed in synovial tissue and blood after MTX-induced remission
38	3	E, D, T	NR	Yes	Yes	Yes (3/3)	Homologous T cell clones in tonsils and skin lesions

D, dermis; E, epidermis, MTX, methotrexate; NR, not recorded; S, synovial tissue; SF, synovial fluid; T, tonsillar tissue.

process, a phenomenon called epitope or determinant spreading [reviewed in Ref. 36]. It should be noted in this context that minor transient T cell clones [30] are likely to represent epitope spreading whereas dominant clones, especially those that persisted during methotrexate treatment [34], are more likely to be directed against the auto-epitope(s) that initiated the autoimmune process. Thus, targeting clones that are secondary to the inflammatory process might explain, to some extent, why it has proved difficult to treat autoimmune diseases in humans with modified peptides, an approach that has consistently been successful in animal models of experimental autoimmunity induced with defined epitopes [reviewed in Ref. 37].

The most recent report on T cell oligoclonality in psoriasis indicates that T cell clones, which expand in the palatine tonsils, might be involved in maintaining psoriatic lesions [38]. Thus, three patients with a history of moderate to severe plaque psoriasis for 1.5, 6, and 10 years all experienced at least 3 years remission after tonsillectomy. They all showed highly restricted T cell receptor (TCR) V β spectratypes of lesional T cells. Furthermore, sequencing of the CDR3 segment of the TCR V β -chain also identified a number of identical clonal rearrangements within the lesional skin of all three patients and, moreover, several of these lesional clonotypes were detected among the cutaneous lymphocyte antigen (CLA) positive T cells within their tonsils. This and the remission of the patients

after the tonsillectomy strongly suggest an egress of pathogenic T cells from the tonsils to the skin.

The consistent finding of oligoclonal T cells in psoriatic lesions strongly indicates that chronic psoriasis is driven by conventional antigen(s) but does not provide any information about the identity or nature of the antigen(s). However, it is now possible to identify T cell clones in the blood with very sensitive functional assays that allow the identification of individual T cells that respond to short peptides by cytokine production (e.g. by means of ELISPOT or flow cytometric detection of cytokine production) [39,40]. In this way we, and others, have tested a number of psoriasis patients and non-psoriatic controls for T cell activation in the presence of short (9–20 amino acid) peptides with determinants that are shared by streptococcal M-protein and human keratins.

T cells cross-reacting with human keratin and streptococci can be detected in the blood of psoriasis patients

An extensive homology between streptococcal M-protein and keratin was first reported about 17 years ago, and this applied to segments of identical amino acid sequences and overall homology [41]. Of about 4200 mammalian proteins that were compared, human type 1 keratins showed the strongest homology with the streptococcal M6 protein. On the basis of this and other findings, we proposed in 1995

that psoriasis is initiated by streptococcal superantigens and maintained by T cells that recognize streptococcal M-protein determinants in the palatine tonsils and homologous keratin determinants in the skin [42]. Subsequently, the frequency of T cells in the blood that were activated by short homologous M and K peptides to produce IFN- γ was determined by the ELISPOT technique in two sets of experiments involving a total of 31 patients with chronic psoriasis, 6 patients with allergic dermatitis and 29 healthy controls [43,44]. The responses were strikingly higher in the psoriasis patients than in the controls, while no difference was observed in the responses to a control antigen (streptokinase/streptodornase (sk/sd)). Notably, M and K peptides that share an ALEEAN amino acid sequence induced stronger and more consistent T cell responses than any of the other peptides. Minimal responses were detected when the patients' T cells were exposed to control K peptides that did not share sequences with M-protein. Moreover, the responses to the homologous peptides could not be detected after only two weeks of treatment with UVB irradiation, which drives epidermal T cells into apoptosis, whereas the responses to the sk/sd control antigen were unaffected by this treatment [43,44].

There is increasing evidence that CD8⁺ T cells have a key role in the pathogenesis of some autoimmune diseases [45,46], including psoriasis [5,6]. With this in mind and the strong association of psoriasis with the HLA-Cw*0602 allele, we next split the amino acid sequence of K17 into a complete set of overlapping nine residue peptides that were then used as a library to compare with sequences of the M-protein [47]. Sets of peptides from K17 and M-protein that showed sequence similarities as well as motifs predicted to bind to HLA-Cw6, were selected together with four K17 and M peptides that did not share sequences or had a poor predicted binding for HLA-Cw6. These peptides were tested against blood lymphocytes from 12 HLA-Cw6 positive and 11 HLA-Cw6 negative patients with chronic psoriasis and 11 healthy HLA-Cw6 positive individuals with a family history of psoriasis. T cells from all the psoriatic patients responded by production of IFN- γ to one or more (up to 10) of the K peptides, whereas the controls either did not respond to any or showed only borderline responses to 4 or fewer of these peptides. The HLA-Cw6 negative psoriatic patients showed T cell responses that were intermediate between those of the HLA-Cw6 positive patients and the controls. Interestingly, the responses were mostly confined to the CD8⁺ T cell population. Moreover, the great majority (>90%) of the responding cells expressed the skin homing CLA determinant. The frequency of T cells responding to the M-peptides was significantly higher in both groups of patients, whereas the controls responded equally well to the control antigens sk/sd and *Candida albicans* cellular proteins [47]. In another study of the potential contribution of CD4⁺ T cells, the whole K17 molecule was scanned for sequences predicted to be HLA DRB1*04, *07 restricted T cell epitopes [48]. These HLA class 2 alleles are significantly associated with psoriasis, although not as strongly as HLA-Cw6. T cells isolated from the blood of 52 HLA DRB1*04 and/or *07 positive psoriasis patients and 48 matched controls were tested with a number of overlapping

K17 peptides with motifs that were predicted to associate with either or both of these HLA class 2 alleles. Two of the peptides induced relatively strong proliferation and IFN- γ production by T cells from the patients, whereas T cells from the non-psoriatic controls showed negligible responses. Interestingly, one of these two peptides contains the ALEEAN sequence that had been reported to activate T cells from psoriasis patients [43,44,47]. The other peptide had an amino acid sequence that had not been reported to be recognized by psoriatic T cells.

More recently, it was reported that it was possible to abolish the T cell proliferation and IFN- γ production, induced by these peptides, by single alanine residue substitutions at a critical TCR contact position [49]. Moreover, these altered peptide ligands induced production of IL-4, and the anti-inflammatory cytokines IL-10 and TGF- β and, furthermore, supernatants from the T cell cultures inhibited keratinocyte proliferation *in vitro* [49].

Does the streptococcal peptidoglycan have a role in psoriasis?

It has been reported that T cell lines (TCLs) grown from lesional dermis, and therefore consisting predominantly of CD4⁺ T cells, do not respond by proliferation to recombinant M-protein [50]. Moreover, cell wall components from streptococci that did not express M-protein induced T cell responses, in terms of IFN- γ production, similar to cell wall components that included M-protein, indicating that the dermal CD4⁺ T cells showed little response to M-protein determinants [50]. The response of the dermal TCLs to different streptococcal cell wall components, including the peptidoglycan (PG) was investigated further, and it was estimated that at least half of the streptococcal cell wall-specific T cells responded to PG. Interestingly, streptococcal PG was detected within lesional dermal macrophages that were within clusters of dermal T cells or in the dermal papillae [51]. PG is known to interact with a number of receptors of innate immunity [52,53], including Toll-like receptor 2 (TLR2), nucleotide-binding oligomerization domains 1 and 2 (NOD 1 and NOD 2) and the recently identified family of PG recognition proteins 1–4 (PGRP 1–4). Furthermore, the genes for TLR2, NOD1, NOD2 and PGRP 2, 3, and 4 are all located in regions that have been reported to show linkage with psoriasis [14], although some of these loci remain to be confirmed. On the basis of these findings and the location of the genes for the PG binding proteins, it was proposed that PG might be a major etiological agent in psoriasis, possibly because psoriasis patients have an altered innate immune response to PG [12]. This interesting proposal is consistent with, and complements, our molecular mimicry model.

Psoriasis and three concurrent features of streptococcal throat infections

A crucial issue in this context is that the TCLs were cultured exclusively from lesional dermis but not the epidermis [50,51], which was used for other experiments not involving T cell responses to M-protein or PG [54]. Therefore, the TCLs consisted mostly of CD4⁺ T cells [50,51] that predominate in the lesional dermis. In contrast, the lesional epidermis is infiltrated mostly by CD8⁺ T cells,

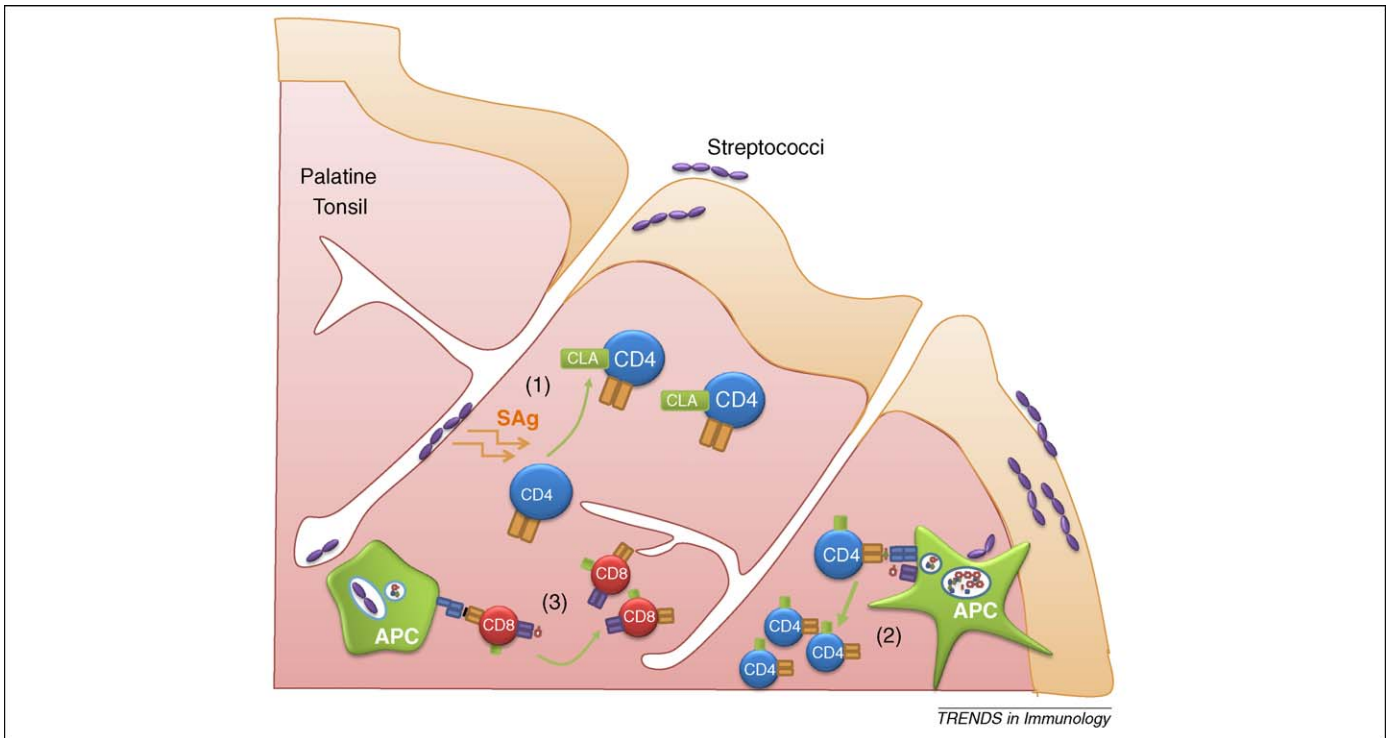


Figure 2. Psoriasis and three concurrent features of streptococcal throat infections. Step 1: Infection or colonization of tonsils by superantigen-producing microbes such as *Streptococcus* spp. increases expression of skin-homing cutaneous lymphocyte-associated antigen (CLA) by tonsillar T cells. Steps 2 and 3: Streptococcal throat infections or their persistence promotes maturation of both effector CD4⁺ (blue) and CD8⁺ (red) T cells that recognize streptococcal components, including PG (red) and M-protein determinants (black). CD8⁺ T cells (but not CD4⁺ T cells) also express Toll-like receptor 2 on their surface (TLR2) (purple), which can bind PG. Macrophages and antigen-presenting cells (APC) with internalized streptococcal components. Internalized PG might also provide adjuvant activity by binding to intracellular innate immune receptors within APCs.

which are required for the development of psoriatic lesions [5]. As shown in Figure 2 and elaborated in Box 1, we propose that APCs in the tonsils and draining lymph nodes present various streptococcal determinants to T cells. At the same time, CLA expression on the resultant effector T cells might be enhanced by streptococcal superantigen [21]

(Figure 2, steps 1 and 3)) which facilitates their egress into the skin. As most CD4⁺ T cells in psoriatic lesions localize to the dermis, they associate with APCs that might be presenting streptococcal components, including PG [51], and some might therefore expand clonally in response to antigen determinants on PG (Figure 3, steps 5 and 7).

Box 1. Proposed etiological and pathogenic sequence in psoriasis

- 1) Genetically determined abnormal innate immune response associated with deviated T cell responses (e.g. IFN- γ or IL-17 bias?) against microbes containing PG (proposed in Ref. [12] and here)
- 2) Increased frequency of streptococcal throat infections in psoriasis patients [18]
- 3) Infection and colonization of tonsils by superantigen-producing microbes increases expression of the skin-homing cutaneous lymphocyte antigen (CLA) by tonsil T cells [21] (Figure 2, step 1)
- 4) Streptococcal throat infections or their persistence promote maturation of effector T cells that recognize streptococcal components including PG and M-protein determinants [12] (and proposed here, Figure 2, steps 2 and 3).
- 5) Association between streptococcal throat infections and psoriasis is strong due to concurrence of superantigen production, PG that binds to innate immune receptors (e.g. TLR2) and M-protein that mimics type 1 keratins in the epidermis (proposed here, Figure 2 steps 1–3).
- 6) Some streptococcal components, including PG and M-protein, enter the bloodstream where they are taken up by monocytes/macrophages (proposed in Ref. 12 and here, Figure 3, step 1) NB Macrophages are not found in efferent lymph nor have they been observed to migrate from (lymphoid) tissues into the circulation.
- 7) Increased frequency in the blood of psoriasis patients of both CD4⁺ and CD8⁺ T cells that respond to antigen determinants that are common to streptococcal M-protein and type 1 keratins [43,44,47–49] (Figure 3, step 2).
- 8) Re-circulating CLA⁺ effector CD4⁺ T cells migrate mainly into lesional dermis but CLA⁺ effector CD8⁺ T cells migrate mostly through the dermis and into the epidermis [5,6] (Figure 3, steps 3 and 4).
- 9) Entry of CD8⁺ T cells is required for the characteristic keratinocyte proliferation in psoriasis [5] (Figure 3 step 4).
- 10) Streptococcal components, including PG, are presented mainly in the dermis and hence primarily to CD4⁺ T cells (Figure 3 step 5). K peptides that share determinants with streptococcal M-protein are predominantly presented in the epidermis and therefore mainly to CD8⁺ T cells (proposed here, Figure 3, step 6).
- 11) Antigen presenting cells at the dermal–epidermal junction present PG determinants to CD4⁺ T cells via HLA class II (Figure 3, step 7), and present keratin determinants to CD8⁺ T cells via HLA class I molecules (Figure 3, step 8). At the same time PG inside antigen-presenting cells might mediate an adjuvant effect for both CD4⁺ and CD8⁺ T cells via intracellular innate immune receptors (proposed here, Figure 3, steps 7 and 8).
- 12) Recruitment of naïve T cells to the tonsils and draining lymph nodes is probably required for maintaining persistent psoriatic plaques. There is a close correlation between the frequency of CLA⁺ T cells in the blood of psoriasis patients and their disease severity [59].

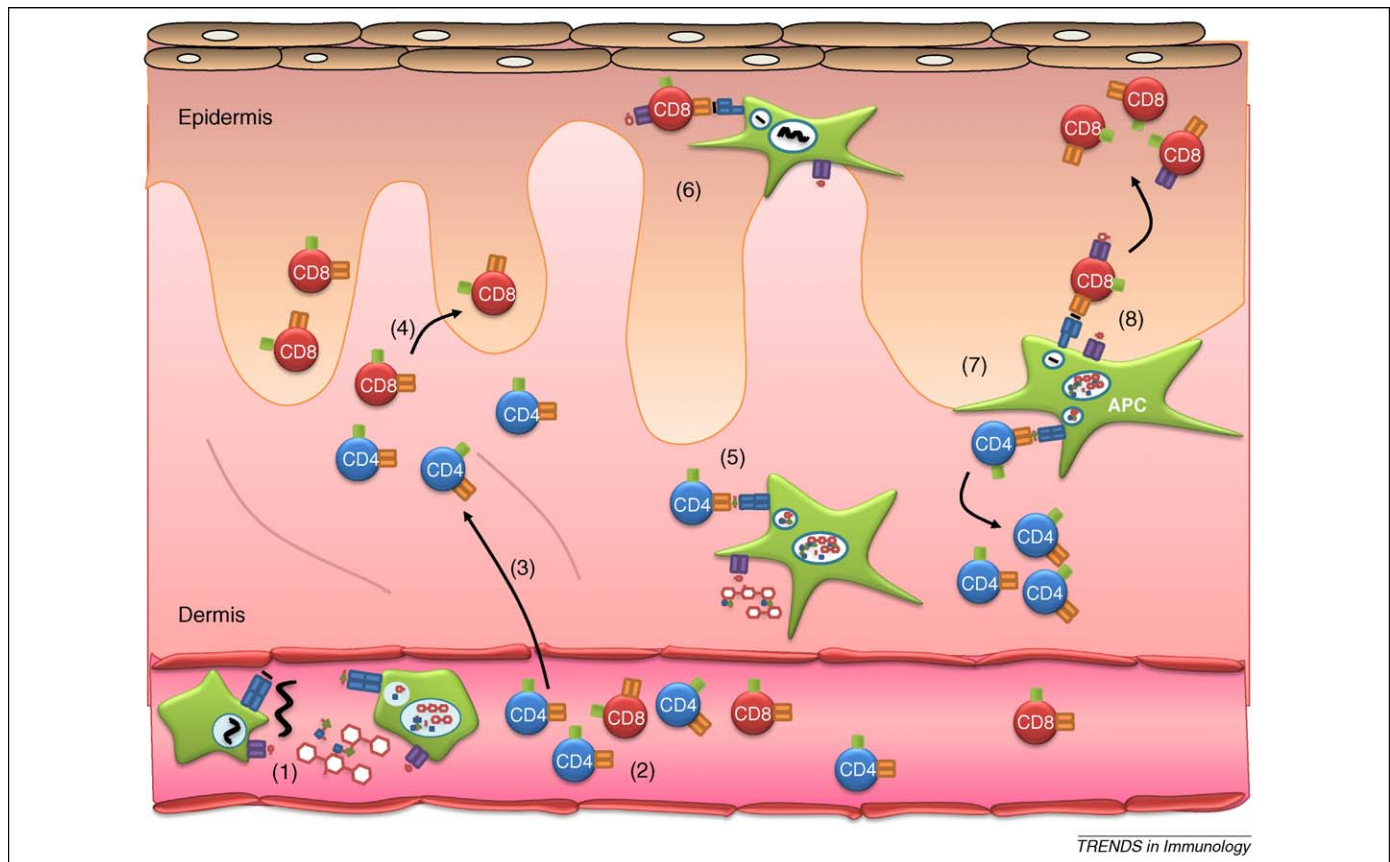


Figure 3. Recruitment of T cells, macrophages, and/or antigen-presenting cells (APCs) into psoriatic lesions. Step 1: Some streptococcal components, including PG (red) and M-protein (black), enter the bloodstream and are taken up by monocytes/macrophages that migrate as APCs into developing psoriatic lesions. Step 2: There is an increased frequency in the blood of psoriasis patients of both CD4⁺ and CD8⁺ T cells, which respond to antigen determinants that are common to both streptococcal M-protein and type 1 Ks. Step 3: Re-circulating CLA⁺ effector CD4⁺ T cells migrate mainly into the lesional dermis. Step 4: CLA⁺ effector CD8⁺ T cells migrate mostly through the dermis and into the epidermis. Entry of CD8⁺ T cells into the epidermis is required for the characteristic keratinocyte proliferation of psoriasis. Step 5: Streptococcal components, including PG, are presented mainly in the dermis and hence mostly to CD4⁺ T cells. Step 6: K peptides that cross-react with streptococcal M-protein determinants are presented predominantly in the epidermis and therefore to CD8⁺ T cells. Step 7: APCs at the dermal-epidermal junction can present PG to CD4⁺ T cells via HLA class II molecules. Step 8: The same junctional APCs present keratin determinants to CD8⁺ T cells via HLA class I. PG might also lower the activation threshold of CD8⁺ T cells expressing TLR2 [55].

Conversely, most CD8⁺ T cells migrate into the lesional epidermis [5] where APCs would present predominantly K peptides, some of which will share sequences with streptococcal M-protein (Figure 3, step 6). It is therefore postulated that most of the oligoclonal T cells observed in lesional epidermis [22] are specific for such cross-reactive determinants that are presented by HLA class I molecules on the surface of keratinocytes, and on DCs located in the epidermis and at the dermis-epidermal junction (Figure 3, step 8). A similar interaction might take place, to some extent, in draining lymph nodes between both naïve and effector CD8⁺ T cells and DCs that have migrated to lymph nodes from lesional epidermis. At the same time, PG inside APCs in psoriatic lesions (Figure 3, steps 7 and 8), the tonsils and lymph nodes draining lesional skin might have an adjuvant effect via intracellular innate immune receptors, and this effect might be different or exaggerated in psoriasis patients [12]. Furthermore, it has been reported recently that CD8⁺ T cells express TLR2 (a receptor for PG), ligation of which lowers their TCR activation threshold [55] (Figure 3, step 8). Thus, the key to the strong association between psoriasis and streptococcal throat infections might be the concurrence in the pathogen of (a) components with adjuvant activity, (b) amino acid

sequences that mimic human keratin, and (c) the release of streptococcal superantigens that have been reported to promote the expression of the skin-homing CLA epitope [21].

Recirculation of pathogenic T cells in psoriasis

A recent proposal has suggested that psoriasis lesions might be initiated and maintained by T cells that reside in the skin without the need for recruitment from the circulating T cell pool [56]. This hypothesis is based mainly on the observation that transplants of uninvolved (i.e. non-psoriatic) skin from psoriasis patients onto SCID mice, which are also deficient in type I and type II interferon receptors (and therefore also with greatly impaired NK cell function, AGR129 mice) became lesional after 4 to 5 weeks, and a marked proliferation of the human T cells in the graft, especially the epidermal CD8⁺ T cells, was observed during this latent period [57]. This is a challenging proposition but thus far it has not been reported how long the psoriatic lesions last in this animal model. It is well documented that DCs have a very short half-life at inflammatory sites and, furthermore, that a substantial proportion of effector T cells also become apoptotic during an ongoing immunological response [reviewed in Ref. 58],

Box 2. Some testable predictions

- 1) Abnormal responses of tonsil T cells from psoriasis patients to streptococcal components including PG and M-protein (under investigation).
- 2) Raised serum levels of peptidoglycan and/or increased frequency in the blood of psoriasis patients of monocytes/macrophages that contain PG (under investigation).
- 3) Increased frequency of CLA⁺ T cells that respond to streptococcal PG in the blood of psoriasis patients (as has been reported for CLA⁺ T cells) that respond to homologous M-protein and keratin peptides [47] (under investigation).
- 4) CD8⁺ T cells isolated from lesional epidermis should preferentially respond to homologous M-protein and K peptides (under investigation).
- 5) Psoriasis should improve after tonsillectomy and the improvement should coincide with reduction in the blood of CLA⁺ T cells that respond to streptococcal components and K determinants (strongly suggestive data are available [60]).

making it likely that recruitment of central memory and naïve T cells is required for maintaining persistent T cell-dependent inflammation. It is therefore unlikely that psoriatic plaques would persist for years without recruitment of memory and naïve T cells from the re-circulating pool. Furthermore, a close correlation between the frequency of CLA⁺ T cells (i.e. those homing to the skin) in the blood and disease severity has been reported in psoriasis patients [59]. It should be noted that the AGR129 mice described above have no lymphoid cells (including functional NK cells), and therefore it is possible that the immunocytes in the transplanted human graft could have a greatly extended survival in this context.

Concluding remarks

Studies published in recent years have been uniformly consistent with the conceptual framework, outlined in 1995, that chronic psoriasis is an autoimmune disease mediated by effector T cells that are primed against conventional streptococcal antigens in the palatine tonsils and subsequently cross-react to keratin determinants in the skin [42]. Thus, T cells in the blood of psoriasis patients recognize determinants that are shared by streptococcal M-protein and human keratin, and these T cells disappear during effective treatment of the disease. However, other streptococcal components, such as PG, might be important in the pathogenesis of psoriasis both as an adjuvant and an antigen recognized directly by T cells in the tonsils, lesional skin, and draining lymph nodes. Because CD8⁺ T cells egress preferentially to the epidermis, they have the opportunity to recognize keratin determinants that are shared with streptococcal M-protein and presented by epidermal APCs. The great majority of the infiltrating CD4⁺ T cells reside in the dermis, where they can recognize streptococcal components, including PG, that are preferentially presented there. In either case, an improvement of psoriasis after tonsillectomy should be associated with reduced frequency of circulating T cells that recognize streptococcal determinants because the palatine tonsils are the major focus for streptococcal infections and carriage. We are carrying out a controlled, prospective and observer blind study on the clinical and immunological impact of tonsillectomy in patients with chronic psoriasis (Box 2). Removal of the tonsils has generally been associated with a

substantial clinical improvement coinciding with a marked decrease in the frequency of cross-reactive keratin and M-protein-specific CD8⁺ T cells in the blood, whereas reduction in the frequency of corresponding cross-reactive CD4⁺ T cells has not been consistent [60]. We conclude that identification of antigen determinants that are recognized by dominant T cell clones in psoriasis are of crucial importance because they might be the appropriate prime targets for highly specific immunotherapy.

Acknowledgements

The authors have been funded by the European Union Training and Mobility of Researchers Programme, The Icelandic Research Fund, The University of Iceland Research Fund and The Science Fund of Landspítali University Hospital. The help of the Icelandic Association of Psoriasis and Eczema Patients (SPOEX) in recruiting volunteers is greatly appreciated.

References

- 1 Brandrup, F. *et al.* (1982) Psoriasis in monozygotic twins: variations in expression in individuals with identical genetic constitution. *Acta Dermatol. Venereol.* 62, 229–236
- 2 Duffy, D.L. *et al.* (1993) Psoriasis in Australian twins. *J. Am. Acad. Dermatol.* 29, 428–434
- 3 Karason, A. *et al.* (2005) Genetics of psoriasis in Iceland: evidence for linkage of subphenotypes to distinct loci. *J. Invest. Dermatol.* 124, 1177–1185
- 4 Valdimarsson, H. *et al.* (1986) Psoriasis: a disease of abnormal keratinocyte proliferation induced by T lymphocytes. *Immunol. Today* 7, 256–259
- 5 Conrad, C. *et al.* (2007) α 1 β 1 Integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. *Nature Med.* 13, 836–842
- 6 Kryczek, I. *et al.* (2008) Induction of IL-17⁺ T cell traffic and development by IFN- γ : mechanisms and pathogenic relevance in psoriasis. *J. Immunol.* 181, 4733–4741
- 7 Leigh, I.M. *et al.* (1995) Keratins (K16 and K17) as markers of keratinocyte hyperproliferation in psoriasis in vivo and in vitro. *Br. J. Dermatol.* 133, 501–511
- 8 Wei, L. *et al.* (1999) IL-1 β and IFN- γ induce the regenerative epidermal phenotype of psoriasis in the transwell skin organ culture system. IFN- γ up-regulates the expression of keratin 17 and keratinocyte transglutaminase via endogenous IL-1 production. *J. Pathol.* 187, 358–364
- 9 Bonnekoh, B. *et al.* (1995) Upregulation of keratin 17 expression in human HaCaT keratinocytes by interferon- γ . *J. Invest. Dermatol.* 104, 58–61
- 10 Lowes, M.A. *et al.* (2008) Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J. Invest. Dermatol.* 128, 1207–1211
- 11 Ma, H.L. *et al.* (2008) IL-22 is required for Th 17 cell-mediated pathology in a mouse model of psoriasis-like skin inflammation. *J. Invest. Dermatol.* 128, 1207–1211
- 12 Baker, B.S. *et al.* (2006) Peptidoglycan: a major aetiological factor for psoriasis. *Trends Immunol.* 27, 545–551
- 13 Bowcock, A.M. and Krueger, J.G. (2005) Getting under the skin: the immunogenetics of psoriasis. *Nature Rev. Immunol.* 5, 699–711
- 14 Valdimarsson, H. (2007) The genetic aspects of psoriasis. *Clin. Dermatol.* 25, 563–567
- 15 Gudjonsson, J.E. *et al.* (2004) Immunopathogenic mechanisms in psoriasis. *Clin. Exp. Immunol.* 135, 1–8
- 16 Nair, R.P. *et al.* (2005) Sequence and haplotype analysis of supports HLA-C as the psoriasis susceptibility1 gene. *Am. J. Hum. Genet.* 78, 827–851
- 17 Prinz, J.C. (2001) Psoriasis vulgaris – a sterile antibacterial skin reaction mediated by cross-reactive T cells? An immunological view of the pathophysiology of psoriasis. *Review. Clin. Exp. Dermatol.* 26, 326–332
- 18 Gudjonsson, J.E. *et al.* (2003) Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. *Br. J. Dermatol.* 149, 530–534

- 19 Tefler, N.R. *et al.* (1992) The role of streptococcal infection in the initiation of guttate psoriasis. *Arch. Dermatol.* 128, 39–42
- 20 Osterlund, A. *et al.* (1997) Intracellular reservoir of *S. pyogenes* *in vivo*: a possible explanation for recurrent tonsillitis. *Laryngoscope* 107, 640–647
- 21 Leung, D.Y. *et al.* (1995) Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. *J. Clin. Invest.* 96, 2106–2112
- 22 Chang, J.C. *et al.* (1994) CD8⁺ T cells in psoriatic lesions preferentially use T-cell receptor V beta 3 and/or V beta 13.1 genes. *Proc. Natl. Acad. Sci. U. S. A.* 91, 9282–9286
- 23 Chang, J.C. *et al.* (1997) Persistence of T-cell clones in psoriatic lesions. *Arch. Dermatol.* 133, 703–708
- 24 Menssen, A. *et al.* (1995) Evidence for an antigen-specific cellular immune response in skin lesions of patients with psoriasis vulgaris. *J. Immunol.* 155, 4078–4083
- 25 Ahangary, G. *et al.* (1997) RT-PCR topography of chronic psoriasis skin based on analysis of T cell receptor B variable region gene usage. *Scand. J. Immunol.* 45, 534–540
- 26 Vecony, M.A. *et al.* (1997) Selective amplification of T cell receptor variable region species in early lesions of psoriasis vulgaris: analysis by anchored polymerase chain reaction and hypervariable region size spectratyping. *J. Invest. Dermatol.* 109, 5–13
- 27 Prinz, J.C. *et al.* (1999) Selection of conserved TCR-VDJ-rearrangements in chronic psoriatic plaques indicates a common antigen in psoriasis vulgaris. *Eur. J. Immunol.* 29, 3360–3368
- 28 Bour, H. *et al.* (1999) T-cell repertoire analysis in chronic plaque psoriasis suggests an antigen-specific immune response. *Hum. Immunol.* 60, 665–676
- 29 Vollmer, S. *et al.* (2001) Dominant lesional T cell receptor rearrangements persist in relapsing psoriasis but are absent from nonlesional skin: evidence for a stable antigen-specific pathogenic T cell response in psoriasis vulgaris. *J. Invest. Dermatol.* 117, 1296–1301
- 30 Lin, W.J. *et al.* (2001) Oligoclonal expansion of intraepidermal T cells in psoriasis skin lesions. *J. Invest. Dermatol.* 117, 1546–1553
- 31 Tassioulas, I. *et al.* (1999) Clonal characteristics of T cell infiltrates in skin and synovium of patients with psoriatic arthritis. *Hum. Immunol.* 60, 479–491
- 32 Borgato, L. *et al.* (2002) The T cell receptor repertoire in psoriatic synovitis is restricted and T lymphocytes expressing the same TCR are present in joint and skin lesions. *J. Rheumatol.* 29, 1914–1919
- 33 Costello, P.J. *et al.* (2001) Psoriatic arthritis joint fluids are characterized by CD8 and CD4 T cell clonal expansions that appear antigen driven. *J. Immunol.* 166, 2878–2886
- 34 Curran, S.A. *et al.* (2004) Nucleotide sequencing of psoriatic arthritis tissue before and during methotrexate administration reveals a complex inflammatory T cell infiltrate with very few clones exhibiting features that suggest they drive the inflammatory process by recognizing autoantigens. *J. Immunol.* 172, 1935–1944
- 35 Steinman, L. (1996) A few autoreactive cells in an autoimmune infiltrate control a vast population of nonspecific cells: a tale of smart bombs and the infantry. *Proc. Natl. Acad. Sci. USA* 93, 2253–2260
- 36 Vanderlugt, C.L. and Miller, S.D. (2002) Epitope spreading in immune-mediated diseases: implications for immunotherapy. *Nat. Rev. Immunol.* 2, 85–95
- 37 Steinman, L. (2004) Immune therapy for autoimmune diseases. *Science* 305, 212–216
- 38 Diluvio, L. *et al.* (2006) Identical TCR beta-chain rearrangements in streptococcal angina and skin lesions of patients with psoriasis vulgaris. *J. Immunol.* 176, 7104–7111
- 39 Betts, M.R. *et al.* (2000) Putative immunodominant human immunodeficiency virus-specific CD8⁺ T-cell responses cannot be predicted by major histocompatibility complex Class I haplotype. *J. Virol.* 74, 9144–9151
- 40 Suni, M.A. *et al.* (1998) Detection of antigen-specific T cell cytokine expression in whole blood by flow cytometry. *J. Immunol. Methods* 212, 89–98
- 41 McFadden, J. *et al.* (1991) Cross-reactivity between streptococcal M surface antigen and human skin. *Br. J. Dermatol.* 125, 443–447
- 42 Valdimarsson, H. *et al.* (1995) Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigens? *Immunol. Today* 16, 145–149
- 43 Sigmundsdottir, H. *et al.* (1997) Circulating T cells of patients with active psoriasis respond to streptococcal M-peptides sharing sequences with human epidermal keratins. *Scand. J. Immunol.* 45, 688–697
- 44 Gudmundsdottir, A.S. *et al.* (1999) Is an epitope on keratin 17 a major target for autoreactive T lymphocytes in psoriasis? *Clin. Exp. Immunol.* 117, 580–586
- 45 Mallone, R. *et al.* (2007) CD8⁺ T cell responses identify β -cell autoimmunity in human type 1 diabetes. *Diabetes* 56, 613–621
- 46 Zozulya, A. *et al.* (2008) The role of CD8 suppressors versus destructors in autoimmune central nervous system inflammation. *Hum. Immunol.* 69, 797–804
- 47 Johnston, A. *et al.* (2004) Peripheral blood T cell responses to keratin peptides that share sequences with streptococcal M proteins are largely restricted to skin-homing CD8 T cells. *Clin. Exp. Immunol.* 138, 83–93
- 48 Shen, Z. *et al.* (2005) HLA DR B1*04, *07-restricted epitopes on keratin 17 for autoreactive T cells in psoriasis. *J. Dermatol. Sci.* 38, 25–39
- 49 Shen, Z. *et al.* (2006) Altered keratin 17 peptide ligands inhibit in vitro proliferation of keratinocytes and T cells isolated from patients with psoriasis. *J. Am. Dermatol.* 54, 992–1002
- 50 Baker, B.S. *et al.* (2001) Skin T cell proliferative response to M protein and other cell wall and membrane proteins of group A streptococci in chronic plaque psoriasis. *Clin. Exp. Immunol.* 124, 516–521
- 51 Baker, B.S. *et al.* (2006) Peptidoglycan and peptidoglycan specific Th-1 cells in psoriasis lesions. *J. Pathol.* 209, 174–181
- 52 Dziarski, R. (2004) Peptidoglycan recognition proteins (PGRPs). *Mol. Immunol.* 40, 877–886
- 53 Natsuka, M. *et al.* (2008) A polymer-type water-soluble peptidoglycan exhibited both Toll-like receptor 2- and NOD2-agonistic activities, resulting in synergistic activation of human monocytic cells. *Innate Immun.* 14, 298–308
- 54 Ovigne, J.M. *et al.* (2002) Epidermal CD8⁺ T cells react with group A streptococcal antigens in chronic plaque psoriasis. *Exp. Dermatol.* 11, 357–364
- 55 Mercier, B.C. *et al.* (2009) TLR2 engagement on CD8 T cells enables generation of functional memory cells in response to suboptimal TCR signal. *J. Immunol.* 182, 1860–1867
- 56 Boyman, O. *et al.* (2007) The pathogenesis of tissue-resident immune cells in psoriasis. *Trends Immunol.* 28, 51–57
- 57 Boyman, O. *et al.* (2004) Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and TNF- α . *J. Exp. Med.* 199, 531–537
- 58 Hilderman, D. *et al.* (2007) Apoptosis and homeostatic control of immune responses. *Curr. Opin. Immunol.* 19, 516–521
- 59 Sigmundsdottir, H. *et al.* (2001) The frequency of CLA⁺ CD8⁺ T cells in the blood of psoriasis patients correlates very closely with the severity of their disease. *Clin. Exp. Immunol.* 126, 365–369
- 60 Thorleifsdottir, R.H. *et al.* (2009) The impact of tonsillectomy on patients with chronic plaque psoriasis. *J. Invest. Dermatol.* 129, S20