Human Translational Research in Psoriasis Using CLA+ T Cells

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Abstract

Focusing on the study of human memory CLA+ T cells to understand psoriasis pathology constitutes an innovative approach to explore the pathological mechanism of this chronic cutaneous inflammatory disease. CLA+ T cells can be considered peripheral cell bio-markers in the study of T-cell mediated human skin diseases. During the last few years, new evidences have been found that link streptococcal infection with IL-17 response in psoriasis by studying the interaction between *Streptococcus pyogenes* with CLA+ T cells and autologous epidermal cells. *S. pyogenes* constitutes the best clinically characterized trigger of psoriasis and by exploring its effect on CLA+ T cells and epidermal cells in psoriasis may allow understanding psoriasis by using patient's clinical samples *ex vivo*.

Keywords: psoriasis, CLA+ T cells, translational research, *Streptococcus pyogenes*, IL17

1. CLA+ T cells and the regional cutaneous immune system

The adaptive immune responses taking place during cutaneous chronic inflammation in psoriasis preferentially involve a subset of memory T lymphocytes, which are related to the skin and that belong to the cutaneous immune system, and constitute one of the best characterized regional immune systems of the body and known for decades [1]. In the humans, the cutaneous lymphocyte-associated antigen (CLA) is a surface cell marker that allows identifying T cells that belong to the cutaneous immune system. The CLA antigen is a carbohydrate expressed by 15% of human circulating T cells, and on most (>90%) skin-infiltrating T cells, contrary to other inflamed organs [2]. CLA is expressed preferentially on memory antigen-experienced T cells.

The CLA is one of the adhesion molecule that, together with chemokine receptors, allows T cells to selectively migrate to the skin, in either homeostatic or inflammatory conditions, by binding to endothelial cell wall via adhesion molecules or ligands. The molecular interactions between CLA/E-selectin, very late antigen-4 (VLA-4)/vascular cell adhesion protein-1 (VCAM-1), lymphocyte function-associated antigen-1 (LFA-1)/intercellular adhesion molecule-1 (ICAM-1), and chemokine ligands for chemokine, C-C motif receptor (CCR) 10, CCR4, CCR6, and CCR8 constitute a code bar system enabling skin infiltration [3].

The importance of circulating CLA+ T cells for understanding the skin immune system is not only based on their capacity to selectively migrate to skin, but also on the fact that these circulating memory T cells are functionally related to the immune response taking place in the cutaneous inflamed lesions. This feature is based on the recirculating capacity of those cells between lesional skin and blood during cutaneous inflammation in psoriasis [3]. The adhesive interaction between LFA-1 and ICAM-1 is one of the mechanisms involved in the transendothelial migration of CLA+ T cells [4]. Interestingly, the blockade of LFA-1/ICAM-1 interaction in psoriasis patients with anti-LFA-1 in patients blocks extravasation and leads to CLA+ T cell lymphocytosis. Such accumulation of CLA+ T cells in the blood has clinical relevance since skin relapse may develop after stopping the anti-LFA-1 treatment [3].

The function and phenotype of circulating CLA+ T cells in T-cell mediated skin disease have been studied in many different human skin conditions. Those skin-seeking memory T cells respond to antigens, allergens, or superantigens that play a key role in disease triggering of different human T-cell mediated skin diseases, see **Table 1**. In addition, their phenotype and function are related to clinical status of the patient. For these reasons, those cells are considered peripheral cell biomarkers of T-cell mediated human cutaneous diseases [3, 5, 6].

Disease	Antigen involved in disease triggering
Atopic dermatitis	House dust mite [59]
	Casein [60]
	TCRVβ for SEB [61]
Contact dermatitis	Nickel [59]
Drug-induced allergic reaction	Betalactams [62]
Herpex simplex	HSV-2 [63]
Vitiligo	Melan-A [64]

Table 1. Selective response of circulating CLA+ T cells to antigens involved in cutaneous disease triggering.

2. Translational research and clinically relevant pathological mechanism of psoriasis

The innovation in psoriasis treatment has benefited from the continuous bidirectional flow of information from the bedside of clinic to the laboratory and vice versa [7]. Innovative pathogenic concepts have been tested in patients through the use of targeted therapeutics leading to

clinically validated mechanism of disease. Those mechanisms that started as a merely scientific hypothesis of disease that can be proven to be relevant in the clinic by specific biological treatments allow improvement in the therapeutic arsenal for patients. At present, it is possible to understand psoriasis from several of its clinically relevant mechanism/targets that has been validated in the clinic since that has provided clinical benefit in patient. The current clinically validated concept of psoriasis is summarized in **Tables 2** and **3**. During the last two decades approximately, it has been demonstrated the key role of the IL-23/Th17 axis in psoriasis [8]. The journey to the current situation in psoriasis treatment started by evidencing that T-cell activity in psoriasis had real implications for the patients. Thus, depletion of T cells [9, 10], costimulation [11], and inhibition of their migration from blood to skin demonstrated improvement in the clinical severity [12]. Not only memory T cells are of translational relevance in psoriasis, but also TNF-α is a key cytokine for this disease. Although originally thought not to be associated to T-cell function, lately it was demonstrated that TNF-α neutralization affects Th17 function [13]. The introduction of ustekinumab, a monoclonal antibody that neutralizes both IL-12 and IL-23, cytokines involved in differentiation of Th1 and Th17 cells, respectively, marked the initiation of the IL-23/Th17 axis era [14]. In contrast to the increased amounts of IL-23, there is no marked increase of IL-12 in psoriatic lesion in comparison to nonlesional or healthy [15]. It became evident that the ustekinumab clinical efficacy was related to inhibition of the IL-23 biological effect.

The next step was to translate the consequence of blocking the IL-23, a cytokine involved in the differentiation of T cells producing IL-17, into the clinic. The selective inhibition of the biological activity of IL-17A, or its receptor IL-17RA, has demonstrated an impressive clinical efficacy in patients in the clinical trials. The most innovative approach currently is to block

Biological treatment	Mechanism action	Target	Relevance
DAB389-IL-2	Toxin acting on cells expressing IL-2 receptor	CD25	T-cells are important in psoriasis [9]
CTLA4-Ig	T cell costimulation blockade	CD80, CD86	Blocking T cell activation improve psoriasis [11]
LFA-3-Ig	Memory T cell depletion	CD2	Memory T cells are relevant in psoriasis [10]
Anti-LFA-1	T cell migration and T-cell costimulation inhibitor	LFA-1	Migration of T cells to psoriasis lesion is involved in disease [12]
Anti-TNF-α	Neutralization of biological activity	TNF-α	Biological activity of TNF-α is involved in psoriasis [65]
Anti-p40 (IL-12/ IL-23)	Neutralization of biological activity	p40 (IL-12/IL-23)	Cytokines involved in generating Th1 and Th17 are relevant in psoriasis [14]
Anti-IL-17A	Neutralization of I biological activity	IL-17A	Other cytokines besides TNF play a role in psoriasis [66]
Anti-IL-17RA	Blockade of receptor	IL-17RA	IL-17 signaling plays a relevant role in psoriasis [67]
Anti-IL-23p19	Neutralization of biological activity	IL-23p19	IL-23/Th17 axis play essential role in psoriasis [16]

Table 2. Targeted therapeutics that have evidenced clinically relevant mechanisms of psoriasis.

Biological treatment	Mechanism of action	Target	Relevance
IL-8	Neutralization of biological activity	IL-8	IL-8 is not clinically validated in psoriasis [68]
IFN-γ	Neutralization of biological activity	IFN-γ	IFN-γ is not clinically validated in psoriasis [69]
IFN-α	Neutralization of biological activity	IFN-α	IFN-α is not clinically validated in psoriasis [70]
IL-22	Neutralization of biological activity	IL-22	IL-22 is not clinically validated in psoriasis [71]

Table 3. Lack of efficacy by targeted therapeutics evidenced nonclinically validated mechanisms of psoriasis.

selectively IL-23, which also has confirmed the clinical relevance of specifically blocking the IL-23/Th17 in psoriasis [16].

In contrast to the mediators or cells that have confirmed its relevance in psoriasis due to its clinical importance in reducing disease severity, there are several well-known mechanisms present in psoriasis that have not been validated in the clinic, since their biological neutralization in the patient has not brought clinical benefit, see **Table 3**. Mediators such us IFN-γ, IFN-α, IL-8, and IL-22 have been neutralized in patients without significant clinical improvement.

When studying psoriasis triggering factors from the translational point of view, perhaps the best characterized environmental factor is throat infection by β-hemolytic streptococci. As it is commented below, there is a great body of evidences that associate streptococcal infection with psoriasis flares or exacerbations in both guttate and plaque psoriasis. This can be considered a translational opportunity of studying psoriasis immune response from a different and innovative perspective.

3. *Streptococcal pyogenes* infection and psoriasis

Throat infection by β-hemolytic streptococci has been associated with both the flare and exacerbation of psoriasis [17–19]. In guttate psoriasis, this infection precedes clinical cutaneous symptoms in 56–97% of the cases [20]. Interestingly, chronic plaque psoriasis patients are more susceptible to throat infections by *Streptococcus pyogenes* (*Sp*) than healthy controls [19], present increased levels of IgG for *S. pyogenes* in comparison to healthy controls [21], and a substantial proportion of patients suffer from disease exacerbations by streptococcal throat infections [22]. The association of *S. pyogenes* infection and psoriasis, besides being clinically evidenced for many years, may also open opportunities to treat psoriasis since several studies have shown that tonsillectomy can bring clinical benefits [23–26] and also improvement in the quality of life of the patients [26].

An immunological model has been proposed to explain how an infection taking place in the throat can lead to a chronic inflammation in a distant tissue such as the skin. One interesting observation is to note that dendritic cells from tonsils and upper respiratory truck are capable of

generating some skin-tropic CLA+ T cells [27], thus indicating that those cells can acquire antigen-specificity for microbes infecting noncutaneous sites. In this regard, streptococcal superantigens promote the expression of CLA on T cells [28], as well as the activation and expansion of CLA+ T cells, at least from guttate psoriasis. Guttate psoriasis is an acute form of psoriasis, which erupts as small drop-shaped papules, and is frequently associated with streptococcal throat infection. In particular, accumulation of $V_\beta 2^+$ T cells in acute guttate lesions has been reported, a variable β chain expressed on T cells that are preferentially expanded through the streptococcal pyrogenic exotoxin (SPE)-C [29], which contained T cells with different junctional sequences in the CDR3 region, thus supporting a superantigen-driven expansion. However, as psoriasis progresses, such superantigen hypothesis does not seem to explain the presence of identical TCR rearrangements in plaque psoriasis patients, probably indicating that a stable antigen-specific T-cell response is involved for longer stages of the disease [30, 31]. Interestingly, T-cell lines isolated from psoriatic lesions have shown strong cross-reactivity to streptococcal antigens [32]. Furthermore, restricted TCRVβ spectratypes shared by CLA+ T cells in streptococcal angina, but not by CLA− T cells, with T cells in psoriasis skin lesions supports the idea of the existence of a tonsillar source of antigen-driven T-cell expansion that then migrate to the skin [33]. Altogether, streptococcal superantigens could facilitate at least early migration of tonsillar T cells to the skin by upregulating CLA expression and could be especially involved in guttate-type flares.

S. pyogenes-primed T cells that reach the skin under postinfection circumstances are, however, unlikely to be maintained by the intracutaneous presence of streptococcal antigens in the skin for long periods of time. Therefore, other antigens would be responsible for the activation of those T cells. The hypothesis of molecular mimicry between streptococcal and skin peptides has been proposed by some authors. This view supports that CD8+ T cells could be cross-reacting to auto-epitopes presented through the context of MHC-I molecules on the surface of activated keratinocytes or cross-presenting dendritic cells [32, 34]. Actually, common determinants have been identified between streptococcal M-protein and skin keratins. Interestingly, the expression of M-protein is only associated with the three groups of β-hemolytic streptococci (A, C and G) that more often cause throat infections that precede the onset or exacerbations of psoriasis lesions [19]. In fact, circulating CLA+ T cells that cross-react with M-protein and human keratin 17, which is upregulated in psoriatic lesions, decrease after tonsillectomy and correlate with clinical improvement [35].

Despite the evidence of streptococcal involvement in psoriasis course, the use of antibiotics has not proven effectiveness in psoriasis [36]. However, it might be explained by the fact that streptococci can exist in intracellular reservoirs in the tonsillar epithelia and macrophages, and that could not be affected by the use of antibiotics. Then, this quiescent load could be reactivated and cause disease symptoms again, whereas tonsillectomy, which has been associated to clinical improvement, might remove this hidden pool of streptococci [22, 37].

Other entry routes for *S. pyogenes* can be considered, such as through the skin barrier itself, and could play a role as instigators of psoriasis disease. In fact, it has been detected in the skin but not in the throats of some guttate psoriasis patients [38]. Such presence, although transitory, might be enough to generate an antibacterial immune response that could lead to autoimmune reactions against local skin-derived peptides [39]. Overall, there is a strong relationship between streptococcal infections and subsequent clinical events in psoriasis that needs further attention.

4. *Streptococcus pyogenes*: an innate trigger that induces IL-17 production through skin-related memory CLA+ T cells in psoriasis

Analyzing the antigen-specific immune responses with clinically relevant stimuli in responding patients allows identifying pathologic translational mechanisms of several immunologic diseases, including psoriasis. This experimental approach can be reproduced *ex vivo* by coculturing circulating memory CLA+ T cells together with autologous epidermal cells from psoriasis patients and are activated by the *S. pyogenes* extract [40]. In this study, it was demonstrated that in psoriasis *S. pyogenes* preferentially activates cocultures of CLA+ T cells and epidermal cells, but not with CLA− T cells from the same patient, nor in cultures using CLA+/CLA− cells from healthy controls. The activation of CLA+ T cells showed at the transcript and protein level a response to the *S. pyogenes* extract with a mixed Th17/Th1/Th22 profile, since IL-17A, IFN-γ, and IL-22 were already upregulated in the coculture at 24 hours after activation and secreted as early as 48 hours. The CLA-dependent immune reaction in the coculture also included several other psoriasis-associated mediators such as the immune cell-chemoattractants CXCL8 (also known as IL-8), CXCL9, CXCL10, and CXCL11, which are expressed in psoriasis lesions [41], and when such enriched media were intradermally injected in mice, an epidermal hyperplasia was found. Furthermore, the presence of epidermal cells in the *ex vivo* model seems crucial for cytokine production through the activation with *S. pyogenes*, proving an intercellular interaction which may imply both CD4+ and CD8+ T cells. This conclusion was based on the observation that cytokine levels were highly impaired after blocking HLA class I and class II molecules. Interestingly, if circulating CLA+ T cells were cocultured with nonlesional epidermal cells, levels of several inflammatory mediators were upregulated when cells were activated with *S. pyogenes*, thus supporting the initial role of CLA+ T cells in driving nonlesional skin to the plaque formation [42, 43]. Overall, this novel model provided first evidence of a direct implication of CLA+ T cells and *S. pyogenes* in psoriasis samples treated *ex vivo*, while no such response was reproduced with healthy samples. These first results shed new light on the study of psoriasis, providing a tool for further valuable translational studies.

Since the closest and clearest relationship between streptococcal infection and subsequent onset of lesions has been described for guttate-type psoriasis, the evaluation of immune responses in the context of *S. pyogenes*-activation of key cellular components of psoriasis lesions from guttate psoriasis patients may generate more faithful results regarding the clinical status of such patients. Moreover, guttate psoriasis represents an important form of psoriasis since it contributes to its natural history. Actually, almost 40% of guttate psoriasis cases develop chronic plaque psoriasis in the future, and guttate-type eruptions are seen in plaque-affected patients [44]. Therefore, early events of psoriasis development can be studied in guttate psoriasis under the abovementioned microbial trigger [45].

A second study based on this *ex vivo* model focused on guttate psoriasis and revealed the importance of the Th17 immune response over other T cell-dependent responses, such as Th1, since IL-17A and IL-17F levels produced by CLA+ T cells in the cocultures in the presence of *S. pyogenes* extract were significantly higher than those of IFN-γ [46].

The importance of Th17 role in initial steps of psoriasis development is also supported by other findings, such as the high levels in serum of IL-17 found in patients with early spreading guttate form [47]. Even a bimodal immunopathology theory proposes that psoriasis is initiated by IL-1/ Th17-dominated responses [48]. In addition to the well-known association of preceding pharyngitis episode, guttate psoriasis onset is mostly confined to individuals carrying the HLA-Cw6 allele [49], a genetic risk factor for early psoriasis. Interestingly, when immune responses from guttate psoriasis samples were classified according with the simultaneous presence of both genetic and environmental factors, that is HLA-Cw6 allele and a prior pharyngitis episode, respectively, the Th17-associated response was higher than that exerted by samples from the other "nonpredisposed" guttate psoriatic individuals. In fact, significant higher levels of IL-17A, IL-17F, and even IL-6, which participates in Th17-differentiation, were found in those "predisposed" guttate psoriasis patients. Furthermore, the treatment of *in vitro* cultured normal keratinocytes with those Th17-predominant supernatants produced by CLA+ T cells in the cocultures, resulted in the upregulation of the IL-17-targeted transcripts *DEFB4*, *S100A7*, *LCN2*, *IL36G*, and *IL8*, which are all overexpressed in psoriasis lesions [50]. Interestingly, filaggrin and loricrin, encoded by *FLG* and *LOR* genes, respectively, which are important skin barrier proteins whose expression is impaired in psoriatic lesions [51, 52], were downregulated in those same treated keratinocytes. Therefore, *S. pyogenes* selective-activation of CLA+ T cells in the presence of epidermal cells from high-responders guttate psoriasis samples recreates a psoriasis-like inflammatory milieu, thus supporting the high translational value of this *ex vivo* model.

Therapies targeting the IL-23/Th17-axis are showing the best efficacy rates in terms of percentage of patients reaching PASI improvement. The observation of rapid normalization of hundreds of psoriasis-related genes as soon as 2 weeks after the use of IL-17A or IL-17RA-blocking antibodies [53, 54] may partly explain the importance of IL-17A effects in psoriasis pathology, and why its blockade provides such impressive clinical improvement. Therefore, the characterization of IL-17-targeted transcripts that are rapidly normalized after these therapies could reveal relevant information regarding to the development of skin lesions.

In this regard, Ruiz-Romeu et al. [55] have taken advantage of the use of CLA+ T cell and epidermal cells activated by SE conditioned supernatants to activate normal keratinocytes and to evaluate gene expression of noncharacterized IL-17A targets. In their study, they characterize the expression of *ZC3H12A*, a gene whose rapid normalization was found in gene arrays of biopsies taken from psoriasis patients treated with the anti-IL-17A monoclonal antibody [53]. *ZC3H12A* encodes for the ribonuclease MCPIP1, and it was upregulated in keratinocytes treated with enriched supernatants in an IL-17A-dependent manner. The fact that lack of upregulation in *Zc3h12a* expression in the skin of an innate psoriasis model induced in *Il17ra*$^{-/-}$ mice supports the key dependence on IL-17 for its increased expression in psoriasis. MCPIP1 activity has been linked to many different biological processes within various cell types, such as inhibition of inflammation, angiogenesis, cell migration, or cell differentiation [56], but no prior evidence of MCPIP1 expression and function in the skin had been reported. In this study, MCPIP1 expression was found to be aberrantly expressed by suprabasal keratinocytes of psoriasis lesions, which is consistent with the distribution of that described for IL-17RA in the psoriatic epidermis [57, 58]. In this regard, only differentiating keratinocytes isolated from psoriatic lesional skin, but not from healthy skin, were susceptible to undergo an increased

expression of MCPIP1 to exogenous IL-17A. Regarding to the potential role of MCPIP1 ribonuclease activity, genes involved in epidermal differentiation, or other altered transcripts in psoriasis lesions, are modified after a *ZC3H12A* knockdown in keratinocytes.

5. Conclusions

The translational approach of developing an *ex vivo* model using peripheral CLA+ T cells and epidermal cells, activated by a clinically relevant innate trigger, such as *S. pyogenes*, can be useful in the characterization of immune responses and new molecular mechanisms that could be involved in the psoriasis pathogenesis.

Acknowledgements

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References

[1]   Picker L, and Butcher E. Physiological and molecular mechanisms of lymphocyte homing. Annu Rev Immunol. 1992; 10: 561-591. 10.1146/annurev.iy.10.040192.003021

[2]   Picker L, Michie S, Rott L, Butcher E. A unique phenotype of skin-associated lymphocytes in humans. Preferential expression of the HECA-452 epitope by benign and malignant T cells at cutaneous sites. Am J Pathol. 1990; 136: 1053-1068.

[3]   Ferran M, Romeu E, Rincon C, Sagrista M, Gimenez Arnau A, Celada A, Pujol R, Hollo P, Jokai H, Santamaria-Babi L. Circulating CLA+ T lymphocytes as peripheral cell biomarkers in T-cell-mediated skin diseases. Exp Dermatol. 2013; 22: 439-442. 10.1111/exd.12154

[4] Santamaria Babi L, Moser R, Perez Soler M, Picker L, Blaser K, Hauser C. Migration of skin-homing T cells across cytokine-activated human endothelial cell layers involves interaction of the cutaneous lymphocyte-associated antigen (CLA), the very late antigen-4 (VLA-4), and the lymphocyte function-associated antigen-1 (LFA-1). J Immunol. 1995; 154: 1543-1550.

[5] Czarnowicki T, Santamaria-Babi L, Guttman-Yassky E. Circulating CLA+ T cells in atopic dermatitis and their possible role as peripheral biomarkers. Allergy. 2016; 72: 366-372

[6] Santamaria Babi L, Perez Soler M, Hauser C, Blaser K. Skin-homing T cells in human cutaneous allergic inflammation. Immunol Res. 1995; 14: 317-324. 90232 [pii];10.1159/000090232

[7] Guttman-Yassky, Krueger J. Psoriasis: evolution of pathogenic concepts and new therapies through phases of translational research. Br J Dermatol. 2007; 157: 1103-1115. BJD8135 [pii];10.1111/j.1365-2133.2007.08135.x

[8] Kim J, Krueger JG. Highly effective new treatments for psoriasis target the IL-23/Type 17 T Cell autoimmune axis. Annu Rev Med. 2017; 68: 255-269. 10.1056/NEJM200107263450403

[9] Gottlieb SL, Gilleaudeau P, Johnson R, Estes L, Woodworth TG, Gottlieb AB, Krueger JG: 1995. Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. Nat Med. 1995; 1: 442-447.

[10] Ellis CN, Krueger GC. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med. 2001; 345: 248-255. 10.1056/NEJM200107263450403

[11] Abrams JR, Kelley SL, Hayes E, Kikuchi T, Brown MJ, Kang S, Lebwohl MG, Guzzo CA, Jegasothy BV, Linsley PS, Krueger JG. Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. J Exp Med. 2000; 192: 681-694.

[12] Gottlieb AB, Miller B, Lowe N, Shapiro W, Hudson C, Bright R, Ling M, Magee A, McCall CO, Rist T, Dummer W, Walicke P, Bauer RJ, White M, Garovoy M. Subcutaneously administered efalizumab (anti-CD11a) improves signs and symptoms of moderate to severe plaque psoriasis. J Cutan Med Surg. 2003; 7: 198-207. 10.1007/s10227-002-0118-1

[13] Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suarez-Farinas M, Fuentes-Duculan J, Novitskaya I, Khatcherian A, Bluth MJ, Lowes MA, Krueger JG. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med. 2007; 204: 3183-3194. jem.20071094 [pii];10.1084/jem.20071094

[14] Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, and Gordon KB. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008; 371: 1665-1674. S0140-6736(08)60725-4 [pii];10.1016/S0140 6736(08)60725-4.

[15] Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, Dhodapkar M, Krueger JG. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med. 2004; 199: 125-130. 10.1084/jem.20030451 [doi];199/1/125

[16] Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, Li K, Campbell K, Marciniak SJ, Wasfi Y, Wang Y, Szapary P, Krueger JG. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol. 2014; 133: 1032-1040. S0091-6749(14)00181-X [pii];10.1016/j.jaci.2014.01.025

[17] Telfer NR, Chalmers RJ, Whale J, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. Arch Dermatol. 1992; 128: 39-42.

[18] Wardrop P, Weller R, Marais J, Kavanagh G. Tonsillitis and chronic psoriasis. Clin Otolaryngol Allied Sci.1998; 23: 67-68.

[19] Gudjonsson JE, Thorarinsson AM, Sigurgeirsson S, Kristinsson KG, Valdimarsson H. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. Br J Dermatol. 2003; 149: 530-534. 5552 [pii]

[20] Prin JC. Psoriasis vulgaris—a sterile antibacterial skin reaction mediated by cross-reactive T cells? An immunological view of the pathophysiology of psoriasis. Clin Exp Dermatol. 2001; 26: 326-332. ced831 [pii]

[21] El-Rachkidy RG, Hales JM, Freestone PP, Young HS, Griffiths CE, Camp RD Increased blood levels of IgG reactive with secreted *Streptococcus pyogenes* proteins in chronic plaque psoriasis. J Invest Dermatol. 2007; 127: 1337-1342. S0022-202X(15)33401-1 [pii];10.1038/sj.jid.5700744

[22] Thorleifsdottir RH, Eysteinsdottir JH, J. Olafsson JH, Sigurdsson MI, Johnston A, Valdimarsson H, Sigurgeirsson. Throat infections are associated with exacerbation in a substantial proportion of patients with chronic plaque psoriasis. Acta Derm Venereol. 2016; 96: 788-791. 10.2340/00015555-2408

[23] Thorleifsdottir RH, Sigurdardottir SL, Sigurgeirsson B, Olafsson JH, Sigurdsson MI, Petersen H, Arnadottir S, Gudjonsson JE, Johnston A, Valdimarsson H. Improvement of psoriasis after tonsillectomy is associated with a decrease in the frequency of circulating T cells that recognize streptococcal determinants and homologous skin determinants. J Immunol. 2012; 188: 5160-5165. jimmunol.1102834 [pii];10.4049/jimmunol.1102834

[24] Hone SW, Donnelly MJ, Powell F, Blayney AW. Clearance of recalcitrant psoriasis after tonsillectomy. Clin Otolaryngol Allied Sci. 1996; 21: 546-547.

[25] Nyfors A, Rasmussen PA, Lemholt K, Eriksen B. Improvement of recalcitrant psoriasis vulgaris after tonsillectomy. J Laryngol Otol. 1976; 90: 789-794.

[26] Thorleifsdottir RH, Sigurdardottir SL, Sigurgeirsson B, Olafsson JH, Sigurdsson MI, Petersen H, Gudjonsson JE, Johnston A, Valdimarsson H. Patient-reported outcomes and clinical response in patients with moderate-to-severe plaque psoriasis treated with tonsillectomy: a randomized controlled trial. Acta Derm Venereol. 2017; 97: 340-345.

[27] Sabat R, Philipp S, Hoflich C, Kreutzer S, Wallace E, Asadullah K, Volk HD, Sterry W, Wolk K. Immunopathogenesis of psoriasis. Exp Dermatol. 2007; 16: 779-798. EXD629 [pii];10.1111/j.1600-0625.2007.00629.x

[28] Leung DY, Gately M, Trumble A, Ferguson-Darnell B, Schlievert PM, Picker LJ. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen, via stimulation of interleukin 12 production. J Exp Med. 1995; 181: 747-753.

[29] Leung DY, Travers JB, Giorno R, Norris DA, Skinner R, Aelion J, Kazemi LV, Kim MH, Trumble AE, Kotb M. Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. J Clin Invest. 1995; 96: 2106-2112. 10.1172/JCI118263

[30] Prinz JC, Vollmer S, Boehncke WH, Menssen A, Laisney I, Trommler P. Selection of conserved TCR VDJ rearrangements in chronic psoriatic plaques indicates a common antigen in psoriasis vulgaris. Eur J Immunol. 1999; 29: 3360-3368. 10.1002/(SICI)1521-4141(199910)29:10<3360::AID-IMMU3360>3.0.CO;2-G[pii];10.1002/(SICI)1521-4141(199910)29:10<3360::AID-IMMU3360>3.0.CO;2-G

[31] Vollmer S, Menssen A, Prinz JC. 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. 2001; 117: 1296-1301. S0022-202X(15)41455-1 [pii];10.1046/j.0022-202x.2001.01494.x

[32] Valdimarsson H, Thorleifsdottir RH, Sigurdardottir SL, Gudjonsson JE, Johnston A. Psoriasis—as an autoimmune disease caused by molecular mimicry. Trends Immunol. 2009; 30: 494-501. S1471-4906(09)00153-7 [pii];10.1016/j.it.2009.07.008

[33] Diluvio L, Vollmer S, Besgen P, Ellwart JW, Chimenti S, Prinz JC. Identical TCR betachain rearrangements in streptococcal angina and skin lesions of patients with psoriasis vulgaris. J Immunol. 2006; 176: 7104-7111. 176/11/7104

[34] Gudjonsson JE, Johnston A, Sigmundsdottir H, Valdimarsson H. Immunopathogenic mechanisms in psoriasis. Clin Exp Immunol. 2004; 135: 1-8. 2310 [pii]

[35] Thorleifsdottir RH, Sigurdardottir SL, Sigurgeirsson B, Olafsson JH, Sigurdsson ML, Petersen H, Arnadottir S, Gudjonsson JE, Johnston A, Valdimarsson H. Improvement of psoriasis after tonsillectomy is associated with a decrease in the frequency of circulating T cells that recognize streptococcal determinants and homologous skin determinants. J Immunol. 2012; 188: 5160-5165. jimmunol.1102834 [pii];10.4049/jimmunol.1102834

[36] Owen CM, Chalmers RJ, O'Sullivan T, Griffiths CE. A systematic review of antistreptococcal interventions for guttate and chronic plaque psoriasis. Br J Dermatol. 2001 145: 886-890.

[37] Osterlund A, Popa R, Nikkila T, Scheynius A, Engstrand L. Intracellular reservoir of *Streptococcus pyogenes* in vivo: a possible explanation for recurrent pharyngotonsillitis. Laryngoscope. 1997; 107: 640-647.

[38] Fahlen A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res. 2012; 304: 15-22. 10.1007/s00403-011-1189-x

[39] Mallbris L, Larsson P, Bergqvist S, Vingard E, Granath F, Stahle M. Psoriasis phenotype at disease onset: clinical characterization of 400 adult cases. J Invest Dermatol. 2005; 124: 499-504. S0022-202X(15)32215-6 [pii];10.1111/j.0022-202X.2004.23611.x

[40] Ferran M, Galvan AB, Rincon C, Romeu ER, Sacrista M, Barboza E, Gimenez-Arnau A, Celada A, Pujol RM, Santamaria-Babi LF. Streptococcus induces circulating CLA(+) memory T-cell-dependent epidermal cell activation in psoriasis. J. Invest Dermatol. 2013; 133: 999-1007. S0022-202X(15)36179-0 [pii];10.1038/jid.2012.418

[41] Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suarez-Farinas M, Cardinale I, Khatcherian A, Gonzalez J, Pierson JC, White TR, Pensabene C, Coats I, Novitskaya I, Lowes MA, Krueger JG. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol. 2008; 159: 1092-1102. BJD8769 [pii];10.1111/j.1365-2133.2008.08769.x

[42] Vissers, WH, Arndtz CH, Muys L, Van Erp PE,. de Jong E M, and van de Kerkhof PC. 2004. Memory effector (CD45RO+) and cytotoxic (CD8+) T cells appear early in the margin zone of spreading psoriatic lesions in contrast to cells expressing natural killer receptors, which appear late. Br J Dermatol. 150: 852-859. 10.1111/j.1365-2133.2004.05863.x [doi];BJD5863

[43] Davison SC, Ballsdon A, Allen MH, Barker JN. Early migration of cutaneous lymphocyte-associated antigen (CLA) positive T cells into evolving psoriatic plaques. Exp Dermatol. 2001; 10: 280-285. exd100408

[44] Langley RG, Krueger GK, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005; 64(Suppl 2): ii18–ii23. 64/suppl_2/ii18 [pii];10.1136/ard.2004.033217

[45] Weisenseel P, Laumbacher B, Besgen P, Ludolph-Hauser D, Herzinger T, Roecken M, Wank R, Prinz JC. Streptococcal infection distinguishes different types of psoriasis. J. Med. Genet. 2002; 39: 767-768.

[46] Ruiz-Romeu E, Ferran M, Sagrista M, Gomez J, Gimenez-Arnau A, Herszenyi K, Hollo P, Celada A, Pujol R, Santamaria-Babi LF. Streptococcus pyogenes-induced cutaneous lymphocyte antigen-positive T cell-dependent epidermal cell activation triggers TH17 responses in patients with guttate psoriasis. J Allergy Clin Immunol. 2016; 138: 491-499. S0091-6749(16)00360-2 [pii];10.1016/j.jaci.2016.02.008

[47] Choe YB, Hwang YJ, Hahn HJ, Jung JW, Jung HJ, Lee YW, Ahn KJ, Youn JI. A comparison of serum inflammatory cytokines according to phenotype in patients with psoriasis. Br J Dermatol. 2012; 167: 762-767. 10.1111/j.1365-2133.2012.11038.x

[48] Christophers E, Metzler G, Rocken M. Bimodal immune activation in psoriasis. Br J Dermatol. 2014;170: 59-65. 10.1111/bjd.12631

[49] Asumalahti K, Ameen M, Suomela S, Hagforsen E, Michaelsson G, Evans J, Munro M, Veal C, Allen M, Leman J, David BA, Kirby B, Connolly M, Griffiths CE, Trembath RC, Kere J, Saarialho-Kere U, Barker JN. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. J Invest Dermatol. 2003; 120: 627-632. S0022-202X(15)30213-X [pii];10.1046/j.1523-1747.2003.12094.x

[50] Chiricozzi A,Guttman-Yassky E, Suarez-Farinas M, Nograles K E, Tian S, Cardinale I, Chimenti S, Krueger JG. Integrative responses to IL-17 and TNF-alpha in human kerati-nocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol. 2011; 131: 677-687. S0022-202X(15)35175-7 [pii];10.1038/jid.2010.340

[51] Kim BE, Howell MD, Guttman-Yassky E, Gilleaudeau PM, Cardinale IR, Boguniewicz M, Krueger JG, Leung DY. TNF-alpha downregulates filaggrin and loricrin through c-Jun N-terminal kinase: role for TNF-alpha antagonists to improve skin barrier. J Invest Dermatol. 2011; 131: 1272-1279. S0022-202X(15)35315-X [pii];10.1038/jid.2011.24

[52] Roberson ED, Bowcock AM. Psoriasis genetics: breaking the barrier. Trends Genet. 2010; 26: 415-423. S0168-9525(10)00129-0 [pii];10.1016/j.tig.2010.06.006

[53] Krueger JG, Fretzin S, Suarez-Farinas M, Haslett PA, Phipps KM, Cameron GS, McColm J, Katcherian A, Cueto I, White T, Banerjee S, Hoffman RW. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. J Allergy Clin Immunol. 2012; 130: 145-154. S0091-6749(12)00695-1 [pii];10.1016/j.jaci.2012.04.024

[54] Russell CB, Rand H, Bigler J, Kerkof K, Timour M, Bautista E, Krueger JG, Salinger DH, Welcher AA, Martin DA. Gene expression profiles normalized in psoriatic skin by treat-ment with brodalumab, a human anti-IL-17 receptor monoclonal antibody. J Immunol. 2014; 192: 3828-3836. jimmunol.1301737 [pii];10.4049/jimmunol.1301737

[55] Ruiz-Romeu E, Ferran M, Gimenez-Arnau A, Bugara B, Lipert B, Jura J, Florencia EF, Prens EP, Celada A, Pujol RM, Santamaria-Babi LF. MCPIP1 RNase Is Aberrantly Distributed in Psoriatic Epidermis and Rapidly Induced by IL-17A. J Invest Dermatol. 2016; 136: 1599-1607. S0022-202X(16)31153-8 [pii];10.1016/j.jid.2016.04.030

[56] Chao J, Dai X, Pena T, Doyle DA, Guenther TM, Carlson MA. MCPIP1 Regulates Fibroblast Migration in 3-D Collagen Matrices Downstream of MAP Kinases and NF-kappaB. J Invest Dermatol. 2015; 135: 2944-2954. S0022-202X(15)60179-8 [pii];10.1038/jid.2015.334

[57] Chiricozzi A, Nograles KE, Johnson-Huang LM, Fuentes-Duculan J, Cardinale I, Bonifacio KM, Gulati N, Mitsui H, Guttman-Yassky E, Suarez-Farinas M, Krueger JG. IL-17 induces an expanded range of downstream genes in reconstituted human epidermis model. PLoS One. 2014; 9: e90284. 10.1371/journal.pone.0090284 [doi];PONE-D-13-37082

[58] Peric M, Koglin S, Kim SM, Morizane S, Besch R, Prinz JC, Ruzicka T, Gallo RL, Schauber J. IL-17A enhances vitamin D3-induced expression of cathelicidin antimicrobial peptide in human keratinocytes. J. Immunol. 2008; 181: 8504-8512. 181/12/8504

[59] Santamaria Babi LF, Picker LJ, Perez Soler MT, Drzimalla K, Flohr P, Blaser K, Hauser C. Circulating allergen-reactive T cells from patients with atopic dermatitis and allergic

contact dermatitis express the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen. J Exp Med. 1995; 181: 1935-1940.

[60] Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DY. Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. J Clin Invest. 1995. 95: 913-918. 10.1172/JCI117743

[61] Torres MJ, Gonzalez FJ, Corzo JL, Giron MD, Carvajal MJ, Garcia V, Pinedo A, Martinez-Valverde A, Blanca M, Santamaria LF. Circulating CLA+ lymphocytes from children with atopic dermatitis contain an increased percentage of cells bearing staphylococcal-related T-cell receptor variable segments. Clin Exp Allergy. 1998; 28: 1264-1272.

[62] Blanca M, Leyva L, Torres MJ, Mayorga C, Cornejo-Garcia J, Antunez-Rodriguez C, Santamaria LF, Juarez C. Memory to the hapten in non-immediate cutaneous allergic reactions to betalactams resides in a lymphocyte subpopulation expressing both CD45RO and CLA markers. Blood Cells Mol Dis. 2003; 31: 75-79. S1079979603000615

[63] Koelle DM, Liu Z, McClurkan CM, Topp MS, Riddell SR, Pamer EG, Johnson AS, Wald A, Corey L. Expression of cutaneous lymphocyte-associated antigen by CD8(+) T cells specific for a skin-tropic virus. J Clin Invest. 2002 110: 537-548. 10.1172/JCI15537

[64] Ogg GS, Rod DP, Romero P, Chen JL, Cerundolo V. High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitilig. J Exp Med. 1998; 188: 1203-1208.

[65] Oh CJ, Das KM, Gottlieb AB. Treatment with anti-tumor necrosis factor alpha (TNF-alpha) monoclonal antibody dramatically decreases the clinical activity of psoriasis lesions. J Am Acad Dermatol. 2000; 42: 829-830. S0190962200907321

[66] Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012; 366: 1190-1199. 10.1056/NEJMoa1109997

[67] Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EH, Baumgartner S. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med. 2012; 366: 1181-1189. 10.1056/NEJMoa1109017

[68] http://www.siliconinvestor.com/readmsgs.aspx?subjectid=24141&msgnum=97&batchsize=10&batchtype=Next

[69] https://business.highbeam.com/436989/article-1G1-110130198/fontolizumab-protein-design-discontinued-usa

[70] Bissonnette R, Papp K, Maari C, Yao Y, Robbie G, White WI, Le C, White B. A randomized, double-blind, placebo-controlled, phase I study of MEDI-545, an anti-interferon-alfa monoclonal antibody, in subjects with chronic psoriasis. J Am Acad Dermatol. 2010; 62: 427-436. S0190-9622(09)00686-0 [pii];10.1016/j.jaad.2009.05.042

[71] Antoniu SA. Discontinued drugs 2011: pulmonary, allergy, gastrointestinal and arthritis. Expert Opin Investig Drugs. 2012; 21: 1607-1618. 10.1517/13543784.2012.712112