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Autoimmune Mechanisms of Psoriasis: Pathogenic Role of the IL-23/IL-17 Axis

Melanie Wolf and Alex Shnyra*

Department of Basic Medical Sciences, Kansas City University of Medicine and Biosciences, Kansas City, USA

***Corresponding author:** Alex Shnyra, Department of Basic Medical Sciences, Kansas City University of Medicine and Biosciences, 1750 Independence Avenue, Kansas City, MO 64106, USA, Tel: +1-816-654-7635; E-mail: ashnyra@kcumb.edu

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Abstract

Psoriasis is a chronic, recurrent, immuno-inflammatory disease of the skin and joints associated with significant morbidity and mortality. Psoriasis affects approximately 2-4% of the Caucasian population worldwide. The precise immuno-inflammatory mechanisms leading to skin psoriasis are still to be fully defined. There is emerging evidence supporting the existence of a relationship between changes in cutaneous microbiota and development of psoriasis. Under certain pathologic conditions associated with dysbiosis of the skin microbiome, pathogenic microbes triggering aberrant immuno-inflammatory responses may spark the onset and relapses of psoriasis. Strong association of certain human leukocyte antigens (HLAs) along with the pathogenic role of IL-17 suggests the involvement of autoimmune mechanisms in psoriasis. Multiple clinical trials targeting the IL-17/IL-23 axis in psoriasis are underway. Here, we review the emerging findings suggesting the autoimmune nature of psoriasis and examine new therapeutic approaches for treatment of this chronic immuno-inflammatory disease.

Background

Psoriasis is a chronic, recurrent, immuno-inflammatory disease of the skin and joints which in the most common form is manifested by erythematous, scaly plaques commonly occurring on the elbows, knees, scalp, and trunk [1]. Psoriasis has a complex genetic background. A recent twin study showed that psoriasis represents a multifactorial disorder in which genetic factors account for about 70% of disease susceptibility, whereas environmental factors account for the remaining 30% [2]. These findings indicate that the heritability is not the only cause of psoriasis, and other environmental factors such as skin microbiota may also contribute to the susceptibility to this immuno-inflammatory disease.

Histologically, psoriasis is characterized by inflammatory hyperproliferation and thickening of the epidermis, accompanied by altered differentiation of keratinocytes and their accumulation in the upper layers of the epidermis [1]. Increased vascularization of psoriatic plaques follows keratinocyte hyperproliferation that results in a massive influx of innate and adaptive immune cells producing an array of inflammatory mediators which sustain the chronic inflammation [3].

Accumulation of inflammatory $CD4^+$ Th1 cells, $CD8^+$ cytotoxic T lymphocytes, and Th17 cells is accompanied by increased expression of IL-17A in psoriatic lesions [4-6]. IL-17A, primarily produced by $CD4^+$ Th17 cells and δγ T cells, operates at the interface of innate and adaptive immunity by activating keratinocytes to produce IL-17C that along with other keratinocyte-derived mediators serves to sustain the chronic inflammation in psoriatic plaques. Taken together, psoriasis is regarded as an IL-17-mediated inflammatory condition in which IL-17-producing $CD4^+$ Th17 T cells, δγ T cells, and keratinocytes play a critical role.

The ability to stimulate acute and chronic inflammation has implicated IL-17 in the pathogenesis of various human systemic and organ-specific autoimmune disorders [7]. In this regard, recent findings that implemented IL-17 in the pathogenesis of psoriasis also suggest an autoimmune nature of this immuno-inflammatory skin disease. The universal involvement of IL-17 in various autoimmune diseases has identified IL-17 as an ideal target for the development of immunotherapeutic approaches [8-10]. Given the critical role of IL-23 in generating Th17 cells [6,11], multiple clinical trials targeting the IL-17/IL-23 axis in the pathogenic mechanisms of psoriasis are underway.

Role of microflora and molecular mimicry in psoriasis

Although the etiology of psoriasis is not fully elucidated, both hereditary and environmental factors contribute to the onset and periodic exacerbations of the disease. Skin plays a vital protective role as a physical barrier and habitat for resident microflora, a diverse community of microorganisms, generally comprised of harmless and beneficial species [12]. Emerging evidence strongly suggests the existence of an intricate relationship between skin microflora and a complex network of keratinocytes, epithelial cells, and immune cells in the skin [13]. In this regard, it has been long suspected that psoriasis may well be associated with alterations in the composition and representation of the cutaneous bacterial microflora, although

classical cultivation-dependent microbiological methods did not permit a detailed identification of the cutaneous bacterial community. Recently, comparative high-throughput pyrosequencing analyses of microbiota in biopsies from psoriatic lesions and normal skin have demonstrated that *Firmicutes* species were significantly overexpressed, whereas Actinobacteria, the most prevalent and diverse phylum in normal skin, and *Propionibacterium* species, in particular, were significantly underrepresented in psoriatic lesions [14]. The followed studies have confirmed the decreased presence of Propionibacteria and also revealed the decreased abundances of *staphylococci* in psoriatic lesions compared to healthy skin [15]. Yet, it remains unclear whether the observed change in skin microbiota is the causative factor in the development of psoriasis.

Although the cause-effect relationship between dysbiosis of the skin microflora and auto-inflammatory mechanisms of psoriasis has yet to be fully elucidated, recent studies showed that tonsillar infections caused by *Streptococcus pyogenes* often precede the onset of psoriasis whereas periodic exacerbations are associated with skin colonization by *Staphylococcus aureus*, Malassezia, or *Candida albicans* [16-18]. Different mechanisms have been proposed to describe how infections can trigger and/or exacerbate autoimmune diseases. Molecular mimicry is a mechanism in which a microbial antigen shares structural similarities with self-antigens and is typically characterized by the appearance of autoantibodies and self-reactive T cell clones. The concept of molecular mimicry has thus been proposed as a triggering mechanism of various autoimmune diseases [19] including the onset and periodic exacerbations of psoriasis [20]. In individuals susceptible to psoriasis, tonsillar infections with group-A hemolytic *Streptococcus pyogenes* may induce the rise of pathogen-specific T cell clones which may also cross-react with keratinocyte-derived autoantigens. Specifically, oligoclonal T cells were identified in the blood and psoriatic lesions which cross-reacted with determinants common to streptococcal M-protein and keratin [21,22]. It appears that those psoriatic T cell clones selectively accumulated and persisted in the lesions but not in the healthy skin of patients with psoriasis [23].

Evidence for an autoimmune etiology

Autoimmunity is characterized by the breakdown of self-tolerance and abnormal antibody-mediated and/or T cell-mediated immune responses against self-antigens. Our understanding of the pathogenesis of psoriasis has evolved greatly over the years, and the question of autoimmunity is frequently debated. However, identification of genetic risk variants, the discovery of multiple autoantigens, and the role of Th17 cells commonly involved in various autoimmune diseases provide strong support for the concept of autoimmune pathogenic mechanisms of psoriasis.

Genetic variations have been identified for many common autoimmune diseases. Genome-wide association (GWA) studies have discovered numerous single nucleotide polymorphisms (SNPs) that confer the susceptibility to various autoimmune diseases [24]. Like other autoimmune diseases, psoriasis has been shown to have a strong genetic component, with a concordance rate in identical twins of 40-70% [2,25]. Over sixty psoriasis susceptibility loci have been identified [26] among which the MHC Class I molecule HLA-Cw*0602 is the most significant since more than 60% of psoriasis patients are hetero- or homozygous for this allele [25]. Other psoriasis susceptibility loci, to name a few, include ERAP1 encoding for an Endoplasmic Reticulum Aminopeptidase 1 [27] and ERAP2 [28], which are both involved in antigen processing and presentation [29], IL23R [30], as well as TNFAIP3 (TNF-alpha induced protein 3), in which polymorphisms have also been implicated in rheumatoid arthritis, type 1 diabetes, celiac disease, and Crohn's disease [31].

The discovery of autoantigens further supports the autoimmune concept in the pathogenesis of psoriasis. Molecular mimicry has been recognized as a triggering factor of many autoimmune diseases [32]. Molecular mimicry has also been implicated in the pathogenesis of psoriasis [20]. Streptococcal throat infection is a known trigger of acute guttate psoriasis, with an incidence of preceding infection ranging between 56-97% [25]. Homology between the streptococcal M-protein and keratin 17 yields cross-reactive $CD8^+$ T cells seen in patients with psoriasis, especially in patients with HLA-Cw*0602 [29]. Another autoantigen that has been implicated in psoriasis is cathelicidin/LL-37, an antimicrobial peptide synthesized by keratinocytes and neutrophils in reaction to infection or trauma to the skin [26]. Autoreactive T cells against cathelicidin were found in the peripheral blood of 75% of patients with moderate to severe psoriasis [33]. It was recently found that ADAMTSL5 (ADAMTS-like protein 5) serves as a psoriasis autoantigen which overexpression by melanocytes is observed in HLA-Cw*0602 positive patients [34]. TCRs of $CD8^+$ T cells recognize ADAMTSL5 presented by melanocytes in psoriatic lesions and generate IL-17, a signature cytokine in psoriasis.

In addition to T cell-mediated immune responses, circulating auto-antibodies against calpastatin, a natural inhibitor of the protease calpain, have been identified in psoriasis patients but not healthy controls [35]. Of importance, anti-calpastatin auto-antibodies were also found in various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjögren's Syndrome, and overlap syndrome which further support the concept of psoriasis as an autoimmune disease [35]. In addition, several autoantibodies such as anti-heat shock protein 65 antibodies [36], anti-stratum corneum antibodies [37] and anti-squamous cell carcinoma antigen antibodies [38] have been identified in psoriasis, although their clinical significance has yet to be determined.

Association between psoriasis and other autoimmune diseases has been the subject of ongoing investigation. A recent retrospective cohort study has demonstrated that patients with psoriasis are at higher risk of developing at least one other autoimmune disease with rheumatoid arthritis having the strongest association (3.6; 95% CI 3.4-3.9) [39]. Another case-control study involving 12,506 psoriasis patients found that 0.29% of the patients had celiac disease compared with 0.11 % in the control group [40]. Psoriasis patients were also found to have higher rates of Crohn's disease and ulcerative colitis [41].

Similarly, association of psoriasis with Hashimoto's thyroiditis, Sjögren's Syndrome and dermatomyositis has been recently reported [42]. Taken together, the results of these association studies suggest a common aberrant mechanism(s) linking the development of classical autoimmune diseases and psoriasis, supporting the concept of psoriasis having an autoimmune nature.

The IL-23/TH17 axis in the pathogenic mechanisms of psoriasis

Since its discovery in the early nineties [43], IL-17 took the central stage in immuno-inflammatory mechanisms underlying the development of autoimmune diseases. Thus, IL-17 was implemented in pathogenic mechanisms of inflammatory bowel diseases, multiple sclerosis, and rheumatoid arthritis, in which both serum and tissue have elevated concentrations of IL-17 (reviewed in [7]. In a similar manner, our understanding of the pathogenesis of psoriasis has evolved around the pathologic role of IL-17 since Th17 cells were identified in the dermis of psoriatic plaques [4]. It was shown that IL-17 mainly produced by Th17 cells and δγ T cells is responsible for downstream activation of an array of transcription factors leading to epidermal hyperplasia, leukocyte recruitment, and amplified skin inflammation [4-6].

The IL-17 family consists of six cytokines, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. Although IL-17B, IL-17C, and IL-17D exhibit pro-inflammatory properties, their exact roles still remain elusive [44]. On the other hand, IL-17E, also known as IL-25, promotes Th2 type responses and suppresses Th1 and Th17 cells [44]. IL-17A and IL-17F are the two most closely related members of the IL-17 family which share 50% amino acid sequence homology [45]. IL-17A and IL-17F may also exist as an IL-17A/F heterodimer. Both IL-17A and IL-17F serve to protect and maintain the skin and mucosal barriers in healthy tissues, however, overproduction of these cytokines also play a central role in the pathogenic mechanisms of psoriasis. The IL-17 receptor (IL-17R) is a heterodimer comprised of five subunits, a.k.a. IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. Psoriasis-relevant IL-17A, IL-17F, and IL-17A/F bind to a heterodimeric IL-17RA/IL-17RC with IL-17A being selectively recognized by IL-17RA and IL-17F by IL-17RC [45].

In the skin, IL-17A and IL-17F are mainly produced by Th17 cells and δγ T cells [45,46]. Unequivocally, IL-17-producing $CD4^+$ Th17 cells are culprits in the development of psoriatic plaques, as they have been isolated in the dermis of psoriatic lesions [47]. In addition to production of IL-17, activated Th17 cells also secrete IL-21 and IL-22 [48]. IL-22 is an IL-10 family cytokine that acts through STAT3 and has been shown to increase epidermal thickness through inhibition of keratinocyte differentiation [49]. Treatment with neutralizing anti-IL-22 antibodies prevented development of psoriasiform disease in mice thereby identifying IL-22 as an important pathogenic factor in psoriasis and potential molecular target for disease therapy [50]. Furthermore, cooperation between IL-17A and IL-22 leads to recruitment of leukocytes in the skin to further potentiate the inflammation. IL-17A and IL-17F also stimulate keratinocytes to synthesize various chemokines including CXCL2, CXCL3, CXCL5, and CXCL8 (IL-8) which mediate the chemotaxis of neutrophils and macrophages to the lesional skin leading to formation of Munro microabscesses, one of the characteristic histologic features of psoriasis [26].

IL-23 plays an important role in activation of Th17 cell-mediated immunity [11]. Following some inciting event, whether it is infection or trauma, autoantigens are released in the epidermis and activate myeloid dendritic cells (mDCs) [51]. Activated mDCs are the main source of IL-23 in psoriatic plaques [52]. Although TGF-β1, IL-6, and IL-1β are required for Th17 cells differentiation from naïve $CD4^+$ cells, IL-23 is the cornerstone cytokine in this process [47]. In the absence of IL-23, the cytokines TGF-β1, IL-6, and IL-1β stimulate differentiation of T regulatory cells capable of potent suppression of inflammation [53].

Of particular importance, IL-23 has crucial roles in the pathogenesis of autoimmunity as it induces local tissue inflammation which is mainly mediated by IL-23-dependent production of IL-17 by Th17 cells [11]. The transcription factor STAT3 is a key facilitator in the IL-23 signaling pathway, and upon activation, it induces transcription of inflammatory cytokines including IL-17A, IL-17F, IL-22, and IFN-γ by Th17 cells [47]. Emerging evidence unequivocally suggests that the IL-23/IL-17 axis represents the central immuno-inflammatory pathway in the pathogenesis of psoriasis [47] and provides the rationale for the development of new anti-IL-17 and anti-IL-23 immuno-therapeutic approaches for treatment of patients with moderate-to-severe psoriasis plaques [26,54].

Targeting the IL-23/IL-17 axis

To date, the antibodies that specifically neutralize IL-23 or IL-17 have shown remarkable effectiveness for the treatment of psoriasis in clinical trials [26]. As December 2018, a search of the ClinicalTrials.gov database has revealed 25 either recruiting, active, or completed clinical trials using anti-IL-17 or anti-IL-17 receptor monoclonal antibodies for treatment of moderate-to-severe psoriasis. In early 2016, the US Food and Drug Administration (FDA) has approved the first anti-IL-17 monoclonal antibody (secukinumab, Novartis Pharmaceuticals) for the treatment of active psoriatic arthritis [55,56]. Follow in the footsteps of Novartis, Eli Lilly has received the US FDA approval for anti-IL-17 monoclonal antibody [57-59] for treatment of moderate-to-severe psoriasis. In February 2017, anti-IL-17 receptor antagonist (Brodalumab, Valeant Pharma) has received the US FDA approval to treat moderate-to-severe plaque psoriasis in people who have not improved with other treatments [60,61].

Similarly, our search of the ClinicalTrials.gov database has revealed 11 clinical trials using anti-IL-23 monoclonal antibodies (as December 18, 2017). In October 2017, the U.S. Food and Drug Administration (FDA) has approved an expanded indication for anti-p40 subunit of IL-12/IL-23 monoclonal antibody (ustekinumab, Janssen Biotech, Inc.) for the treatment of adolescents (12 years of age or older) with moderate to severe plaque psoriasis [62,63].

Conclusion

Psoriasis has long been viewed as a chronic immune-mediated inflammatory disease of skin and small joints which is most commonly manifested by the formation of demarcated erythematous plaques. Although the etiology of psoriasis has been elusive, emerging evidence strongly implicates molecular mimicry as a triggering factor of psoriasis in genetically susceptible individuals. Autoreactive T cells and circulating autoantibodies were also found in psoriatic patients. Taken together, these findings support the concept that psoriasis is an autoimmune disease. Furthermore, accumulated evidence unequivocally shows that IL-17 and IL-23 cytokines are key players in the pathogenesis of psoriasis. In this regard, better understanding of the immunopathology of psoriasis has led to the development of new therapeutic modalities which selectively target IL-17 and IL-23. Biological agents, such as neutralizing anti-IL-17 and anti-IL-23 monoclonal antibodies, have been developed and tested in multiple clinical trials showing their effectiveness in the treatment of moderate to severe plaque psoriasis. Despite the efficacy of these biological agents anti-IL17 and IL-23 antibodies may potentially cause a systemic immunosuppression associated with an increased risk of infections and malignancies. Therefore, future clinical studies are needed to establish the safety record of these biological agents by showing that the benefits of anti-IL-17 and anti-IL-23 therapies overweight any potential adverse effects of these drugs in the treatment of moderate to severe plaque psoriasis.

References

1. Schön MP, Boehncke WH (2005) Psoriasis. N Engl J Med 5: 1899-1912.
2. Lønnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, et al. (2013) Heritability of psoriasis in a large twin sample. Br J Dermatol 169: 412-416.
3. Baliwag J, Barnes DH, Johnston A (2015) Cytokines in psoriasis. Cytokine 73: 342-350.
4. Lowes MA, Kikuchi T, Fuentes Duculan J, Cardinale I, Zaba LC, et al. (2008) Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 128: 1207-1211.
5. Kryczek I, Bruce AT, Gudjonsson JE, Johnston A, Aphale A, et al. (2008) Induction of IL-17+ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. J Immunol 1: 4733-4741.
6. Res PC, Piskin G, De Boer OJ, Van der Loos CM, Teeling P, et al. (2010) Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. PLoS One 24: e14108.
7. Fouser LA, Wright JF, Dunussi Joannopoulos K, Collins M (2008) Th17 cytokines and their emerging roles in inflammation and autoimmunity. Immunol Rev 226: 87-102.
8. Hofstetter HH, Ibrahim SM, Koczan D, Kruse N, Weishaupt A, et al. (2005) Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. Cell Immunol 237: 123-130.
9. Sonderegger, Michael O, Robert A, Bachmann, Kopf M, et al. (2006) Neutralization of IL-17 by active vaccination inhibits IL-23-dependent autoimmune myocarditis. Eur J Immunol 36: 2849–2856.
10. Lubberts E (2008) IL-17/Th17 targeting: on the road to prevent chronic destructive arthritis? Cytokine 41: 84-91.
11. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, et al. (2005) Sedgwick JD, McClanahan T, Kastelein RA, Cua DJ. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med 17: 233-240.
12. Grice EA, Segre JA (2011) The skin microbiome. Nat Rev Microbiol 9: 244-253.
13. Findley K, Grice EA (2014) The Skin Microbiome: A Focus on Pathogens and Their Association with Skin Disease. PLoS Pathogens 10: e1004436.
14. Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ (2008) Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS One 23: e2719.
15. Fahlén A, Engstrand L, Baker BS, Powles A, Fry L (2012) Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res 12: 1522.
16. Paulino LC, Tseng CH, Strober BE, Blaser MJ (2006) Molecular analysis of fungal microbiota in samples from healthy human skin and psoriatic lesions. J Clin Microbiol 44: 2933-2941.
17. Fry L, Baker BS (2007) Triggering psoriasis: The role of infections and medications. Clin Dermatol 25: 606615.
18. Paulino LC, Tseng CH, Blaser MJ (2008) Analysis of Malassezia microbiota in healthy superficial human skin and in psoriatic lesions by multiplex real-time PCR. FEMS Yeast Res 8: 460-471.
19. Rose NR (2017) Negative selection, epitope mimicry and autoimmunity. Curr Opin Immunol 49: 51-55.
20. Diluvio L, Vollmer S, Besgen P, Ellwart JW, Chimenti S, et al. (2008) Identical TCR beta-chain rearrangements in streptococcal angina and skin lesions of patients with psoriasis vulgaris. J Immunol 176: 7104-7111.
21. Sigmundsdottir H, Sigurgeirsson B, Troye Blomberg M, Good MF, Valdimarsson 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.
22. Baker BS, Brown DW, Fischetti VA, Ovigne JM, Porter W, 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.
23. Vollmer S, Menssen A, Prinz JC (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: 1296-301.
24. Lucas CL, Lenardo MJ (2009) Identifying genetic determinants of autoimmunity and immune dysregulation. Curr Opin Immunol 37:28-33.
25. Valdimarsson H, Thorleifsdottir RH, Sigurdardottir SL, Gudjonsson JE, Johnston A (2008) Psoriasis--as an autoimmune disease caused by molecular mimicry. Trends Immunol 30: 494-501.
26. Hawkes JE, Chan TC, Krueger JG (2017) Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 140: 645-653.

27. Strange A, Capon F, Spencer CC (2010). Genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nature genetics 42: 985-990.

28. Tsoi LC, Spain SL, Knight J (2012) Identification of fifteen new psoriasis susceptibility loci highlights the role of innate immunity. Nature genetics 44: 1341-1348.

29. Liang Y, Sarkar MK, Tsoi LC, Gudjonsson JE (2017) Psoriasis: a mixed autoimmune and autoinflammatory disease. Curr Opin Immunol 49: 1-8.

30. Filer C, Ho P, Smith RL, Griffiths C, Young HS, et al. (2008) Investigation of association of the IL12B and IL23R genes with psoriatic arthritis. Arthritis Rheum 58: 3705-3709.

31. Bazsó A, Szodoray P, Szappanos Á, Korda J, Pálfi P, et al. (2015) Systemic Autoimmune, Rheumatic Diseases and Coinciding Psoriasis: Data from a Large Single-Centre Registry and Review of the Literature. Mediators Inflamm 2015: 657907.

32. Cusick MF, Libbey JE, Fujinami RS (2012) Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol 42: 102-111.

33. Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, et al. (2014) The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun 3: 5621.

34. Arakawa A, Siewert K, Stöhr J (2015) Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 212: 2203-2212.

35. Matsushita Y, Shimada Y, Kawara S, Takehara K, Sato S (2005) Autoantibodies directed against the protease inhibitor calpastatin in psoriasis. Clin Exp Immunol 139: 355-362.

36. Jablonska S, Chorzelski TP, Beutner EH, Maciejowska EJarzabek C M, Rzesa G (1978) Autoimmunity in psoriasis. Relation of disease activity and forms of psoriasis to immunofluorescence findings. Arch Dermatol Res 261: 135-146.

37. Rambukkana A, Das PK, Witkamp L, Yong S, Meinardi MM, et al. (1993) Antibodies to mycobacterial 65-kDa heat shock protein and other immunodominant antigens in patients with psoriasis. J Invest Dermatol 100: 87-92.

38. El Rachkidy RG, Young HS, Griffiths CE, Camp RD (2008) Humoral autoimmune responses to the squamous cell carcinoma antigen protein family in psoriasis. J Invest Dermatol 128: 2219–2224.

39. Wu JJ, Nguyen TU, Poon KYT, Herrinton LJ (2012) The association of psoriasis with autoimmune diseases. J Am Acad Dermatol 67: 924-930.

40. Birkenfeld S, Dreiher J, Weitzman D, Cohen AD (2009) Celiac disease associated with psoriasis. Br J Dermatol 161: 1331-1334.

41. Hsu LN, Armstrong AW (2012) Psoriasis and autoimmune disorders: A review of the literature. J Am Acad Dermatol 67: 1076-1079.

42. Akiyama M, Ueno T, Kanzaki A, Kuwana M, Nagao M, et al. (2016) Association of psoriasis with Hashimoto's thyroiditis, Sjögren's Syndrome and dermatomyositis. J Dermatol 43: 711–712.

43. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, et al. (1995) Herpesvirus saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. Immunity 3: 811-821.

44. Iwakura Y, Ishigame H, Saijo S, Nakae S (2011) Functional specialization of interleukin17 family members. Immunity 1: 149-162.

45. Goepfert A, Lehmann S, Wirth E, Rondeau JM (2017) The human IL-17A/F heterodimer: a two-faced cytokine with unique receptor recognition properties. Scientific Reports 7: 8906.

46. McGeachy MJ, Cua DJ (2008) Th17 cell differentiation: The long and winding road. Immunity 28: 445-453.

47. Di Cesare A, Di Meglio P, Nestle FO (2009) The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 129: 1339-1350.

48. Ouyang W, Kolls JK, Zheng Y (2008) The Biological Functions of T Helper 17 Cell Effector Cytokines in Inflammation. Immunity 8: 454-467.

49. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, et al. (2005) IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol 15: 3695-3702.

50. Ma HL, Liang S, Li J (2008) IL-22 is required for Th17 cell–mediated pathology in a mouse model of psoriasis-like skin inflammation. J Clin Invest 118: 597-607.

51. Zaba LC, Fuentes Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, et al. (2009) Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. J Invest Dermatol 129: 79-88.

52. Tesmer LA, Lundy SK, Sarkar S, Fox DA (2008) Th17 cells in human disease. Immunol Rev 223: 87-113.

53. Bettelli EY, Carrier W Gao, Korn T, Strom TB, Oukka M, et al. (2006) Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 441: 235-238.

54. Gaffen SL, Jain R, Garg AV, Cua DJ (2014) The IL-23–IL-17 immune axis: From mechanisms to therapeutic testing. Nat Rev Immunol 4: 585-600.

55. Langley RG, Elewski BE, Lebwohl M (2014) Secukinumab in plaque psoriasis-results of two phase 3 trials. N Engl J Med 4: 326.

56. Thaçi D, Blauvelt A, Reich K (2015) Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol 73: 400.

57. Liu L, Lu J, Allan BW, Tang Y, Tetreault J, et al. (2016) Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. J Inflamm Res 9: 39-50.

58. Gordon KB, Blauvelt A, Papp KA (2016) Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med 375: 345-356.

59. Farahnik B, Beroukhim K, Zhu TH (2016) Ixekizumab for the Treatment of Psoriasis: A Review of Phase III Trials. Dermatol Ther 6: 25-37.

60. Gordon K, Kimball A, Chau D (2014) Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory. Br J Dermatol 170: 705-715.

61. Farahnik B, Beroukhim K, Abrouk M (2016) Brodalumab for the Treatment of Psoriasis: A Review of Phase III Trials. Dermatol Ther 6: 111-124.

62. Ritchlin C, Rahman P, Kavanaugh A (2014) Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-

blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 73: 990-999.

63. Kavanaugh A, Puig L, Gottlieb AB (2015) Maintenance of Clinical Efficacy and Radiographic Benefit Through Two Years of Ustekinumab Therapy in Patients With Active Psoriatic Arthritis: Results From a Randomized, Placebo-Controlled Phase III Trial. Arthritis Care Res 67: 1739-1749.