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Current Opinion in Immunology

Atopic dermatitis and psoriasis: two different immune diseases or one spectrum?

Emma Guttman-Yassky[1] and James G Krueger[2]

Psoriasis and atopic dermatitis (AD) are common T-cell mediated inflammatory diseases of the skin that can be treated by specific cytokine antagonists or more broad immunosuppressive drugs. The diseases are similar in that epidermal keratinocytes respond to T-cell derived cytokines by altering growth and differentiation responses, accounting for major parts of the overall disease phenotype. When studied across European-American populations, psoriasis and AD display differing T-cell polarity and different arrays of cytokines. Psoriasis is a disease largely driven by Th17 T-cells and associated IL-17 activation, while AD has a strong Th2 component associated with IL-4 and IL-13 over-production, and both diseases have activation of Th22 T-cells and Th1 pathways with increased IL-22 and IFNγ production, respectively. AD is a disease frequently associated with increased IgE production and overt allergies or asthma, most likely due to increased Th2 activation, which is largely lacking in psoriasis. Hence, psoriasis and AD can be viewed as distinct diseases with differing clinical, tissue, and molecular disease phenotypes, but this view does not account for specific subtypes of AD, including Asian-origin, intrinsic, and pediatric AD, that have a prominent IL-17 component and also tissue patterning that overlaps with distinctive psoriasis histopathology. Hence, when considering the range of AD phenotypes, a case can be made that psoriasis and AD exist across a spectrum where polar T-cell axes can be variably present and create some overlapping disease characteristics. Today, ~90% of psoriasis patients have extremely controlled disease by targeting the IL-23/Th17 T-cell axis with IL-23 or IL-17-targeting antibodies. An outstanding question is whether targeting a single cytokine axis in AD, for example, Th2 axis, will lead to disease suppression in the majority of patients and across all subtypes, including those with higher IL-17 expression, or whether it is necessary to personalize therapies and target multiple T-cell axes to attain similar disease improvement to psoriasis.

Addresses
[1] Department of Dermatology, Icahn School of Medicine at the Mount Sinai Medical Center, New York, NY, USA
[2] Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY, USA

Corresponding author: Guttman-Yassky, Emma (Emma.Guttman@mountsinai.org)

Current Opinion in Immunology 2017, **48**:68–73

This review comes from a themed issue on **Allergy and hypersensitivity**

Edited by **Cezmi Akdis**

For a complete overview see the Issue and the Editorial

Available online 1st September 2017

http://dx.doi.org/10.1016/j.coi.2017.08.008

Introduction

Psoriasis and Atopic Dermatitis (AD) are clearly separable diseases using clinical criteria [1–5]. AD usually has disease onset in infancy or early childhood and may affect 15–25% of all children, but a significant fraction these cases resolve so that AD affects 7–10% of adults [5–7]. Psoriasis is occasionally present in young children, but its peak onset is late adolescence and early adulthood, while it affects ~3% of adults in populations of European descent and typically <0.5% of other races [2,3,5]. Particularly when comparing psoriasis and AD in European-American populations (EA-AD), different skin regions tend to be affected (extensor vs. flexor) and the skin lesions differ in that psoriasis tends to be more clearly demarcated, chronic plaques, usually with coarse scale, while AD ranges from patches to thin plaques, often with indistinct borders between affected and unaffected skin. About 80% of EA-AD patients also have allergic/atopic features with elevated IgE levels and many of these also have asthma, seasonal allergies, or food allergies. Psoriasis has no association with allergic disease, but it is frequently associated with psoriatic arthritis [8,9]. However, when viewed as pathogenic disease processes in the skin, there are many overlaps and similarities in underlying immune activation and the resulting alterations in tissue structure and function, particularly when considering intrinsic, Asian, and pediatric forms of AD [5,10–15]. This review is focused on describing pathogenic disease mechanisms across the spectrum of both diseases and associated subtypes with a perspective that many immunological mechanisms overlap between psoriasis and AD and thus some treatment approaches may be common across the disease spectrum [8].

Psoriasis

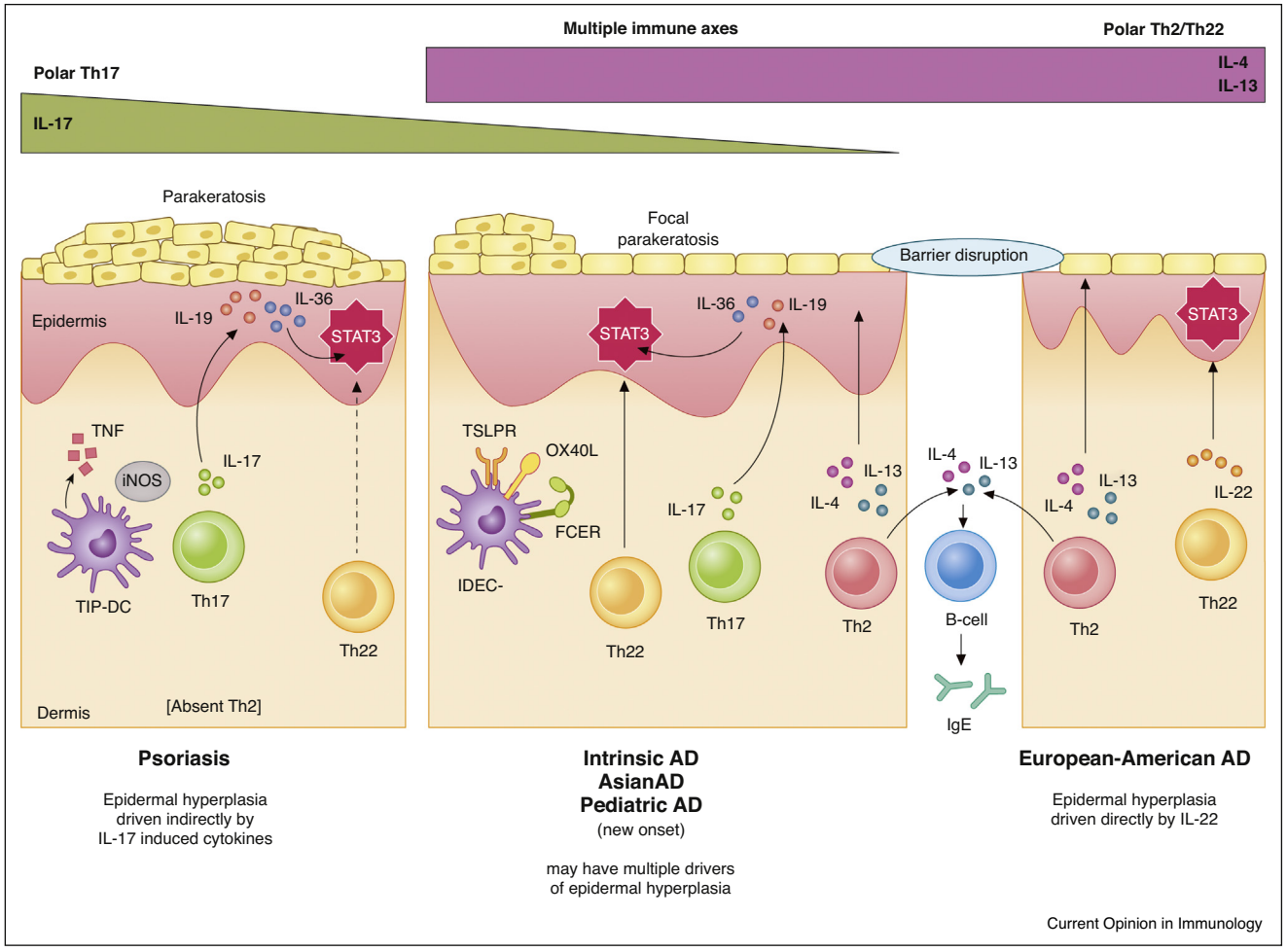
Here we are considering psoriasis vulgaris as the main disease form, particularly as less common variants, for example, pustular, inverse, or guttate psoriasis, do not have detailed molecular profiles. Psoriasis is best defined as a patterned reaction of the skin to activated immune cells and cytokines. Until very recently, disease models included pathogenic roles for Th1, Th17, and Th22 T-cell subsets which elaborated the class-defining cytokines interferon-γ, IL-17, and IL-22, respectively [2,16,17]. However, it is now clear that antagonism of IL-17 is sufficient to reverse cellular and molecular disease features, so the most current disease model considers that the main driver of psoriasis is the Type 17 (Th17, Tc17) T-cell and that specific auto-antigens are likely activators [18–20]. Cytokines synthesized by activated Type 17 T-cells include IL-17 (IL-17A/IL-17F), IL-26, IL-29 and TNF [21,22]. These cytokines collectively activate NFκB, C/EBPβ or δ, and STAT1 in keratinocytes and other skin-resident cells, creating a broad 'feed forward' inflammatory response that not only self-amplifies, but also extends to activation and recruitment of Th1 and Th22 T-cell subsets into psoriatic lesions [23]. Epidermal hyperplasia, associated with STAT3 activation, is induced indirectly by IL-17 though increased production of IL-19 and/or IL-36 in epidermal keratinocytes [19]. The auto-antigens LL37 and ADAMTSL5 have increased levels in psoriasis lesions as a part of the IL-17 directed response, which may be a factor for disease chronicity [24–26]. IL-22 might also contribute directly to epidermal hyperplasia, as could IL-20 (a product of dendritic cells in psoriasis), as these cytokines are also STAT3 activators [27]. The epidermal response in psoriasis is typified by keratinocyte maturation with retained nuclei (parakeratosis), as well as neutrophil influx into the epidermis. The epidermal reaction to IL-17, which includes additive and synergistic responses with TNF and IL-22, leads to up-regulation of hundreds of gene products in skin lesions and to a very typical IL-17 pathway molecular disease profile. Psoriasis lesions across most of the body surface have a nearly identical molecular disease profile and this extends even to mild psoriasis lesions. The most characteristic features of psoriasis include marked epidermal hyperplasia and high production of psoriasin (S100A7), other S100 proteins, and many anti-microbial proteins such as lipocalin 2 and β-defensin 2 [19]. This epidermal response is directed by marked up-regulation of the transcription factors C/EBPβ or δ in highly differentiated keratinocytes in upper spinous and granular layers, the region where highest production of psoriasis-related proteins occurs. The epidermal reaction in psoriasis is probably best conceptualized as a patterned response to IL-17 that induces protective innate immunity to *Candida albicans* skin infection and where an absence of IL-17 increases risk of chronic mucocutaneous candidiasis [22,28]. Rather than driven by an exogenous antigen that activates Th17 T-cells, psoriasis would represent chronic activation of this pathway through endogenous (auto-) antigens and on a disease background where negative immune regulation (Tregs and immune checkpoints) is relatively defective [29,30]. Many risk alleles of psoriasis inheritance encode proteins that direct the differentiation of Type 17 T-cells. Thus we consider that psoriasis is largely an example of 'polar' Type 17 immunity creating a characteristic tissue phenotype and this view is cemented by the observation that ~90% of patients with psoriasis vulgaris can be successfully treated by specific IL-17 antagonists [19].

As illustrated in Figure 1a, psoriasis is associated with tissue infiltration by many myeloid dendritic cells that produce TNF and iNOS (TIP-DCs) as well as IL-23 [16,31]. The activation and survival of T17 T-cells in psoriasis lesions is highly dependent on IL-23, as shown by treatment with specific IL-23 antibodies [20,32–34]. At this level of mechanism, psoriasis is distinguished from AD by (1) the absence of Th2 T-cells that synthesize IL-4, IL-5, and IL-13, (2) the absence of IgE antibodies, which are strongly dependent on activated Th2 T-cells, and (3) differences in the CD11c+ dermal DC populations [8,35,36] which favor Th2 T-cell activation in AD (Figure 1b,c). Activated B-cells are largely absent in psoriasis patients, whereas activated B-cells that produce IgE are commonly seen in the circulation of AD patients. Systemic inflammation does occur commonly in psoriasis as evidenced by increased levels of pro-inflammatory cytokines, for example, IL-17 and TNF [37–39], increased activation of circulating T-cells, and co-morbid diseases such as psoriatic arthritis, obesity, metabolic dysregulation, and cardiovascular disease that stem from inflammatory etiologies. A future challenge in psoriasis is better treatment of psoriasis-associated co-morbid conditions that drive a shorter lifespan of psoriasis patients. Highly effective treatments for moderate-to-severe psoriasis are now centered on cytokines of the IL-23/Type17 axis: IL-17 or IL-17 receptor antibodies, TNFα antagonists, and emerging IL-23 antagonists, as well as ustekinumab, which is a dual IL-12/IL-23 antagonist [8,40]. We note that TNFα serves two roles in psoriasis: it is an upstream activator of TIP-DCs for synthesis of IL-23 and it synergizes with IL-17 for induction of many key psoriasis-related genes in keratinocytes [41]. Thus, in the context of psoriasis, a TNFα antagonist is an indirect antagonist of the IL-23/Type 17 T-cell pathway.

Atopic dermatitis

If psoriasis represents an example of a disease driven by a single polar immune pathway, AD represents a disease (or disease spectrum) driven by multiple polar immune pathways that create different disease features [6,10,13,42–44]. Two T-cell subsets — Th2 and Th22 — are commonly present and activated across the major subtypes of AD (Figure 1b,c). The epidermal hyperplasia response in chronic AD is probably driven directly by IL-22 produced

Figure 1



This cartoon diagrams common T-cell immune axes and associated cytokines in psoriasis and atopic dermatitis (left and right) from European-American populations versus Asian atopic dermatitis (middle). Varying degrees of 'polar' T-cell cytokines are seen across the disease forms, but importantly high Th2 activation is a feature across atopic dermatitis sub-types, but it is largely absent in psoriasis. Asian atopic dermatitis thus combines features of both psoriasis and atopic dermatitis as defined through study of European-American populations. Allergy (IgE class-switching) is proposed to originate in atopic dermatitis from immunoglobulin isotype switching driven by IL-4 and IL-13 contributed from activated Th2 T-cells.

by Th22 T-cells, as this disease feature was more responsive to an IL-22 antibody in AD as compared to use of the same antibody in psoriasis patients; still the STAT3 activation response in keratinocytes would be similar in AD and psoriasis, although different 'IL-20 family' cytokines may be drivers [5,6,11,14,15]. Reduced keratinocyte terminal differentiation and the associated epidermal barrier defect in AD would arise in most patients though direct effects of IL-22 and Th2 cytokines (IL-4 and IL-13) on keratinocyte differentiation. The allergic association with AD probably represents the effect of chronic activation of Th2 T-cells with IgE isotype class-switching driven by IL-4 and IL-13 [44,45]. Th2 T-cell activation is present in virtually all cases of AD, irrespective of whether IgE levels are elevated (intrinsic vs. extrinsic AD), so the actions of Th2 chemokines are probably more directly related to the skin phenotype [46,47]. Some subtypes of AD also have a strong association with Type 17 T-cells and increased production of IL-17 [6,10]. Interestingly, new onset pediatric AD has only an expanded Th2 frequency in the blood, but skin lesions have robust activation of Th2, Th17, and Th22 T-cell populations [11,13,48]. In EA-AD cases, the Th17 axis must then be down-regulated in adults with extrinsic AD, but it remains expressed at an increased level in intrinsic AD cases [15]. Asian AD is a disease with both psoriasis and EA-AD features, as well as robust activation of Th2, Th17, and Th22 T-cells in skin lesions, overall similar to pediatric AD [14]. However, another immunologic distinction between pediatric and adult cases is that presence and activation of Th1 T-cells appears mainly in adults with chronic AD. Potentially activation of the

IL-12/Th1 axis could be suppressive of IL-17 production in individual cases, as proposed for psoriasis, but Asian AD — studied thus far only in adults — has co-expression of IL-17 and interferon-γ at elevated levels. Asian AD has more epidermal acanthosis than EA-AD as well as foci of parakeratosis, as seen in psoriasis. Neutrophil infiltration has been described more consistently in Asian AD versus EA-AD, which is another overlap with the psoriasis phenotype [49,50]. Hence Asian AD represents a blended phenotype between psoriasis and EA-AD, but with allergy potentially being even more common in Asian AD patients, the key distinction from 'pure' psoriasis would be Th2 T-cell activation driving IgE responses and overt allergy [14,51]. Immunological comparisons between AD and psoriasis patients within Asian populations deserve more study, especially with higher AD prevalence and lower psoriasis prevalence in these regions [5]. An important question is whether higher Th2 activation is conferred by the genetic make-up of Asian populations and thus some cases of 'pure' psoriasis might be converted to an AD phenotype by increased Th2 activation, although other details such as antigen-specificity, auto-reactivity, and dendritic cell polarity might also be disease distinctions. Thus another aspect of the psoriasis versus AD comparison is in the dermal dendritic cell phenotype. It is considered that TSLP is a key cytokine directing the activation of Th2 T-cells. TSLP is produced at high levels in both psoriasis and AD, but dendritic cells in AD selectively have high level expression of the TSLP receptor. In addition, dendritic cells in AD have prominent expression of OX40L, which directs Th2 polarization of T-cells via induced OX40 expression on activated T-cells. Another distinguishing marker of 'atopic' DCs is high expression of the Fc-receptor for IgE (FcεR), which again is a link to allergic inflammation [2,12,52].

Therapeutic targeting in atopic dermatitis (AD)

Therapeutic targeting in AD is thus more complicated than in psoriasis, as multiple immune axes contribute different pathogenic disease features [3,4,8]. Broad inhibition of T-cell activation (across all activated axes) with cyclosporine is highly effective at suppressing AD, but this drug can be used only for relatively brief periods due to renal toxicity and relapses are rapid upon discontinuation [53]. It is thus desirable to develop well-tolerated biologic agents or other drugs that can be used to manage AD on a chronic basis, as in psoriasis. Remarkable progress has been made with the recent approval of dupilumab, an antibody to the IL-4 receptor which blocks the receptor binding of IL-4 and IL-13 [54–56]. With this treatment, ~60% of patients attain an EASI75 response and ~35% attain an EASI90 response. This drug also lowers IgE levels in over the first 12 weeks of treatment, but not to levels that would prevent allergic responses [57]. At face value, the outcome of dupilumab treatment argues for Th2-mediated pathogenesis in AD, but inflammatory pathways modulated by this drug extend to the IL-23/Th17/Th22 axes, perhaps mediated by effects of IL-4 receptor blockade in cutaneous dendritic cells [55]. Also, as a 'pure' Th2 disease, one would expect that therapeutic success might be comparable to IL-17 antagonists in psoriasis where PASI75 and PASI90 responses are ~90% and ~60%, respectively, using ixekizumab or brodalumab [58,59]. Therapeutic success has also been demonstrated with the ILV-094 anti-IL-22 antibody, establishing a pathogenic contribution of IL-22 in AD [10]. Thus, AD might best be considered a 'multi-axis' immune disease and with need for combined blockade of Th2, Th22, and potentially Th17 immune axes, as these pathways are expressed in different AD sub-types. Whether the IL-23/Type 17 axis is important in AD pathogenesis must still be determined by selective antagonism in clinical studies [60], but if it contributes to pathogenesis in Asian AD or other subsets, then AD might be a disease where personalized treatment approaches are needed. The emerging development of bi-specific and tri-specific antibodies also provides a potential means to target a more complex set of pathogenic cytokines than in psoriasis vulgaris, a disease effectively targeted by single cytokine-targeting.

In sum, both psoriasis and AD are examples of diseases in which the increased understanding of the molecular maps and inflammatory pathways is leading to successful therapeutic developments. Although psoriasis is centered on Type 17 responses, AD is Type 2 and Type 22-skewed, with common Type 1 polarization in chronic lesions. Although AD lags behind psoriasis in terms of clinical improvement rates, there is rapid therapeutic development and target validation in this disease, with many ongoing clinical trials. Future studies should evaluate whether some AD subsets, such as Asian AD patients, can benefit from psoriasis-based treatments.

Acanthosis: Increased epidermal hyperplasia
Parakeratosis: Retained Nuclei in the outer layers of the epidermis.

Funding

Authors received no funding for this manuscript.

Conflict of interest statement

The authors declare no conflicts of interest.

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