limits their ability to assess whether tanning addiction is a causal or correlative factor relative to the behavioral health conditions assessed in this study. Future research will benefit from longitudinal studies to determine whether tanning addiction is a predictor or indicator of these comorbidities (for example, whether tanning addiction leads to OCD or is a symptom of OCD). Examining potential mediators of the associations between tanning addiction and behavioral health conditions will facilitate the evaluation of mechanisms of interventions to address tanning addiction. The Miller et al. study is an important first step in identifying targets for intervention.

**Intervention Directions**

The U.S. Preventive Services Task Force (USPSTF) recommends behavioral counseling for the primary prevention of skin cancer (USPSTF et al., 2018). The USPSTF defines behavioral counseling interventions as those that reduce UV exposure, which would include those that promote the avoidance of indoor tanning (USPSTF et al., 2018). However, the literature on tanning behavior lacks interventions designed to address tanning addiction specifically. Research to design, implement, and disseminate effective interventions for tanning addiction is of paramount importance.

Miller et al. (2018) call for further research to develop intervention approaches to address tanning addiction in the context of the comorbidities identified in their study. Research is needed to further elucidate common factors that influence tanning addiction and behavioral health conditions. Indoor tanning-specific interventions likely will be needed in addition to, or as a component of, interventions that address comorbidities. Miller et al. extend previous research by describing the prevalence of tanning addiction in adolescents and examining behavioral health conditions that are associated with tanning addiction to inform interventions. Alongside this focus on interventions, continued advancement of measurement tools to screen for tanning addiction, in adolescents and the general population, will enhance research to assess prevalence of tanning addiction, identify correlative or causal factors, and evaluate the effectiveness of interventions.

**CONFLICT OF INTEREST**
The author states no conflict of interest.

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**IL-17C: A Unique Epithelial Cytokine with Potential for Targeting across the Spectrum of Atopic Dermatitis and Psoriasis**

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Both atopic dermatitis (AD) and psoriasis are characterized by complex inflammatory circuits that may be regulated through “feed-forward” mechanisms in the epidermis that amplify cellular immune responses through production of keratinocyte-derived cytokines and inflammatory mediators. IL-17C is a unique cytokine that is produced by keratinocytes and that is involved in such synergistic loops that may be responsible for amplifying the inflammation in both diseases. This may ultimately lead to induction of $100A$s and other molecules that accompany epidermal hyperplasia. Thus, antagonism of IL-17C may be beneficial in both psoriasis and AD patients. The IL-17C neutralizing antibody MOR 106 was able to inhibit both T helper type 2 cells and T helper type 17/T helper type 22-skewed inflammatory loops that drive different features of AD and psoriasis. The therapeutic potential of IL-17C antagonism in AD is supported by a recently reported small phase 1 clinical trial in patients with AD.


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Clinical Implications

- IL-17C is a keratinocyte-produced cytokine that is overexpressed in atopic dermatitis and psoriasis.
- IL-17C stimulates synthesis of many inflammatory products also induced by IL-17A/F.
- An IL-17C antibody improves skin inflammation in models and in atopic dermatitis.

The view of atopic dermatitis (AD) and psoriasis as polar immune diseases, with AD largely being T helper (Th) type 2 driven and psoriasis being Th17/Th1 driven, has recently been expanded to include roles for other “polar” T-cell subsets. Based on emerging data from targeted therapeutics, AD appears to be both Th2 and Th22 driven, with variable Th1 and Th17 activation (Guttman-Yassky et al., 2017, 2018; Guttman-Yassky and Krueger, 2017). However, whereas psoriasis appears to be a relatively homogeneous disease that is centered on Th17/IL-23–driven inflammation, AD shows heterogeneity across different phenotypes (Esaki et al., 2016; Noda et al., 2015; Suarez-Farinas et al., 2013). For example, although sharing Th2 activation, some AD phenotypes (including Asian AD, intrinsic AD, and pediatric AD) show higher IL-17 expression and histologic features that are also seen in psoriasis (Esaki et al., 2016; Noda et al., 2015; Suarez-Farinas et al., 2013). Although novel Th2 targeting strategies for AD such as dupilumab (targeting the IL-4R) show significant benefit in AD patients, there is still a large proportion of patients who do not achieve complete or near complete disease resolution, as evidenced by Eczema Area and Severity Index-90 results approximating 30%. In contrast, treating psoriasis with Th17/IL-23 antagonists leads to Psoriasis Area and Severity Index-90 responses in 70–80% of patients (Hawkes et al., 2017; Kim and Krueger, 2017). Hence, AD may be a more heterogeneous disease phenotype that reflects interactions between Th2 cytokines with variable contributions of IL-17, IL-22, and other cytokines.

Although psoriasis and AD may have differing mixtures of driver cytokines derived from distinct polar T-cell subsets, some features of the epidermal response are similar and include strong overexpression of S100A7, S100A9, and S100A9 proteins in keratinocytes. There is also the view that complex inflammatory circuits in both diseases may be regulated through a “feed-forward” mechanism in the epidermis that amplifies cellular immune responses through high-level production of keratinocyte-derived cytokines and inflammatory mediators. As will be discussed further, overproduction of IL-17C by keratinocytes in both AD and psoriasis may drive feed-forward inflammation, including induction of the S100A7–A9 proteins that accompany psoriasiform hyperplasia in both conditions.

The IL-17 family of cytokines includes IL-17A and IL-17F, which are products of activated lymphocytes, and IL-17E (IL-25) and IL-17C, which are products of epidermal keratinocytes and other nonimmune cell types. IL-17C was discovered as a gene with a role in AD (IL-1A) (Ramirez-Carrozzi et al., 2011), the actions of this cytokine may come to dominate the IL-17 response axis in chronic inflammatory conditions.

Vandeghinste et al. (2018) propose that antagonism of IL-17C may be beneficial in both psoriasis and AD patients. IL-17C is a unique cytokine with distinct features (Fritz et al., 2017; Song et al., 2011). Unlike other members of the IL-17 family, such as IL-17A and IL-17F that are produced by Th17 T cells, IL-17C is an epidermal cytokine primarily produced by keratinocytes in the skin (Ramirez-Carrozzi et al., 2011). Furthermore, expression of IL-17C has been shown to be induced in model systems by innate proinflammatory cytokines that were suggested to have a role in AD (IL-1β or psoriasis (TNF-α) (Conrad and Gilliet, 2018; Ewald et al., 2017; Kezic et al., 2012; Suarez-Farinas et al., 2015). Although IL-17C has been previously implicated in psoriasis (Johansen et al., 2009; Johnston et al., 2013), with increased expression in psoriasis lesions, its role in AD has not been previously appreciated.

Vandeghinste et al. (2018) tested IL-17C expression in skin lesions from psoriasis and AD showing increased protein expression compared with control skin. The authors also showed amelioration of inflammation in an IL-23 injection mouse model of psoriasis inflammation, a model of acute AD (low calcemic Vitamin D3 analog MC903), and the flaky tail mouse model of established eczematous dermatitis using an antibody to IL-17C, MOR106 (MorphoSys, Planegg, Germany), that binds to and inhibits both mouse and human IL-17C (MorphoSys, 2018). Although the IL-23 injection mouse model has been previously
proposed to simulate psoriasis, this model shows even better homology to the AD phenotype (Ewald et al., 2017; Suarez-Farinas et al., 2015). Nevertheless, a MOR106-attenuated psoriasis-form dermatitis to levels similar to those achieved upon dexamethasone administration in all models. Furthermore, the AD-like models showed reductions in Th2-related products such as IL-4, IL-33, TSLP, and CCL17 that promote atopic or allergic manifestations, whereas the IL-23—induced mice exhibited reductions in Th17/Th22-related products such as IL-17A, IL-22, lipocalin 2, S100A8, and S100A9. In vitro keratinocyte cultures showed that the IL-17C antagonist MOR106 effectively reduced IL-17-induced genes such as defensin-β (DEFB4).

These data have important therapeutic implications for both AD and psoriasis, because the IL-17C neutralizing antibody MOR106 was able to inhibit both Th2- and Th17/Th22-skewed inflammatory loops, which drive different features of AD and psoriasis. Thus, overexpression of IL-17C could be a common denominator of both diseases, but more work is needed to examine expression of IL-17C in distinct AD subtypes (intrinsic/extrinsic, European American/Asian, and pediatric onset), which have differing levels of IL-17, IL-22, and IFN-γ expression. The therapeutic potential of IL-17C antagonism in AD is supported by a recently reported clinical trial that tested placebo versus three different doses (1, 4, and 10 mg/kg) of the MOR106 antibody in 25 patients with moderate to severe AD (clinicaltrial.gov NCT02739009). In a late-breaking presentation at the 2018 American Academy of Dermatology meeting (Thaci, 2018), this trial showed that approximately 80% of AD patients treated with higher doses of MOR106 attained Eczema Area and Severity Index-50 improvement compared with less than 20% in the placebo arm. Continuing improvement in drug-treated patients was observed during a follow-up period of 8 weeks. Although the study was small, these data are encouraging and support further studies in larger cohorts of patients with AD across different AD phenotypes, around the globe, and in other inflammatory skin diseases, particularly psoriasis.

In sum, IL-17C seems to be an intriguing epithelial cytokine that may have a potential role in inflammatory skin diseases because of its unique properties of amplifying inflammation, regardless of the primary stimuli of the disease. It is also tempting to speculate that IL-17C might be a key link between the cutaneous microbiome and induction of IL-17—centered inflammation. Future clinical trials with IL-17C—targeting strategies will shed light on its pathogenic role in these diseases.

**CONFlict OF INTEREST**

The authors state no conflict of interest.

**REFERENCES**


