bowel disease, and asthma (reviewed in Gensollen and Blumberg, 2017). The mechanism may involve imprinting of poorly defined immune responses during an early-life "window of opportunity" by interactions between commensal organisms and the host that have profound implications for subsequent disease propensity. For example, microbial colonization during pregnancy in mice has powerful effects on innate immunity in the offspring (Gomez de Aguero et al., 2016).

The intriguing study by Mehta et al. using a novel SSc-relevant immunization approach to model scleroderma provides evidence that early-life antibiotic exposure causes durable gut dysbiosis associated with exacerbated later-life fibrosis. Whether the profibrotic effects of gut dysbiosis are specific to the novel model induced by anti-topoisomerase-I immunity, or are reproducible in more commonly used and extensively characterized disease models, is an important question to be addressed. Additionally, the cellular mechanisms underlying this phenomenon remain to be elucidated. For instance, is increased later-life fibrosis propensity in the immunized mice due to antibiotic-induced early-life alterations shaping the immune system, or due to persistence of the microbiome alterations? Although the clinical implications of the findings by Mehta et al. are not yet clear, the findings are in line with accumulating evidence that early-life dysbiosis causes durable alterations in the intestinal microbiota that are associated with long-lasting health effects and implicated in a variety of autoimmune, atopic, and inflammatory diseases in adulthood. The present findings add fibrotic conditions to this list, suggest new directions in contemplating the role of environment in SSc pathogenesis, and should inspire further investigations. Ultimately, delineating the nature and contribution of gut dysbiosis to SSc pathogenesis might present new therapeutic opportunities.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Per journal regulations, we are restricted to a limited number of references. However, many original papers are cited in the listed review articles. We acknowledge partial support by grants from National Institutes of Health (K08 HL130601 to KJH and R56 AG054207 to JV).

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Desmoglein 3-Reactive B Cells "Hiding" in Pemphigus Lesions

Hayato Takahashi[1]

Pemphigus vulgaris is an autoimmune blistering disease caused by anti-desmoglein 3 IgG autoantibodies. It is accepted that interactions between autoreactive B and T cells are key to humoral autoimmunity targeting desmoglein 3. This orchestrated process usually occurs in secondary lymphoid organs, including the spleen and lymph nodes. Thus, it seems likely that autoreactive B cells reside and produce autoantibodies in these tissues. Yuan et al. analyzed lymphocytes in the lesional skin of patients with pemphigus vulgaris using several experimental techniques and concluded that desmoglein 3-reactive B cells were present. This finding expands our understanding of the pathogenesis of pemphigus and should be considered when following the clinical course of skin lesions and thinking about adjunctive therapy.

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Pemphigus is an autoimmune blistering disease that is induced by autoantibodies against the cadherin-type desmosomal adhesion molecules, desmoglein (Dsg) 1 and 3. Pemphigus vulgaris and pemphigus foliaceus are classical subtypes of pemphigus. Patients with pemphigus foliaceus produce only

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Clinical Implications

- Desmoglein 3-reactive B cells accumulate in the lesional skin of patients with pemphigus vulgaris.
- IL-17 and IL-21 are produced by lesional T cells.
- T and B cells colocalized and CCL19 was upregulated in inflamed lesional skin.

anti-Dsg1 antibodies, which can induce acantholysis within the granular layer of the epidermis, whereas patients with pemphigus vulgaris produce anti-Dsg antibodies, which can induce acantholysis at suprabasilar locations in the oral mucosa (in patients with anti-Dsg3 only) and skin (in patients with anti-Dsg3 and anti-Dsg1). Typically, biopsies from recent bullous lesions show acantholysis with only a few inflammatory cells in the dermis. In contrast to pemphigoid, pemphigus blister formation is not regularly accompanied by inflammation. Eosinophilic spongiosis is the only inflammatory hallmark that is regularly described in the early phase of disease as a characteristic finding in pemphigus (Emmerson and Wilson-Jones, 1968).

It was recently reported that a large numbers of T lymphocytes (2×10^{10} cell per person) reside in healthy human skin, although inflammation is not apparent in vertical histologic sections (Clark et al., 2006). This number is almost twice the number of T cells that circulate in peripheral blood. A previous report indicated that detecting B cells in skin using immunohistochemistry is difficult (Nihal et al., 2000), and there is no reliable information on how many B cells reside in normal skin. Thus, detection of small numbers of B cells in normal or lesional skin may be very significant.

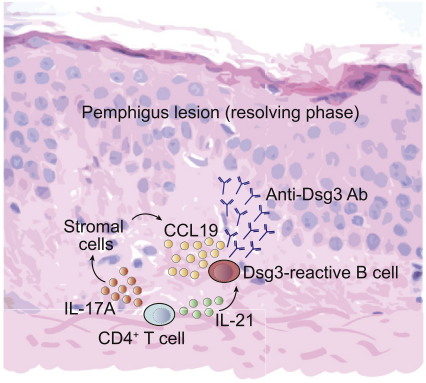

Figure 1. Accumulation of Dsg3-sepcific B cells in pemphigus lesions. In the resolving phase of pemphigus lesions, stromal cells likely produce CCL19 chemokine that recruits lymphocyets and promotes tertiary lymphoid organ formation. Dsg3-reactive B cells and $CD4^+$ T cells are included in among the cells that are recruited. $CD4^+$ T cells in lesional skin produce IL-21 and IL-17A that facilitate antibody production from B cells and induce epithelial cells and stromal cells to produce chemokines, respectively. Ultimately, lesional Dsg3-specific B cells produce anti-Dsg3 antibodies, probably, in vivo. CCL, CC chemokine ligand; Dsg, desmoglein.

Inflammation in chronic lesions in patients with pemphigus has been thought to be nonspecific and perhaps secondary to epithelial barrier dysfunction. The paper by Yuan et al. (2017) reports that B cells are included among the inflammatory cells in skin lesions of patients with pemphigus vulgaris. No acantholysis was observed in the histology shown in Figure 3 of the paper. Thus, skin lesions analyzed in this study might be nonbullous lesions or re-epithelized resolving lesions. However, the B-cell accumulation in pemphigus vulgaris lesions was not nonspecific because Dsg3-reactive B cells were enriched in lesional tissue as compared with the systemic circulation.

This interesting observation raises some new questions. What mechanisms are responsible for the accumulation of Dsg3-reactive B cells in skin? Is a special antigen-presenting cell, such as a follicular dendritic cell that presents antigens directly to B cells, involved in the antigen-specific B-cell recruitment in skin? Is there a tertiary lymphoid organ (TLO) that functions as a scaffold for this process? Answers to these questions would further our understanding of skin immunology, especially as it relates to tissue B cells.

Unlike primary lymphoid organs (thymus and bone marrow) and secondary lymphoid organs (spleen and lymph node), the anatomic locations of TLOs are not fixed and TLOs can be induced during chronic inflammation. Histologically, distributions of T and B cells are compartmentalized in lymphoid organs. TLOs feature lymphoid follicles and support immune responses. In fact, germinal center formation (Takemura et al., 2001), activation-induced cytidine deaminase expression (Bombardieri et al., 2007) that is essential for class-switch recombination and somatic hypermutation in germinal center, and even recombination-activating gene (Rag) expression (Armengol et al., 2001) have been observed in TLOs.

TLOs can be induced by *Helicobacter pylori* infection (Mazzucchelli et al., 1999) and hepatitis C virus infection (Mosnier et al., 1993), and can sustain chronic inflammation that counters invading pathogens by producing antibodies to pathogen components. In autoimmune diseases, TLOs have been observed in synovia of patients with rheumatoid arthritis (Takemura et al., 2001) and thyroids of patients with autoimmune thyroid disease (Armengol et al., 2001). Anti-cyclic citrullinated peptide antibody and rheumatoid factor-producing cells were also detected in TLOs in lung tissue in patients with rheumatoid arthritis with pulmonary complications (Rangel-Moreno et al., 2006). Developmental aspects of TLOs have been clarified. Stromal cell-derived homeostatic chemokines (e.g., CXCL13, CXCL12, CCL21, and CCL19) are important in lymphocyte homing and compartmentalization during secondary lymphoid tissue development (Aloisi and Pujol-Borrell, 2006), and those chemokines are similarly upregulated in TLOs. Stromal cell production of CXCL12 and CXCL12/13, induced by IL-17 (Fleige et al., 2014) and IL-22 (Barone et al., 2015) respectively, has been shown to be important for TLO formation.

Yuan et al. (2017) demonstrated IL-17 and IL-21 production by a small number of $CD4^+$ T cells, CCL19 upregulation, and colocalization of T and B cells in lesional skin, suggesting the possibility of TLO formation in pemphigus skin lesions (Figure 1). T cells and B cells were diffusely distributed, and compartmentalization was not observed. Thus, whether TLOs occur in pemphigus lesions is uncertain. Importantly, however, lesional B cells

produced anti-Dsg3 antibodies without stimulation in vitro, suggesting that these cells probably produce autoantibodies in vivo (Figure 1). How important is local production of autoantibodies in pemphigus? In the case of pemphigus foliaceus, skin lesions sometimes persist in very limited areas, such as seborrheic areas, despite systemic therapy and clearing of lesions elsewhere. Theoretically, circulating autoantibodies should affect all areas. These observations suggest that autoreactive B cells could accumulate in chronic lesions, where local inflammation might contribute to further autoantibody production and lesional recalcitrance.

The paper by Yuan et al. (2017) reports an unexpected discovery and provides additional insights into the pathogenesis of pemphigus. If the mechanisms that facilitate B-cell accumulation and antibody production in pemphigus lesions can be defined, local treatment for that targets autoreactive B cells might become attractive as a supporting therapy in the future.

CONFLICT OF INTEREST

The author states no conflict of interest.

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Pushing the Envelope in Psoriasis: Late Cornified Envelope Proteins Possess Antimicrobial Activity

Nathan K. Archer[1], Migena N. Dilolli[1] and Lloyd S. Miller[1,2,3,4]

Deletion of late cornified envelope (LCE) genes *LCE3B* and *LCE3C* (*LCE3B/C-del*) is a psoriasis risk factor linked to the major psoriasis risk gene *HLA-C*06*. Niehues et al. demonstrate that *LCE3B/C-del* leads to increased keratinocyte *LCE3A* expression. They also show that LCE3A/B/C possess antimicrobial activity but do not obviously regulate epidermal barrier integrity. These findings implicate LCE proteins in psoriasis pathogenesis via a new functional role.

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Gene polymorphisms in psoriasis

Psoriasis is a common inflammatory skin disease that is thought to primarily be mediated by dysregulated T helper type 1 (Th1) and Th17 immune responses (Nestle et al., 2009). Psoriasis also has a genetic predisposition, and recent genome-wide association studies have identified more than 60 susceptibility loci that account for 20–25% of the heritability of psoriasis (Tsoi et al., 2012). The functional consequences of these gene associations in psoriasis have been difficult to study, although therapeutic targeting of blockade of tumor necrosis factor, IL-12, and IL-23 supports important roles of genetic variations in *TNFAIP3*, *IL12B*, and *IL23R* (Johnston et al., 2013; Tejasvi et al., 2012). This is especially the case with two of the strongest genetic risk factors associated with psoriasis including the major histocompatibility complex class I gene *HLA-C*06:02* (odds ratio ~2.6–5) (also known as PSORS1) and

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