Is Local Production of Autoantibodies in Skin Lesions Relevant in Pemphigus?

Hisashi Nomura¹ and Masayuki Amagai¹,²

Pemphigus is an autoimmune bullous disease characterized by IgG production against desmogleins. The major sites of autoantibody production are thought to be lymph nodes, spleen, and bone marrow. Previously, it has been suggested that autoreactive B cells might exist in the skin lesions in pemphigus and produce autoantibodies. In their report, Zhou et al. expanded their previous studies and reported that ectopic lymphoid-like structures were found in pemphigus skin lesions, wherein B-cell differentiation and lesional B-cell expansion might progress. This finding provides novel insights into B-cell biology in pemphigus.


Pemphigus is an autoimmune bullous disease in which autoantibodies bind to desmoglein (Dsg), a cell adhesion molecule in the epidermis. Pemphigus thus results in the loss of cell-cell adhesion between keratinocytes, leading to blister formation in the skin and mucous membranes (Amagai et al., 1991; Kasperkiewicz et al., 2017). Pemphigus vulgaris (PV), which affects predominantly mucous membranes, is caused by IgG autoantibodies against Dsg3, whereas PV affecting both the skin and mucosa is induced by IgG autoantibodies against Dsg1 and Dsg3. Pemphigus foliaceus (PF) only affects the skin and is caused by IgG autoantibodies against Dsg1 (Kasperkiewicz et al., 2017). These autoantibodies are generated by antibody-secreting cells derived from Dsg-specific B cells, and rituximab, a monoclonal antibody against CD20⁺ B cells, has been shown to be effective as a treatment for pemphigus (Joly et al., 2017). Despite this clear evidence that autoreactive B cells play a pivotal role in the pathophysiology of pemphigus, the detailed mechanism by which Dsg3-specific B cells generate autoantibodies has not been fully elucidated. Although the primary sites of autoantibody production are thought to be lymph nodes, spleen, and bone marrow, whether or not ectopic autoantibody production exists in other sites, especially in skin and mucous membranes, is unclear.

Recently, Yuan et al. (2017) reported that Dsg3-reactive B cells were found in pemphigus skin lesions and produced Dsg3-specific antibodies in vitro, suggesting that these cells could also produce autoantibodies in vivo. This unique observation offered new insights into B-cell biology in pemphigus with an opportunity to further clarify detailed pathomechanisms underlying the accumulation of these B cells and autoantibody production in lesions. In their report, Zhou et al. (2019) reported that diffuse ectopic lymphoid-like structures (ELSs) that resembled tertiary lymphoid structures (TLSs) were found in skin lesions of patients with both PV and PF. They suggested that B-cell differentiation and lesional B-cell expansion might occur in TLSs.

The role of TLSs in autoimmune diseases has recently attracted substantial research attention. TLSs are generated at sites of autoimmunity-mediated inflammation, including the synovium in rheumatoid arthritis (RA) and the salivary gland in Sjögren syndrome (Corsiero et al., 2019). TLSs can provide a suitable environment for the active differentiation, proliferation, and germinal center (GC) reaction of autoreactive B cells, leading to the production of autoantibodies (Corsiero et al., 2019). Although little is known about the functions of TLSs in skin, several features are coming to light through studies of dermatological diseases. For example, aggregates of B cells and plasma cells or lymphoid follicles containing GCs have recently been identified in lesions of lupus profundus (Kogame et al., 2018). Assemblages of B cells and T cells have also been detected in skin manifestations of Sjögren syndrome (Roguedas et al., 2010). By forming such localized TLSs, autoreactive B cells may exacerbate skin diseases.

The new contribution by Zhou et al. (2019) suggests the possibility that B-cell differentiation and expansion may occur in pemphigus ELSs in skin. They identified centroblasts, plasmablasts, and plasma cells in pemphigus lesions, thereby suggesting B-cell differentiation in ELSs. They also demonstrated that mRNA expression levels corresponding to B-cell differentiation—associated transcription factors BCL-6, BLIMP-1, and IRF4 were elevated in pemphigus lesions. BCL-6 is an essential factor for induction of GC responses, and IRF-4 plays a crucial role in the early phase of GC formation and plasma cell development. BLIMP-1 is an indispensable protein required to promote the differentiation of B cells into plasma cells. Thus, the elevated expression levels of these transcription factors in pemphigus lesions further suggested that the GC reaction and plasma cell differentiation may occur in the ELSs of pemphigus lesions.

Through B-cell receptor repertoire analysis, Zhou et al. (2019) detected clonal expansions in lesional B cells, which might recirculate among lesions, lymph nodes, and peripheral blood. A previous study indicated that a dominant antigen-specific local immune response shapes synovium-specific B cell clones in the TLSs of RA, and specific B cell clones expand within salivary glands in primary Sjögren

¹Department of Dermatology, Keio University School of Medicine, Tokyo, Japan; and ²Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan

Correspondence: Masayuki Amagai, Department of Dermatology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582 Japan. E-mail: amagai@keio.jp

© 2019 The Authors. Published by Elsevier, Inc. on behalf of the Society for Investigative Dermatology.

See related article on pg 309
Clinical Implications

- Ectopic lymphoid-like structures are found in lesional skin in patients with pemphigus.
- B cell differentiation and expansion are suggested in ectopic lymphoid-like structures in skin.
- These findings may provide an explanation for persistent skin lesions in localized forms of pemphigus.

syndrome (Pipi et al., 2018). The new observations by Zhou et al. (2019) suggest that specific clones also can be generated in pemphigus ELSs located in skin. It is interesting that lesional B cell clones overlap with peripheral B cell clones, and that a much higher fraction of clonal B cells was detected in the skin lesions than in peripheral blood.

Zhou et al. (2019) also indicate that multiple chemokines and chemokine receptors can be involved in the migration of lesional B cells. Lesional B cells expressed CXCR5 and CCR6 less often than peripheral B cells. This observation is in line with a previous report on synovial B cells in RA (Armas-González et al., 2018). Moreover, mRNA levels of CXCL13 (Yuan et al., 2017) and CCL20, encoding the respective ligands of CXCR5 and CCR6, were significantly elevated in pemphigus lesions. Because the surface expression of chemokine receptors is usually reduced via ligand binding, this suggests that CXCL13 and CCL20 negatively regulate the expression of CXCR5 and CCR6 in B cells upon binding. CXCR5 and CCR6 were also suggested to play a role in the migration of naive and memory B cells to the inflammatory synovium in RA (Armas-González et al., 2018). Thus, these chemokines may also be utilized to recruit naive and memory B cells into ELSs to coordinate GC reactions and drive the differentiation of lesional B cells into plasma cells and the migration of peripheral B cells into ELSs.

The findings reported by Zhou et al. (2019) bring new insights into the clinical complexities of pemphigus. In some cases, localized recalcitrant lesions persist without detectable circulating Dsg-specific antibodies, which could be explained by local antibody production from ELSs in pemphigus skin lesions (Vinay et al., 2015). In some cases, topical steroid monotherapy has been reported to be effective in localized pemphigus (Scully et al., 1999), and the effectiveness of intralesional rituximab (Vinay et al., 2015) has also been reported. These observations suggest ongoing local autoimmune reactions in lesional ELSs.

Important innovative studies always provoke further questions that remain to be answered. First, how sizeable is the contribution by local production of IgG autoantibodies in skin lesions to systemic circulating autoantibody levels? Second, if blister formation is caused by the Dsg-specific IgG autoantibodies produced in situ, does B-cell infiltration into skin precede blister formation? Or does anti-Dsg B-cell infiltration occur after blister formation induced by anti-Dsg IgG autoantibodies? Third, are lesional B cells that expand in skin and share repertoires with peripheral B cells specific for desmogleins? Do single-chain variable fragments or monoclonal IgG antibodies derived from the variable region sequences represented in lesional B cells bind specifically to desmogleins?

The findings of Zhou et al. (2019) open a door to potentially novel insights into autoimmune pathophysiological mechanisms that are operative in pemphigus.

ORCIDs
Hisashi Nomura: https://orcid.org/0000-0001-8586-6789

Masayuki Amagai: https://orcid.org/0000-0003-3314-7052

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES