Autoantibody-Mediated Macrophage Responses Provide the Missing Link between Innate and Adaptive Immune Dysfunction in Hidradenitis Suppurativa

John W. Frew[1,2,3]

Hidradenitis suppurativa is considered to be a T helper 17–mediated inflammatory disorder. However, the role of prominent B-cell and plasma cell infiltrates has not been incorporated into pathogenic understanding of the disease. In their new article in the *Journal of Investigative Dermatology*, Carmona-Rivera et al. (2021) present new insights regarding autoantibody-mediated macrophage activation, which bridges the link between the innate and adaptive immune responses in severe hidradenitis suppurativa.

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Hidradenitis suppurativa (HS) is a common inflammatory skin disease manifesting in recurrent episodes of painful nodules and abscesses in flexural areas of skin. It also manifests with epithelialized dermal tunnels, which are often hidden below the skin, that are associated with painful malodorous drainage and extensive scar tissue formation (Navrazhina et al., 2021a). HS is a complex immunological disorder with evidence of systemic inflammation. Our understanding of disease pathogenesis has slowly shifted from that of an infectious disorder, to an inflammatory disorder of apocrine glands, to a disorder of the follicular infundibulum, to a systemic disease with features of both autoinflammation and autoimmunity. The precise pathogenesis of HS remains incompletely understood. In their new article in the *Journal of Investigative Dermatology*, Carmona-Rivera et al. (2021) present exciting novel evidence linking the well-characterized innate immune dysfunction in HS with activation of the adaptive immune system and autoantibody formation. Multiple autoantibodies targeting cellular membrane and nuclear components were identified in serum, and autoantibodies against cytokines were identified in lesional tissue. The severity of clinical disease, as measured by Hurley stage, strongly correlated with the presence of autoantibodies in tissue. These immune complexes stimulated the production of proinflammatory cytokines in vitro, including those involved in the amplification of the T helper (Th) 17 immune response.

HS as a Th17-mediated disorder

The evidence for innate immune dysfunction in HS is largely based on cutaneous Th17 dysregulation, supported by observations of psoriasiform hyperplasia in epidermal histopathology and elevated expression of Th17-associated genes, including *IL17A*, *IL17C*, *IL17F*, *CXCL1*, and *CXCL8*. Th17 axis immune dysregulation is also reflected in the serum of patients with HS, with elevation of CXCL1, CXCL8, LCN2, and other neutrophil-associated proteomic signatures that correlate with disease severity in serum.

The morphologies of HS lesions have direct associations with the degree of inflammation both in tissue (as identified by RT-PCR) and serum (as identified by proteomics) (Navrazhina et al., 2021a, 2021b). Epithelialized tunnels (mostly seen in Hurley stage 2 and Hurley stage 3 disease) have significant elevations in inflammation compared with overlying nodules (Navrazhina et al., 2021b). These tunnels also feature significant inflammatory infiltrates composed of dendritic cells (DCs), monocytes, macrophages, activated T cells, B cells, and neutrophils, including those undergoing NETosis. Although all of these cells are also present in the superficial dermis in HS lesions, they are present to a lesser extent, and they exhibit significantly decreased levels of inflammatory cytokines and chemokines.

The mechanistic roles of B cells and plasma cells in HS remain unclear

The presence of B cells and plasma cells in the tissue and serum of patients with HS (Byrd et al., 2019; Gudjonsson et al., 2020; Musilova et al., 2020) differentiates HS from other Th17 inflammatory dermatoses, such as psoriasis vulgaris. In tissue-based RNA sequencing, Ig and activated B-cell signatures are among the most highly dysregulated genes compared with nonlesional tissue and healthy controls. Autoantibodies against citrullinated peptides in NETosis (Byrd et al., 2019) and anti–*Saccharomyces cerevisiae* antibodies have been identified in severe disease (Assan et al., 2020). There has been discussion in the literature regarding whether such B cells and antibodies are merely bystanders or are pathogenically linked to HS through as-yet-unknown mechanisms (Frew et al., 2020).

Linking innate and adaptive immune dysfunction in HS

In their new article in the *Journal of Investigative Dermatology*, Carmona-Rivera et al. (2021) provide the first mechanistic evidence that H2B and cit-Histone H4 antibodies derived from patients with severe HS have the ability to stimulate the production

[1]*Laboratory of Translational Cutaneous Medicine, Ingham Institute of Applied Medical Research, Sydney, Australia;* [2]*Department of Dermatology, Liverpool Hospital, Sydney, Australia; and* [3]*University of New South Wales, Sydney, Australia*

Correspondence: John W. Frew, Department of Dermatology, Liverpool Hospital, Suite 7, Level 1, 45-47 Goulburn Street, Liverpool, 2170 Sydney, Australia. E-mail: john.frew@unsw.edu.au

of TNF-α, IL-8, IL-6, and IL-12/23 (p40) in M1 and M2 macrophages (Figure 1). This effect was potentiated by the presence of multiple IgG immune complexes from the serum of patients with HS. This provides an established link between the innate immune dysregulation seen in HS and the observed signatures of adaptive immune response, B-cell and plasma cell activation in the setting of severe HS (Figure 1). Proinflammatory activation of these macrophages is then likely to feed back to potentiate Th17 immune responses in T cells, DCs, and keratinocytes in HS lesions, leading to a self-perpetuating inflammatory cascade that characterizes severe forms of this disease. This evidence correlates with what is seen in the clinic, with current biologic therapeutics demonstrating lower rates of clinical response in patients with Hurley stage 3 disease.

This mechanism may not be applicable to all forms (particularly milder forms) of HS. The samples used in both this study and previous studies from the same group (Byrd et al., 2019) utilize tissue from African American patients with severe Hurley stage 3 disease with epithelialized tunnels. This concurs with observations of other groups that the B-cell, plasma cell, and autoantibody signatures in HS are only seen in those with severe systemic inflammation, which has been linked to the presence of epithelialized tunnels (Navrazhina et al., 2021b).

An additional implication of Carmona-Rivera's findings relates to the utility of serum autoantibodies as disease activity biomarkers in HS. The association of specific serum and tissue autoantibodies with clinical disease states in HS has the potential to be developed and appropriately validated as disease activity biomarkers in HS. With the development of novel therapeutics, including those more or less efficacious in the setting of disease heterogeneity (Navrazhina et al., 2021b), it is plausible to consider serum autoantibodies as potential biomarkers to stratify disease and inform targeted therapy recommendations in the future.

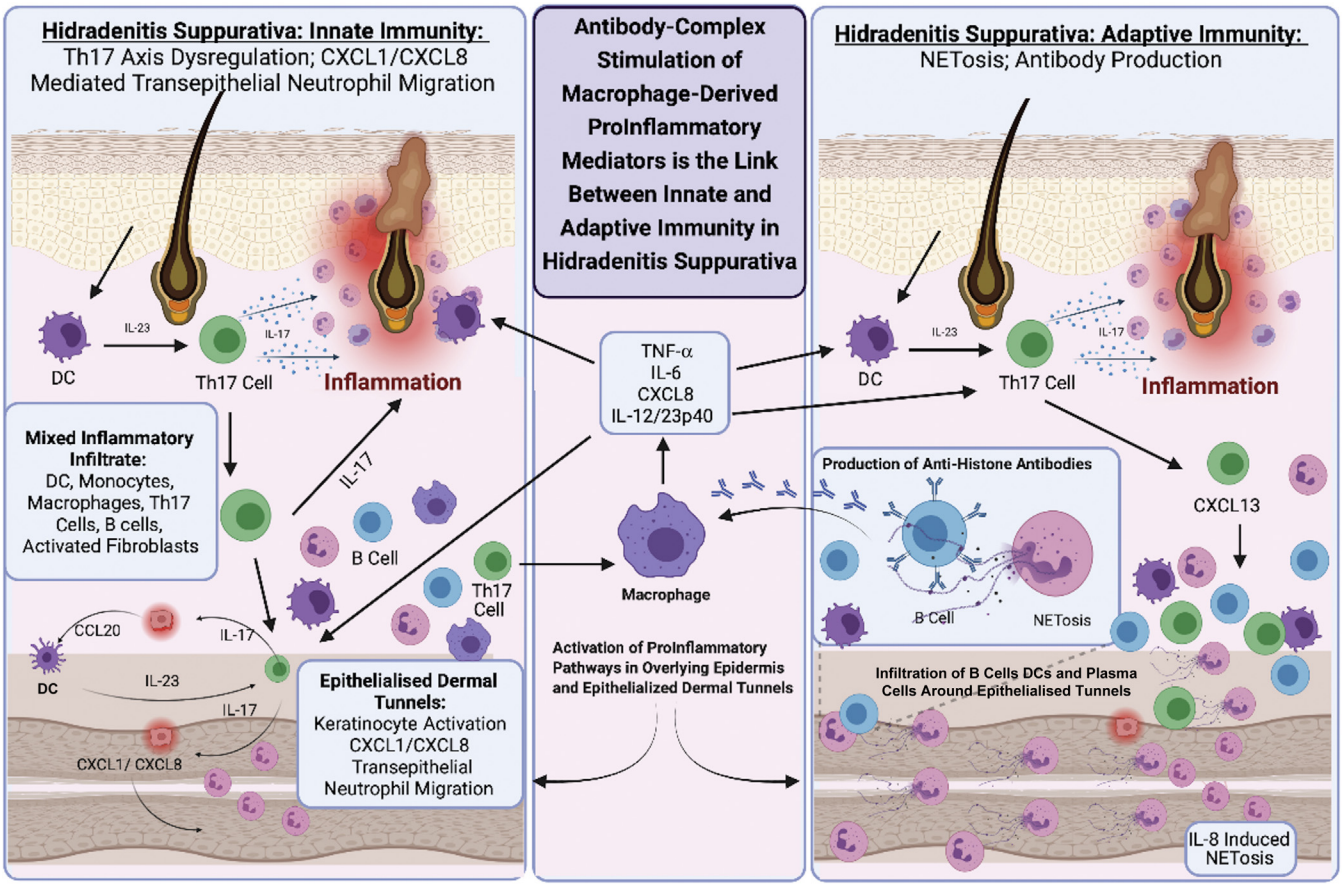

Figure 1. Autoantibody-mediated stimulation of macrophages bridges the connection between the innate and adaptive immune systems in hidradenitis suppurativa. The innate immune system in hidradenitis suppurativa has been characterized as largely a disorder of Th17 immunity with various predisposing factors (genetics, smoking, obesity) leading to DC activation, Th17 polarization with the resulting inflammatory infiltrates, and proneutrophilic milieu resulting in follicular rupture and ongoing chronic inflammation. A similar mechanism has recently been uncovered in epithelialized tunnels in the dermis with pseudopsoriasiform hyperplasia similar to the overlying epidermis (left panel). The adaptive immune system, including B cells and plasma cells, represents the most dysregulated genes in expression studies. Autoantibodies are found against a number of cellular, microbial, and cytokine targets, although until recently the mechanistic relevance of these observations has been unclear (right panel). The evidence presented, demonstrating proinflammatory cytokines produced by M1 and M2 macrophages on exposure to immune complexes and citrullinated autoantibodies, links the presence of B cells and plasma cells to known innate immune dysregulation in hidradenitis suppurativa and explains the ongoing self-perpetuating inflammatory cascade seen in severe disease. This also suggests novel therapeutic approaches targeting common cellular pathways in macrophages and B cells to intervene in this inflammatory cascade. DC, dendritic cell; Th, T helper type.

Novel therapies may include B cell– and macrophage-targeted therapies

These findings imply that, in severe recalcitrant HS, B cell–directed therapies may reduce the autoinflammatory cascade in HS lesions. This hypothesis is supported by reports of long-term disease remission and reduction in HS severity with the use of rituximab in the setting of coexistent lymphoma (Scheinfeld, 2013). It is also supported by recent observations that suggest that adalimumab (currently the sole Food and Drug Administration–approved biologic therapy for HS) acts by inhibiting the activity of B cells in severe HS (Lowe et al., 2020). A novel potential therapeutic target arising directly from these findings includes spleen Y kinase (SYK), an important kinase involved in the development of B cells and activity of macrophages (Gudjonsson et al., 2020). SYK is identified as upregulated in B cells in HS (Lowe et al., 2020; Gudjonsson et al., 2020), and SYK inhibitors are currently used in autoimmune hematological disorders, including idiopathic thrombocytopenia. Further research investigating the clinical impact of B cell–directed therapies (including SYK inhibition) in severe HS should be a priority for further translational research in the field.

ORCID

John W. Frew: http://orcid.org/0000-0001-5042-3632

CONFLICT OF INTEREST

JWF has conducted advisory work for Janssen, Boehringer Ingelheim, Pfizer, Kyowa Kirin, LEO Pharma, Regeneron Pharmaceutical, ChemoCentryx, AbbVie, and UCB; participated in trials for Pfizer, UCB, Boehringer Ingelheim, Eli Lilly, and CSL; and received research support from Ortho Dermatologics and Sun Pharmaceutical.

REFERENCES

Assan F, Gottlieb J, Tubach F, Lebbah S, Guigue N, Hickman G, et al. Anti-saccharomyces cerevisiae IgG and IgA antibodies are associated with systemic inflammation and advanced disease in hidradenitis suppurativa. J Allergy Clin Immunol 2020;146:452–455.e5.

Byrd AS, Carmona-Rivera C, O'Neil LJ, Carlucci PM, Cisar C, Rosenberg AZ, et al. Neutrophil extracellular traps, B cells, and type I interferons contribute to immune dysregulation in hidradenitis suppurativa. Sci Transl Med 2019;11:eaav5908.

Carmona-Rivera C, O'Neil L, Patino-Martinez E, Shipman W, Zhu C, et al. Autoantibodies present in hidradenitis suppurativa correlate with disease severity and promote release of proinflammatory cytokines in macrophages. J Invest Dermatol 2021. In Press.

Frew JW, Grand D, Navrazhina K, Krueger JG. Beyond antibodies: B cells in hidradenitis suppurativa: bystanders, contributors or therapeutic targets? Exp Dermatol 2020;29:509–15.

Gudjonsson JE, Tsoi LC, Ma F, Billi AC, van Straalen KR, Vossen ARJV, et al. Contribution of plasma cells and B cells to hidradenitis suppurativa pathogenesis. JCI Insight 2020;5:e139930.

Lowe MM, Naik HB, Clancy S, Pauli M, Smith KM, Bi Y, et al. Immunopathogenesis of hidradenitis suppurativa and response to anti–TNF-α therapy. JCI Insight 2020;5:e139932.

Musilova J, Moran B, Sweeney CM, Malara A, Zaborowski A, Hughes R, et al. Enrichment of plasma cells in the peripheral blood and skin of patients with Hidradenitis suppurativa. J Invest Dermatol 2020;140:1091–1094.e2.

Navrazhina K, Frew JW, Gilleaudeau P, Sullivan-Whalen M, Garcet S, Krueger JG. Epithelialized tunnels are a source of inflammation in hidradenitis suppurativa. J Allergy Clin Immunol 2021a;147:2213–24.

Navrazhina K, Garcet S, Gonzalez J, Grand D, Frew JW, Krueger JG. In-depth analysis of the hidradenitis suppurativa serum proteome identifies distinct inflammatory subtypes. J Invest Dermatol 2021b;141:2197–207.

Scheinfeld N. Hidradenitis suppurativa: a practical review of possible medical treatments based on over 350 hidradenitis patients. Dermatol Online J 2013;19:1.