The Journal of Allergy and Clinical Immunology
Manuscript ID: Reply to JACI-D-17-01722

Reply to Dr Valerio De Vita

Masashi Akiyama, MD, PhD

Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Key words: autoinflammation, autoinflammatory keratinization diseases, keratinization, hidradenitis suppurativa, acne inversa, gamma-secretase, follicular hyperkeratosis

Corresponding Author:
Masashi Akiyama M.D., Ph.D.
Department of Dermatology
Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya
Aichi 466-8550, Japan
Tel: +81-52-744-2318, Fax: +81-52-744-2318
E-mail: makiyama@med.nagoya-u.ac.jp

Conflicts of interest*: None declared*

Word, reference, table and figure counts: 489 words, 7 references, 0 tables, 0 figures

Reply

To the Editor:

I thank De Vita et al.[1] for their correspondence and for proposing that hidradenitis suppurativa (HS), also called acne inversa, should be regarded as an autoinflammatory keratinization disease (AIKD). In broad outline, I welcome their proposal and agree that HS has an autoinflammatory pathogenesis in which the primary inflammatory sites are the epidermis and the upper dermis, including the hair follicle epithelium.

Our article[2] defines AIKDs as having characteristic features that include the following: The primary and main inflammation sites are in the epidermis and the upper dermis, hyperkeratosis results from the inflammation at those sites, and primary genetic causative factors associated with the hyperactivation of innate immunity (autoinflammation) are present.

As De Vita et al.[1] point out, it has been clarified that HS shows the features of an AIKD in many respects. At the primary stage of HS inflammation, hyperkeratosis of the follicular epithelium with the occlusion and dilatation of the follicle by keratin plug formation is thought to play an important role[3]. Interestingly, keratin plug formation is also a characteristic feature of pityriasis rubra pilaris, which is an AIKD[4]. In addition, tissue IL-1, TNF, IL-17 and caspase-1 levels are known to be elevated in HS lesions[3,5]. Indeed, anti-tumor necrosis factor (TNF) monoclonal antibody (adalimumab) and recombinant interleukin (IL)-1 receptor antagonist (anakinra) have been reported to be effective as treatments for HS[3]. HS-like lesions are seen in various autoinflammatory diseases/syndromes[6].

Recently, mutations in the genes of the γ-secretase complex have been reported in a small number of HS patients/families[7]. In HS cases with mutations in the γ-secretase genes *NCSTN*, *PSENEN* and PSEN1, hyperkeratosis of the infundibular epithelium and hair follicle occlusion have been reported to be the primary event in the pathogenesis of HS lesions, and the inflammation reactions

are thought to be secondary events[7]. Model mouse studies demonstrated that dysfunction of γ-secretase leads to aberrant differentiation of the hair follicle epithelium via Notch signaling[7]. However, it is uncertain whether hyperkeratosis of the hair follicle epithelium actually precedes the inflammatory response in HS cases without γ-secretase gene mutations.

Taking all the facts into consideration, HS, especially familial HS, is assumed to be a subtype of AIKD in which hyperkeratosis of the hair follicle epithelium is the primary pathogenic event. To understand the pathogenesis and to devise efficient treatments for HS, it is significant to consider HS as an AIKD triggered by hyperactivation of innate immunity in the hair follicle. However, there may be some controversy as to whether HS should be regarded as an AIKD, because the clinical features of HS lesions in the late stage are quite different from those of other common keratinization diseases, even if the initial event of pathogenesis is hyperkeratosis of the hair follicle epithelium. Before reaching a definitive conclusion as to whether HS should be included as an AIKD, we should wait for the HS pathogenesis to be more fully elucidated, including novel causative genes other than γ-secretase genes.

Masashi Akiyama, MD, PhD

From the Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan. E-mail: makiyama@med.nagoya-u.ac.jp

Disclosure of potential conflict of interest: The author declares that he has no conflicts of interest.

REFERENCES

1. De Vita V, McGonagle D. Hidradenitis suppurativa as an autoinflammatory keratinization disease. J Allergy Clin Immunol 2018;

2. Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization diseases. J Allergy Clin Immunol 2017; 140: 1545-7.

3. Saunte DML, Jemec GBE. Hidradenitis Suppurativa: Advances in Diagnosis and Treatment. JAMA 2017; 318: 2019-32.

4. Takeichi T, Sugiura K, Nomura T, Sakamoto T, Ogawa Y, Oiso N, *et al.* Pityriasis rubra pilaris type V as an autoinflammatory disease by CARD14 mutations. JAMA Dermatol 2017; 153: 66-70.

5. Moran B1, Sweeney CM2, Hughes R3, Malara A3, Kirthi S4, Tobin AM4, Kirby B3, Fletcher JM5. Hidradenitis Suppurativa Is Characterized by Dysregulation of the Th17:Treg Cell Axis, Which Is Corrected by Anti-TNF Therapy. J Invest Dermatol 2017; 137: 2389-95.

6. Gasparic J, Theut Riis P, Jemec GB. Recognizing syndromic hidradenitis suppurativa: a review of the literature. J Eur Acad Dermatol Venereol 2017; 31: 1809-16.

7. Pink AE, Simpson MA, Desai N, Trembath RC, Barker JNW. γ-Secretase mutations in hidradenitis suppurativa: new insights into disease pathogenesis. J Invest Dermatol 2013; 133: 601-7.