



## Reporter Cell Lines

The family keeps growing

[Learn more >](#)

InvivoGen



The Journal of  
**Immunology**

This information is current as  
of April 20, 2019.

### Comment on "Dermatitis Herpetiformis Sera or Goat Anti –Transglutaminase-3 Transferred to Human Skin-Grafted Mice Mimics Dermatitis Herpetiformis Immunopathology"

Emiliano Antiga, Marzia Caproni and Paolo Fabbri

*J Immunol* 2011; 187:595; ;

doi: 10.4049/jimmunol.1190031

<http://www.jimmunol.org/content/187/2/595.1>

**References** This article **cites 7 articles**, 2 of which you can access for free at:  
<http://www.jimmunol.org/content/187/2/595.1.full#ref-list-1>

Why *The JI*? [Submit online.](#)

- **Rapid Reviews! 30 days\*** from submission to initial decision
- **No Triage!** Every submission reviewed by practicing scientists
- **Fast Publication!** 4 weeks from acceptance to publication

*\*average*

**Subscription** Information about subscribing to *The Journal of Immunology* is online at:  
<http://jimmunol.org/subscription>

**Permissions** Submit copyright permission requests at:  
<http://www.aai.org/About/Publications/JI/copyright.html>

**Email Alerts** Receive free email-alerts when new articles cite this article. Sign up at:  
<http://jimmunol.org/alerts>

*The Journal of Immunology* is published twice each month by  
The American Association of Immunologists, Inc.,  
1451 Rockville Pike, Suite 650, Rockville, MD 20852  
Copyright © 2011 by The American Association of  
Immunologists, Inc. All rights reserved.  
Print ISSN: 0022-1767 Online ISSN: 1550-6606.



**Comment on “Dermatitis Herpetiformis Sera or Goat Anti-Transglutaminase-3 Transferred to Human Skin-Grafted Mice Mimics Dermatitis Herpetiformis Immunopathology”**

By passive transfer of anti-transglutaminase-3 (TG3) Abs to SCID mice engrafted with normal human skin, Zone et al. (1) reproduced the immunopathological pattern of dermatitis herpetiformis (DH), confirming the answer to a long-standing question regarding the source of IgA in DH skin.

However, although growing evidence has shown that TG3 probably represents the target Ag of DH (2, 3), the immunopathogenesis of the disease, that is considered the specific cutaneous expression of celiac disease (CD), is still under debate.

In particular, it is not clear why only a small cohort of patients with CD will develop DH. The authors proposed that epitope spreading from transglutaminase-2 (the main Ag in CD patients) to TG3 could determine IgA anti-TG3 Abs production in a subset of celiac patients who then develop DH. This explanation, however, is not fully convincing, considering that DH is not uncommon in children (4, 5), who, according to the authors’ theory, would not have had time to undergo epitope spreading and develop anti-TG3 Abs (1, 6). Furthermore, doubts arise about the pathogenetic role of IgA anti-TG3 Abs, because 1) not all anti-TG3-positive celiac patients will develop DH (6), 2) at least a subgroup of celiac patients without DH show IgA deposits at the dermal papillae (7), and 3) the authors were not able to reproduce DH lesions with transfer of anti-TG3 Abs (1).

In conclusion, although the article by Zone et al. provides more insight into the nature of IgA deposits found in DH, further studies are required to explain the real role of IgA anti-TG3 Abs.

Emiliano Antiga,\*† Marzia Caproni,\* and Paolo Fabbri\*

\*Department of Medical and Surgical Critical Care, Section of Dermatology, University of Florence, 50129 Florence, Italy; and †Department of Clinical Physiopathology, University of Florence, 50129 Florence, Italy

Address correspondence and reprint requests to Dr. Emiliano Antiga, Department of Medical and Surgical Critical Care, Section of Dermatology, University of Florence, Piazza Indipendenza 11, 50129 Florence, Italy. E-mail address: emiliano.antiga@unifi.it

**References**

1. Zone, J. J., L. A. Schmidt, T. B. Taylor, C. M. Hull, M. C. Sotiriou, T. D. Jaskowski, H. R. Hill, and L. J. Meyer. 2011. Dermatitis herpetiformis sera or goat anti-transglutaminase-3 transferred to human skin-grafted mice mimics dermatitis herpetiformis immunopathology. *J. Immunol.* 186: 4474–4480.

2. Sárdy, M., S. Kárpáti, B. Merkl, M. Paulsson, and N. Smyth. 2002. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. *J. Exp. Med.* 195: 747–757.

3. Caproni, M., E. Antiga, L. Melani, and P. Fabbri; Italian Group for Cutaneous Immunopathology. 2009. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. *J. Eur. Acad. Dermatol. Venereol.* 23: 633–638.

4. Fry, L. 2002. Dermatitis herpetiformis: problems, progress and prospects. *Eur. J. Dermatol.* 12: 523–531.

5. Bardella, M. T., C. Fredella, V. Saladino, C. Trovato, B. M. Cesana, M. Quatrini, and L. Prampolini. 2005. Gluten intolerance: gender- and age-related differences in symptoms. *Scand. J. Gastroenterol.* 40: 15–19.

6. Hull, C. M., M. Liddle, N. Hansen, L. J. Meyer, L. Schmidt, T. Taylor, T. D. Jaskowski, H. R. Hill, and J. J. Zone. 2008. Elevation of IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis. *Br. J. Dermatol.* 159: 120–124.

7. Cannistraci, C., I. Lesnori La Parola, G. Cardinali, G. Bolasco, N. Aspite, V. Stigliano, and M. Picardo. 2007. Co-localization of IgA and TG3 on healthy skin of coeliac patients. *J. Eur. Acad. Dermatol. Venereol.* 21: 509–514.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1190031

**Response to Comment on “Dermatitis Herpetiformis Sera or Goat Anti-Transglutaminase-3 Transferred to Human Skin-Grafted Mice Mimics Dermatitis Herpetiformis Immunopathology”**

Dr. Antiga and colleagues question the hypothesis we have proposed, which addresses the immunopathogenesis of dermatitis herpetiformis (DH). Briefly stated, in some patients with celiac disease (CD) and Abs to tissue transglutaminase, Abs to epidermal transglutaminase (TG3) develop through epitope spreading. If IgA anti-TG3 titers are sufficient, immune complexes can precipitate in the dermal papilla, and these become fixed. Finally, other unidentified proinflammatory factors trigger the cutaneous eruption of pruritic vesicles and papules.

Their first objection is the timing of development through epitope spreading. They state that DH is common in children, an assertion with which we disagree. Our own data showed a mean age of onset of 40 y in Utah (1). The reference they cite by Fry (2) actually states, “DH usually begins in young adults (15–40). However, it may commence at any age, the youngest recorded being ten months and the oldest being 90 years.” The article they cite by Bardella et al. (3) is a retrospective series of 1436 patients with gluten sensitivity from a pediatric gastroenterology practice. This prevalence of cutaneous granular IgA deposition they report seems high, given the overall incidence of CD and DH, but there is no information regarding the dermatological symptoms, only the presence of dermal IgA on skin biopsy specimens. The data in Finland demonstrate only occasional children under 16 y of age with DH, with the highest incidence in men 60–69 y of age (4). Epitope spreading can progress at various rates, with clinical examples showing intermolecular spread over months to many years (5, 6). That it

progresses in months rather than decades in occasional cases does not seem to negate our hypothesis.

Their second objection is that the deposition of IgA–TG3 immune complexes is not sufficient to cause clinical disease. We agree. The reference they cite by Cannistraci et al. (7) found dermal IgA in nine of nine adult CD patients at amounts lower than those in clinical DH patients. This finding agrees with a large body of data showing that dermal IgA deposition is necessary, but not sufficient, for DH. These data include the Cannistraci report, as well as that of Fry et al. (8), that IgA persists years beyond clinical resolution in patients on a gluten-free diet; that IgA is present in nonlesional skin, which is our work (9); and that lesions resolve acutely with an elemental diet (10). Although not addressed in the article under discussion, we believe that intestinal inflammation driven by gluten as well as local cutaneous factors is important in the development of lesions. Our animal model will be useful in addressing these factors. None of these considerations alter the fact that all DH patients have gluten sensitivity, and all DH lesions have granular IgA in the dermal papilla. We therefore strongly disagree with their questioning of the pathogenic role of this IgA–TG3 deposition.

Laurence J. Meyer

Department of Dermatology, University of Utah, Salt Lake City, UT 84112

Address correspondence and reprint requests to Dr. Laurence J. Meyer, Department of Dermatology, University of Utah Health Care, 30 North 1900 East, 4A330 School of Medicine, Salt Lake City, UT 84132. E-mail address: Laurence.Meyer@hsc.utah.edu

## References

1. Smith, J. B., J. E. Tulloch, L. J. Meyer, and J. J. Zone. 1992. The incidence and prevalence of dermatitis herpetiformis in Utah. *Arch. Dermatol.* 128: 1608–1610.
2. Fry, L. 2002. Dermatitis herpetiformis: problems, progress and prospects. *Eur. J. Dermatol.* 12: 523–531.
3. Bardella, M. T., C. Fredella, V. Saladino, C. Trovato, B. M. Cesana, M. Quatrini, and L. Prampolini. 2005. Gluten intolerance: gender- and age-related differences in symptoms. *Scand. J. Gastroenterol.* 40: 15–19.
4. Salmi, T. T., K. Hervonen, H. Kautiainen, P. Collin, and T. Reunala. 2011. Prevalence and incidence of dermatitis herpetiformis: a 40-year prospective study from Finland. *Br. J. Dermatol.*
5. Pigozzi, B., A. Peserico, L. Schiesari, and M. Alaibac. 2008. Pemphigus foliaceus evolving into pemphigus vulgaris: a probable example of “intermolecular epitope spreading” confirmed by enzyme-linked immunosorbent assay study. *J. Eur. Acad. Dermatol. Venereol.* 22: 242–244.
6. Recke, A., C. Rose, E. Schmidt, E. B. Bröcker, D. Zillikens, and C. Sitaru. 2009. Transition from pemphigus foliaceus to bullous pemphigoid: intermolecular B-cell epitope spreading without IgG subclass shifting. *J. Am. Acad. Dermatol.* 61: 333–336.
7. Cannistraci, C., I. Lesnoni La Parola, G. Cardinali, G. Bolasco, N. Aspite, V. Stigliano, and M. Picardo. 2007. Co-localization of IgA and TG3 on healthy skin of coeliac patients. *J. Eur. Acad. Dermatol. Venereol.* 21: 509–514.
8. Fry, L., J. N. Leonard, F. Swain, W. F. Tucker, G. Haffenden, N. Ring, and R. M. McMin. 1982. Long term follow-up of dermatitis herpetiformis with and without dietary gluten withdrawal. *Br. J. Dermatol.* 107: 631–640.
9. Zone, J. J., L. J. Meyer, and M. J. Petersen. 1996. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. *Arch. Dermatol.* 132: 912–918.
10. Kadunce, D. P., M. P. McMurry, A. Avots-Avotins, J. P. Chandler, L. J. Meyer, and J. J. Zone. 1991. The effect of an elemental diet with and without gluten on disease activity in dermatitis herpetiformis. *J. Invest. Dermatol.* 97: 175–182.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1190032