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

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Letters to the Editor

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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.

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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.

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