TO THE EDITOR

Dermatitis herpetiformis (DH), a cutaneous manifestation of celiac disease, is characterized by the deposition of granular IgA in dermal papillary tips. The target antigen of the IgA is transglutaminase 3 (TG3) (Sardy et al., 2002), which co-localizes with the antibody in the deposits. The TG3-specific IgA antibodies are a product of an immune reaction that occurs in the gastrointestinal tract to gluten, a protein found in cereal grains. TG3 is expressed in various cell types in the body, including keratinocytes, where it maintains the integrity of the stratum corneum by connecting epidermal structural proteins (Hitomi, 2005). The IgA-aggregated TG3 retains its activity (Taylor et al., 2015).

In 1978, Plisnik et al. (1978) demonstrated that TG purified from human stratum corneum was enzymatically enhanced by trypsin, organic solvents, and chaotropic salts. They found chaotropic agents caused a 10-fold increase in TG activity. The authors speculated the increase in activity was due to conformational change in the enzyme by loss of hydrophobic effect, allowing for increased effectiveness of the active site. This article peaked our interest because a well-known agitator of DH, potassium iodide (KI), is a chaotropic salt.

Since the first reported observation in 1891 that iodine and related compounds can trigger DH (From and Thomsen, 1974), oral or topical iodides were used to diagnose DH, even though its mechanism of action was not known (Alexander, 1975). KI, when applied topically to uninvolved DH skin, will elicit vesicular lesions with perivascular cellular infiltrates similar to those that occur in spontaneously occurring lesions (Reitamo et al., 1981). Lesion progression will vary with the concentration of KI. Clinical testing revealed that 2/21 DH patients had a papular and/or vesicular reaction to a 0.6 M KI topical patch, while 14/21 patients developed a vesicular reaction when the topical KI concentration was increased to 1.8 M (Michaelsson and Svensson, 1975).

We hypothesized that the IgA-aggregated enzyme in DH skin would show a similar increase in activity when subjected to comparable concentrations of KI. The procedure we used in testing for TG3 activity was similar to our earlier reported procedure with slight modifications (Taylor et al., 2018).
Initial immunofluorescence tests revealed that Alexa Fluor 488, the fluorescein label for cadaverine, a primary amine donor for detecting active TG, was sensitive to high concentrations of KI. Biotin-labeled cadaverine (Invitrogen, Eugene, OR) was used as a substitute. Also, the substrate incubation time, as well as the temperature, were reduced to accommodate TG3’s rate of enzymatic activity. Five DH patients on dapsone and one on a gluten-free diet were biopsied for uninvolved skin after being on a regular diet. Skin cryosections were incubated in 0, 1, and 2 M KI concentrations with biotin-labeled cadaverine for 15 minutes at room temperature. Slides were developed with rhodamine-labeled avidin (Jackson ImmunoResearch, West Grove, PA). Microscopy revealed strong and extensive staining of cadaverine in 2 M KI and moderate to strong staining in 1 M KI (Figure 1). The no KI control sections showed minimal staining of cadaverine. DH skin sections incubated in 2 M KI with EDTA, which chelates calcium, revealed no staining. These results strongly suggest that the enzymatic activity of TG3 in the IgA deposits of DH skin was directly dependent on the concentration of KI. Interestingly, the 1 M and 2 M KI sections showed staining also in the basal and spinous layers of the epidermis. Three other TG family members are expressed in the various layers of the epidermis and would be, in addition to TG3, targets for KI (Eckert et al., 2005).

We hypothesized that the increase in TG3 activity displayed by the binding of cadaverine could be reversed by removing the KI and allowing time for the increase in hydrophobic effect to refold the enzyme, thus slowing its activity. Skin sections from three DH biopsies were incubated as before for 15 minutes in 2 M KI, but without the cadaverine. The substrate was applied after the KI solution was removed and the slides washed for 15 or 30 minutes. Semi-quantitative measurements determined the 15-minute washed slides with <20% of the staining noted in the positive KI control, and the 30-minute washed slides with minimal to no staining (Figure 2). We conclude that the active site of TG3 in the IgA deposits of DH skin is conformationally altered by high concentrations of KI, allowing increased activity and that this regulation is due to reversible steric changes brought about by hydrophobic effects.

Clinically, DH patients dramatically worsen when exposed to iodide in commercial preparations using KI as an expectorant and when ingesting high-iodide compounds (Alexander, 1975). We believe that the clinical worsening of DH in response to KI and the KI patch test are directly dependent on the activity of TG3. The delay of 12 to 24 hours seen in the clinical reaction to patch testing can arguably be explained by the time it takes for KI skin absorption and lesion formation. Moreover, the...
results imply that lesion development in DH patients not exposed to KI is likely dependent on the aberrant activity of IgA-bound TG3. The inclusion of TG in the pathology of a disease such as DH is not unique. Not only is a TG-catalyzed reaction responsible for the pathogenesis of celiac disease (Dieterich et al., 1997), aberrant TG activity has been implicated in a number of neurodegenerative disorders, such as Alzheimer’s disease (Selkoe et al., 1982), Parkinson’s disease, and other polyglutamine diseases (Citron et al., 2002, Iuchi et al., 2003). We propose the aberrant TG3 activity in DH patients compromises skin integrity. Nidogen and anchoring fibrils, critical components that support the adhesion function of the basement membrane, have been shown to be susceptible targets of TG (Aeschlimann and Paulsson, 1991, Raghunath et al., 1996).

The University of Utah Institutional Review Board approved this study and did not require patient consent for de-identified and otherwise discarded clinical specimens; the study was conducted according to the Declaration of Helsinki Principles.

**CONFLICT OF INTEREST**
The authors state no conflict of interest.

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**REFERENCES**


**Selective Use of Cyclosporine for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis May Exclude Patients with Poor Prognostic Factors**


TO THE EDITOR

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a severe mucocutaneous drug reaction associated with significant morbidity and mortality. Because of the rarity of the disease, evidence-based treatment guidelines are lacking. Questions remain as to whether patients should be managed with supportive care alone or receive immunosuppressive regimens, such as systemic steroids, intravenous immunoglobulins, or cyclosporine (Creamer et al., 2016). A recently published systematic review (Zimmermann et al., 2017) and a meta-analysis (Gonzalez-Herrada et al., 2017) report mortality benefit from treatment with cyclosporine, with the meta-analysis reporting an overall mortality risk ratio of 0.41 (95% confidence interval = 0.21–0.80). However, patients receiving cyclosporine in published cohorts were younger than their counterparts and lacked established risk factors for SJS/TEN mortality, such as renal failure. Because selection bias may artificially inflate the reported benefits of cyclosporine, we suggest the results of these analyses be interpreted with caution. Going forward, any criteria used to exclude patients from receiving cyclosporine should be clearly reported, especially the presence or absence of comorbidities that affect mortality.

The best evidence for a survival benefit from cyclosporine comes from an open label, phase 2 study from a

Abbreviations: SCORTEN, Score of Toxic Epidermal Necrosis; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis

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