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Production of Low Titers of Anti-Desmoglein 1 IgG Autoantibodies in Some Patients with Staphylococcal Scalded Skin Syndrome

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TO THE EDITOR

Staphylococcal scalded skin syndrome (SSSS) is a generalized blistering skin disease caused by *Staphylococcus aureus* producing exfoliative toxin (ET). ET is a serine protease that specifically digests desmoglein 1 (Dsg1), the autoimmune target for pemphigus foliaceus (PF). Out of 30 patients with SSSS, six (20.0%) patients developed low titers of anti-Dsg1 IgG, but no detectable anti-Dsg3 IgG, 7 days or more after the onset of the disease. Although other genetic or environmental factors are necessary for the full development of pemphigus, this finding provides evidence that infection could trigger the autoimmune reaction.

A major question in understanding the pathophysiology of autoimmune disease is what triggers the immune response. One postulated mechanism, molecular mimicry, has been that infectious agents might cause antibodies that bind self-antigens, a good example being streptococcal antigens in rheumatic heart disease (Wucherpfennig, 2001). In such cases, the antibodies that are produced against the infectious agent are thought to coincidentally crossreact with normal tissues. The recent elucidation of the pathophysiology of an antibody-mediated tissue-specific autoimmune disease, PF, and two related infectious diseases, bullous impetigo (BI) and SSSS, all of which target the same molecule, Dsg1, suggested to us another mechanism by which an infectious agent could trigger an autoimmune response. In this mechanism, we hypothesize that a bacterial toxin could bind to and partially degrade a self-antigen, with the modified self-antigen triggering the immune response.

Impetigo is the most common bacterial infection of children and 30% of these patients have BI, which is caused by *S. aureus* that produces ETs. SSSS is a generalized form of BI, which occurs in newborns, young children, and adults with renal failure and/or who are immunocompromised. In the early 1970s, ETs of two major serotypes, ETA and ETB, were shown to produce blisters in the superficial epidermis when passively transferred to neonatal mice (Melish and Glasgow, 1970). It took almost 30 years to elucidate the pathophysiological mechanism of action of ETs, which have recently been shown to be glutamate-specific serine proteases that specifically bind and cleave Dsg1 (Amagai *et al.*, 2000). Desmogleins are cadherin-type cell—cell adhesion molecules found in desmosomes and play a critical role in maintaining tissue integrity in epithelial and other tissues (Green and Gaudry, 2000).

Desmogleins are also affected in the skin autoimmune blistering disease, pemphigus (Payne *et al.*, 2004). Among four isoforms of desmoglein, Dsg1 is targeted by IgG autoantibodies in PF, which shows superficial epidermal blisters with identical histological findings to SSSS/BI. Thus, in both PF and SSSS/BI the inactivation of Dsg1 causes superficial blisters in skin.

If, as postulated above, altered antigen, in this case Dsg1, could trigger an immune response, we would expect that some patients with SSSS or BI produce at least low-level antibodies against Dsg1. To address this hypothesis, we examined a total of 58 serum samples from 30 patients with SSSS and 12 serum samples from 12 patients with BI after informed consent with

Abbreviations: BI, bullous impetigo; Dsg1, desmoglein 1; ET, exfoliative toxin; PF, pemphigus foliaceus; SSSS, staphylococcal scalded skin syndrome

adherence to the Helsinki Guidelines was obtained from patients or their guardians (Table 1). The diagnosis was confirmed by typical clinical findings as well as by culture of *S. aureus*. We tested the sera by ELISA and immunoblot analyses against recombinant human Dsg1 and Dsg3 expressed in the baculovirus system. For ELISA, we used the cutoff value which was determined by receiver-operating-characteristic curves as described previously (11.0 for Dsg1 ELISA, 10.0 for Dsg3 ELISA) (Amagai *et al.*, 1999).

We found that six out of 30 (20.0%) cases with SSSS developed low titers of anti-Dsg1 IgG autoantibodies as detected by ELISA (4/30) or immunoblot analyses (4/30), although none of them developed any detectable anti-Dsg3 IgG antibodies during the course of the study (Table 1). Although it was difficult to obtain paired sera because most of the patients were infants or small children, four patients with SSSS demonstrated the shift from negative to positive anti-Dsg1 IgG. One patient (SSSS no. 1 in Table 2, 10 months old, female) developed anti-Dsg1 IgG at day 16 after the onset of SSSS, whereas she did not have significant titers of anti-Dsg1 IgG at days 3 and 10, and another patient (SSSS no. 3, 14 months old, female) showed a slight increase of anti-Dsg1 IgG between days 4 and 9, as determined by ELISA (Figure 1). Two additional patients (SSSS no. 4, 3 years old, female; SSSS no. 5, 4 years old, female) developed anti-Dsg1 IgG between days 10 and 20 and days 7 and 14, respectively, as determined by immunoblotting (Figure 2). Another case of SSSS (SSSS no. 2, 4 years old, female) showed positive anti-Dsg1 IgG at days 10 and 15 by ELISA as well as immunoblotting, although we could not prove that she had negative anti-Dsg1 IgG at an earlier phase of the disease (Figure 1). Finally, another patient with

Table 1. Anti-Dsg1 IgG production in patients with SSSS and bullous impetigo

Disease	Total cases examined	Male	Female	Average age (years)	Anti-Dsg1 IgG			Anti-Dsg3 IgG		
					Total	ELISA	IB	Total	ELISA	IB
SSSS	30	16	14	2.4	6	4	4	0	0	0
Bullous impetigo	12	7	5	5.3	0	0	0	0	0	0

Dsg1, desmoglein 1; SSSS, staphylococcal scalded skin syndrome.

Table 2. Summary of SSSS patients with production of low titers of anti-Dsg1 IgG

Patients	Sex	Age	Days after onset	ELISA		IB	
				Dsg1	Dsg3	Dsg1	Dsg3
SSSS no. 1	F	10 months	3	1.6	1.4	–	–
			10	3.2	2.4	–	–
			16	**17.3**	4.2	–	–
SSSS no. 2	F	4 years	10	**42.9**	2.9	+	–
			15	**33.5**	2.0	+	–
SSSS no. 3	F	14 months	4	8.8	0.9	–	–
			9	**12.9**	1.1	–	–
SSSS no. 4	F	3 years	10	0.7	0.4	–	–
			20	1.2	0.7	+	–
			37	0.2	0.0	+	–
SSSS no. 5	F	4 years	7	0.0	0.0	–	–
			14	0.0	0.0	+	–
SSSS no. 6	F	2 years	6	**11.0**	0.0	+	–

Dsg1, desmoglein 1; SSSS, staphylococcal scalded skin syndrome.
Bold values indicate positive ELISA scores.

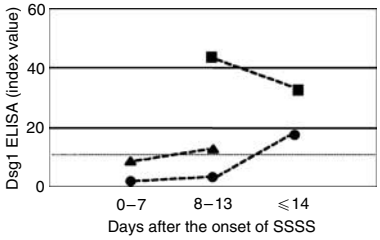

Figure 1. Seroconversion of anti-Dsg1 IgG antibodies in patients with SSSS. Time course of anti-Dsg1 IgG production as determined by ELISA against Dsg1 after the onset of SSSS in three patients. The dashed line indicates the cutoff value (11.0) for Dsg1 ELISA. The cases shown in this figure are as follows: closed circle, SSSS no. 1; closed square, SSSS no. 2; closed triangle, SSSS no. 3 in Table 2.

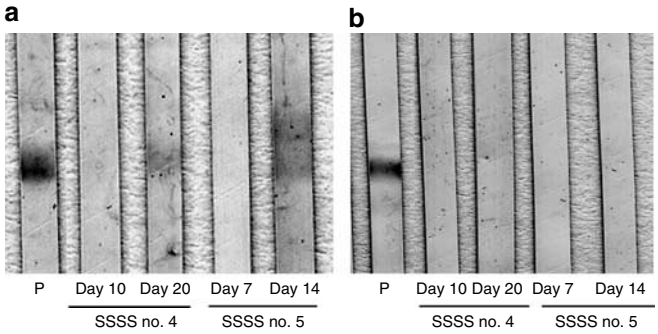

Figure 2. Seroconversion of anti-Dsg1 IgG antibodies in patients with SSSS. Time course of anti-Dsg1 and anti-Dsg3 IgG production by immunoblot analysis against recombinant (**a**) Dsg1 and (**b**) Dsg3. P: (**a**) a PF serum and (**b**) a PV serum as positive controls.

SSSS had positive anti-Dsg1 IgG by ELISA as well as immunoblotting, although serum was obtained only at day 6 (SSSS no. 6 in Table 2). No anti-Dsg3 IgG was detected either by ELISA or by immunoblotting in these patients studied throughout their course, indicating the specificity of the reactivity against Dsg1 (Table 1). No apparent IgM reactivity against Dsg1 or Dsg3 was detected by ELISA (data not shown). None of the 12 patients with BI, whose sera were taken with a range of days 2–33, showed any detectable IgG production against either Dsg1 or Dsg3 as determined by ELISA and immunoblotting (Table 1).

These findings indicate that a small number of patients of SSSS develop low titers of IgG antibodies specific for Dsg1 after binding and systemic digestion of Dsg1 by staphylococcal ETs. This observation is specific for patients with SSSS because none of the patients with BI showed any sign of anti-Dsg1 antibody production. This may be because a single episode of BI may be too limited to cause an immune response. Although none of these patients develop PF after SSSS, which is not known as a predisposing factor for PF, the findings presented here provide evidence that infection which modifies self-antigen can trigger the production of IgG autoantibodies against the self-antigen. Of course, these patients do not develop clinically overt PF. We would speculate that other genetic or environmental factors are needed to extend the immune response to encompass pathogenic antibodies and to produce overt clinical PF. For example, in the endemic form of PF, fogo selvagem, that is found in rural areas of South America, it might be possible that repeated modification of Dsg1 by chronic or recurrent staphylococcal infection in genetically susceptible individuals might trigger disease.

Thus, our data are consistent with the hypothesis that a bacterial toxin can modify a self-antigen to result in an autoantibody response. The relevance of this finding to onset of autoimmune diseases remains to be proven.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Both Pimecrolimus and Corticosteroids Deplete Plasmacytoid Dendritic Cells in Patients with Atopic Dermatitis

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TO THE EDITOR

Atopic dermatitis (AD) is one of the most common inflammatory skin disorders characterized by pruritus, a chronically relapsing course and typically distributed lesions with dry skin, excoriations, and lichenification (Leung *et al.*, 2004). Topical treatment of acute lesions with corticosteroids (CS) is a mainstay in the therapy of the AD; however, long-term application is limited by CS-related side effects (e.g., skin atrophy) (Stoppolino *et al.*, 1983). The calcineurin inhibitors tacrolimus and pimecrolimus are now available as ointment/cream preparations and have proven to be a novel option for the topical treatment of AD (Ruzicka *et al.*, 1997; Luger *et al.*, 2001).

AD skin lesions harbor a variety of inflammatory cells, of which dendritic cells (DCs) represent a major fraction. Besides resident Langerhans cells and inflammatory dendritic epidermal cells,

Abbreviations: AD, atopic dermatitis; BMV, beta-methasone-17-valerate; CS, corticosteroids; DC, dendritic cell; MFI, mean fluorescence intensity; pDC, plasmacytoid DC