Pathogenicity of anti-desmoglein 3 IgA1 autoantibodies is Fc-dependent in IgA pemphigus

S. Emtenani¹, J.G. Johns¹, A. Recke^{1,2}, S. Mayer-Hain³, C. Sunderkötter^{3,4}, L. Komorowski⁵, C. Probst⁵, J.E. Hundt¹, T. Hashimoto⁶, D. Zillikens²,
E. Schmidt^{1,2}, R.J. Ludwig¹, C.M. Hammers^{1,2,7}

¹ Lübeck Institute of Experimental Dermatology (LIED), Lübeck, Germany

² Department of Dermatology, University of Lübeck, Lübeck, Germany

³ Department of Translational Dermatoinfectiology, University of Münster, Münster, Germany

⁴ Department of Dermatology and Venerology, University Hospital of Halle, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

⁵ Institute of Experimental Immunology, EUROIMMUN AG, Lübeck, Germany

⁶ Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

⁷ Department of Dermatology, University of Pennsylvania, Philadelphia, USA

Background and Aims

- IgA pemphigus is characterized by tissue-bound and circulating IgA, but not IgG, autoantibodies (autoAbs) against epidermal cadherins, particularly desmogleins (Dsgs) or desmocollins (DsCs).
- Patients typically present with vesiculopustular skin eruptions, intraepidermal acantholysis and prominent neutrophilic infiltrates.
- Molecular pathomechanisms of IgA pemphigus are insufficiently understood and a model system is missing.
- We here cloned and characterized monoclonal antibodies (mAbs) from a patient with IgA pemphigus vulgaris (IgA PV) and established an *in vitro* model for this disease.

Clinical/histological findings (1-3), α-IgA DIF (4), and α-IgG DIF (5) in our IgA PV patient. α-IgA IIF for IgA PV (6), LAD-IgA (7), and normal human serum (NHS, 8) on ME substrate. α-IgG IIF for IgA PV on ME substrate (9).

Methodology and Results

Three Dsg3-specific IgA mAbs, in form of single-chain variable fragments (scFvs), were isolated by antibody phage display (APD) from an IgA PV patient with high serum anti-Dsg3 IgA1 reactivity.

mAb designation	IIF titer (ME)	Dsg3	Dsg1	Ca ²⁺ sens.	Linear epitopes	H-CDR3	VH gene	VH mut#	L-CDR3	VL gene	VL mut#
IgA1-PV.D3.3-1	1:10000	+	-	+	+	ARSTGSSVDYYGMNV	3-23*04	19	LLFVGGTWW	L8-61*01	38
IgA1-PV.D3.3-6	1:10000	+	-	+	+	ARSTGSSVDYYGMNV	3-23*04	21	LLFVGGTWW	L8-61*01	38
IgA1-PV.D3.4-8	1:1000	+	-	+	+	ARDDVETLDY	3-30*04	31	MQGLRLPVT	K2-28*01	16

Inhibition ELISAs indicated that the isolated mAbs bind to similar or identical Dsg3 epitopes as serum-derived polyclonal IgA/IgG autoAbs.

Pathogenic potential of polyclonal serum Abs and IgA1 PV mAbs under concurrent elimination of Dsg1 by exfoliative toxin A (ETA)

I. *In vitro* keratinocyte dissociation assay

II. Human skin organ culture injection

Fc-dependent cellular mechanisms are needed for pathology in IgA pemphigus

Successful generation of a recombinant human full anti-Dsg3 IgA1 mAb (F779-IgA1): Inhibition ELISA suggested that F779-IgA1 shares same or similar epitope with mAb 3-6 from APD.

Anti-Dsg3 IgA1-Fc:FcαR interaction mediates epidermal pathogenicity in IgA pemphigus, without requiring concurrent inactivation of Dsg1 by autoAbs or ETA.

Complete blockade of pathogenic anti-Dsg3 IgA1-Fc:FcαR interaction by an IgA binding peptide

Inhibitory effect of IgA binding peptide on NET (neutrophil extracellular trap) formation

Conclusion

- Interaction of the anti-Dsg3 IgA1-Fc-part with the FcαR is required and necessary pathogenicity in IgA pemphigus, without requiring concurrent Dsg1 inactivation.
- Blocking the interaction of anti-desmosomal IgA and FcαR-bearing cells may be a well suited therapeutic avenue for this difficult-to-treat skin disorders.