Anti-desmoglein 3 autoantibodies cloned from the IgA1 repertoire of an IgA pemphigus patient are directly pathogenic, but not sufficient for disease induction

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Background and Aims

- IgA pemphigus presents with a wide spectrum of clinical, histopathological, and immunological features
- All have tissue-bound IgA, but not IgG autoantibodies (auto-Abs) against epidermal cell adhesion proteins that mediate cell-cell adhesion.
- Molecular pathomechanisms of IgA pemphigus are insufficiently understood and a model system is missing
- We here studied a patient with intraepidermal neutrophilic IgA dermatosis (IEN)/IgA pemphigus vulgaris (IgA-PV) by cloning and characterizing monoclonal antibodies (mAbs) from that patient.

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

Methodology and Results

I. Dsg-IgA ELISA and IFT on HEK293 cells detected serum IgA1 Abs against Dsg3. These Dsg-reactive Abs recognize conformational and linear epitopes.

II. Cloning and characterization of anti-Dsg3 PV-IgA1 mAbs (APD)

III. Three Dsg3-reactive mAbs from two B-cell clones (by H-CDR3) were isolated from IgA-PV patient. These mAbs bind to the same epitopes as serum Abs from this patient do.

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

Inhibition ELISA for mAbs 3-1 and 3-6 with same patient's serum

IV. Cross-reactivity of our Dsg3-mAbs to murine keratinocytes

V. Pathogenic potential of IgA-PV serum Abs and IgA1-PV scFvs

1) In vitro keratinocyte dissociation assay

2) Human skin organ culture injection study

Conclusion: mAbs cloned from our IGAD patient (IEN/IgA-PV) are pathogenic, but not sufficient for induction of disease

- Confirming compensation model of Dsg3/1 molecules described in classical, IgG-mediated pemphigus diseases
- An additional factor, i.e., cells with IgA Fc receptors (FcαRs), is likely to be involved in disease induction
- We established an excellent basis for development of *in vitro* and *in vivo* models of disease

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