The pathogenesis of pemphigus: controversy versus complexity

Di Zenzo G¹, Borradori L⁴,⁵, Muller EJ²,³,⁴,⁵

¹Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell’Immacolata, IDI-IRCCS, Rome, Italy.

²Molecular Dermatology and Stem Cell Research, Department of Clinical Research, Medical Faculty, University of Bern, 3008 Bern, Switzerland

³Institute of Animal Pathology, Vetsuisse Faculty, Bern, Switzerland

⁴DermFocus, Vetsuisse Faculty, Bern, Switzerland

⁵Department of Dermatology, University Hospital of Bern, Bern, Switzerland

Corresponding author:
Giovanni Di Zenzo
Laboratory of Molecular and Cell Biology
Istituto Dermopatico dell’Immacolata, IDI-IRCCS
Via Monti di Creta 104
00167, Rome, Italy
E-mail: g.dizenzo@idi.it

Life is highly complex and, as quantum physics would predict, follows the rule of “everything is possible with varying probabilities”. Accordingly, science may be sometimes as confusing as political debates, where the same matter is addressed in different and misleading ways even in the absence of a real controversy. The Viewpoint by Ahmed et al. provides a paradigmatic example of a debate about two theories for pemphigus pathogenesis, i.e. “Monopathogenic vs. multipathogenic explanations of
The readers should consider as take home message the following points:

1. **Heterogeneity in pemphigus.** Two major types of pemphigus have been described, *pemphigus vulgaris* (PV) and *pemphigus foliaceus* (PF). The vast majority of patients with PV and PF have mucous and/or cutaneous lesions (2) associated with IgG auto-antibodies (Abs) against desmoglein (Dsg) 3 and/or Dsg1. The profile of anti-Dsg1 and anti-Dsg3 autoAbs mostly correlates with the clinical phenotype, determining occurrence of cutaneous and/or mucous membrane lesions. However, in up to 5-10% of cases, particularly in PV patients, this is not the case, thus indicating variations to a common theme. Furthermore, in over the last decade the pemphigus group of diseases is has turned out to be more heterogeneous than originally thought, encompassing different entities with overlapping and immunopathological features.

2. **The clinical phenotype is determined by multiple factors.** As observed in many immune-mediated and other diseases, the clinical phenotype in a given patient is affected by a variety of modifying factors, including gene polymorphisms, epigenetic makeup, defects in structural proteins, immune response molecules, signaling molecules, as well as environmental and exogenous factors, such as drugs. Their impact on the phenotype should always be kept in mind in such a complex biological system as the human body. In addition, autoAb titers, their predominant IgG subclasses and recognized epitopes and antigens also influence disease expression. These observations support that additional physiological factors (e.g. shown in case of EGFR deletion (3)) do modulate the clinical phenotype (4).

3. **Pemphigus can be caused by anti-Dsg without non-Dsg autoAbs (the monopathogenic theory).** Evidence that anti-Dsg1 and/or anti-Dsg3 autoAbs alone are sufficient for cell-cell dissociation *in vitro* and *in vivo* is indisputable and compelling. Among others, the phenotype of PV patients with Dsg3 without Dsg1 autoAbs is recapitulated by the monospecific anti-Dsg3 Ab AK23 alone (s1); after passive transfer into neonatal or adult mice, it consistently induces hair follicle and/or palate blisters, and when combined with anti-Dsg1 autoAbs, it provokes PV-like skin lesions (3, 5, 6, s2, s3). Similar results were reported with distinct cloned human Dsg3 autoAbs (7) (Table 1). In this context, the seemingly alternate phenotypes of Dsg mutations or deletion in human or mice, argued by authors of the multipathogenic theory, are not a strong argument. Mutations in a given gene induce a variety of phenotypes depending - among others - on the site of mutation and genetic background. Furthermore, in our hands, Dsg3 knockout mice exhibit hair follicle and palate blisters like described above for PV/AK23 (unpublished). This said, the reader should not be mistaken! The authors of the monopathogenic hypothesis, a virtual theory animating this debate, support that autoAbs to Dsg3/Dsg1 alone are sufficient. However, they do not claim exclusivity of the antigenic target.
There is one query against the “Dsg3/Dsg1 autoAb alone are sufficient” which seems compelling and stands on top of the list: “Epidermal integrity “does not “primarily depend on the desmosomal expression of Dsg1 and Dsg3”. This query only point to is only “half of the story”. The idea that loss of transadhesion between Dsg molecules in desmosomes would be sufficient for blister induction has long evolved. Demonstrated multiple times (e.g. 3, 5, 6, s2, s3), the initial event of loss of transadhesion between Dsg3 molecules, certainly pathogenic, is not enough. Only when coupled with altered signal transduction mediated by Dsg3 cadherin receptors, to which autoAbs preferentially bind, will desmosomes start to lose their cohesive grip.

Cadherins receptors are now widely acknowledged to survey a variety of signaling networks, including a mitochondrial cross talk, to dictate cell fate (7). Hence, in particular PV is not about loss of adhesion or adhesion of Dsg1 and Dsg3 in desmosomes in the first place but about altered signal transduction upon anti-Dsg3 autoAb binding to Dsg3 receptors. It is without any question that these signal alterations can be mimicked by a variety of other factors which alone or together with Dsg autoAbs recapitulate or enhance the disease.

4. Pemphigus can be caused/enhanced by requires both autoAbs to Dsgs and non-Dsgs antigens (the multipathogenic theory). Autoimmune diseases are often characterized by a vast number of autoantigens which are not associated with pathogenicity. Different approaches, including cloning of pemphigus autoAbs from affected patients (unpublished), have allowed to characterize - besides pathogenic and non-pathogenic anti-Dsg autoAbs (7) additional Abs of different specificities and Ig isotype (such as IgAHowever), most of these autoAbs, including those targeting keratinocyte mitochondria (9), do not possess acantholytic potential on their own but may act synergistically with anti-Dsg3 antibodies to increase acantholysis. It has also been claimed that antibodies targeting keratinocyte mitochondria contribute to the process of acantholysis (Table1). One interesting exception are autoAbs to other desmosomal cadherins such as the desmocollins which can cause a pemphigus-like disease in humans without anti-Dsg autoAbs (8, s4). The observation that there are patients with a clinical pemphigus phenotype but lacking anti-Dsg autoAbs as well as Abs of other known specificity, such as anti-desmocollins, raises the question about the pertinence of a debate on about-a monopathogenic or multipathogenic theory.

5. Is it worth the debate? The statement that the “individual authors may or may not support one view or the other” found in the footnote of the Viewpoint of Ahmed et al well summarizes how the matter is challenging. The wealth of available data discussed in this viewpoint indeed convinces us of the extraordinary biological complexity of the pathogenesis of pemphigus making a scientific debate futile. For educational purposes, it is sometimes necessary to talk about major concepts (pemphigus pathogenesis is induced by autoAb against Dsgs) rather than exciting exceptions (other antigens and additional factors), paying the price in terms of loss of complexity.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES
Table 1. Survey of Dsg and non-Dsg autoAbs with pathogenic activity in pemphigus

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<th>Pathogenic antibodies (mAb)</th>
<th>References</th>
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<tr>
<td>Dsg3</td>
<td>2 murine mAbs (AK23, AK19)</td>
<td>s1</td>
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<tr>
<td>Dsg3</td>
<td>8 murine mAbs (NAK1,2,4,7,8,9,10,11)</td>
<td>s7</td>
</tr>
<tr>
<td>Dsg3</td>
<td>2 human mAbs ((D3)3c/9; (D31)2/28)</td>
<td>s8</td>
</tr>
<tr>
<td>Dsg3</td>
<td>1 human mAb (PVMAB786)</td>
<td>s9</td>
</tr>
<tr>
<td>Dsg3</td>
<td>4 human mAbs (PVE 4-8, PV2 4.2, PV2 3.2, PV2-VH1-69)</td>
<td>s10</td>
</tr>
<tr>
<td>Dsg3</td>
<td>1 human mAb (F779)</td>
<td>s11</td>
</tr>
<tr>
<td>Dsg3</td>
<td>3 human mAbs (PVA224, PVB28, PVB124)</td>
<td>s12</td>
</tr>
<tr>
<td>Dsg1</td>
<td>2 human mAbs ((D31)2/29, (D1)11/10)</td>
<td>s8</td>
</tr>
<tr>
<td>Dsg1</td>
<td>2 human mAbs (3-07/1e 3-30/3h)</td>
<td>s13</td>
</tr>
<tr>
<td>Dsg1</td>
<td>1 human mAb (F24-9)</td>
<td>s14</td>
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<tr>
<td>Desmocollin 3</td>
<td>Polyclonal AutoAbs and 1 murine mAb (U114, Progen)</td>
<td>8, s4</td>
</tr>
<tr>
<td>Pemphaxin</td>
<td>Polyclonal AutoAbs amplify the activity of anti-Dsg AutoAbs</td>
<td>s5</td>
</tr>
<tr>
<td>α9-acetylcholine receptor</td>
<td>Polyclonal AutoAbs amplify the activity of anti-Dsg AutoAbs</td>
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<td>Anti-mitochondrial antibodies</td>
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SUPPLEMENTAL REFERENCES


