ROLE OF INFLAMMATION IN EB:
Implication for new therapeutic approaches

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Bullous skin diseases are characterized by genetic abnormalities related to structural epidermal proteins or organ-specific autoantibodies against the same proteins.

Recently, different inflammatory processes have been demonstrated in both inherited and acquired RB, revealing that this overlapping might cause implications in terms of disease course and outcome.
Autoantibodies are the primary cause of the disease in EBA, whereas they can be produced as a secondary event due to genetically determined skin damage in IEB contribuing significantly to the worsening of the disease.
As occurs in autoimmune diseases, environmental factors are likely to be combined with hereditary in triggering disease’s manifestations.

Role of inflammation in EB: implication for new therapeutic approaches

Genetic determined tissue damage

Autoimmune process
Role of inflammation in EB: implication for new therapeutic approaches

A significative cytokine imbalance was demonstrated in EB, suggesting the presence of a systemic inflammatory disorder
Role of inflammation in EB: implication for new therapeutic approaches

In several patients with EB high levels of anti-skin antibodies are detected, proportional to the severity of the disease.
Autoimmunity and Cytokine Imbalance in Inherited Epidermolysis Bullosa

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In press
Study BACKGROUND

Genotype-phenotype correlations in EB were not always shown: subjects with the same genetic mutations were frequently found to have very different clinical characteristics.

In addition to genetic mutations, other factors could be significant in the progression of the disease.
Aim of the study

To determine serum anti-skin autoantibodies and cytokine concentrations in a group of subjects with different EB types to study the correlations with EB phenotype and disease severity.
## Study population

<table>
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<tr>
<th>42 EB patients (13 EBS, 22 DEB, 5 JEB, 2 Kindler syndrome)</th>
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<td>38 controls</td>
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The EB cases not classified as RDEB were considered together because a preliminary evaluation did not show any significant difference between the various types.

## Anti-skin autoantibodies detection

- Desmoglein 1 (DSG1)
- Desmoglein 3 (DSG3)
- Bullous pemphigoid 180 (BP180)
- Bullous pemphigoid 230 (BP230)
- Type VII Collagen (COL7)

## Cytokine measurement

- Interleukin (IL) 1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12
- Tumor necrosis Factor (TNF) α, TNFβ
- Interferon (IFN) γ
1. **EB patients vs. controls**

**Antibodies**

Significantly higher in the EB patients than in the controls
SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

1. EB patients vs. controls

The same trend evidenced for many cytokines, in particular IL-1β, IL-2, IL-6, IL-10, TNF-β, and IFN-γ. Only IL-4 and TNF-α serum levels did not differ between the groups.
2. REDB patients vs. other EB patients

**Antibodies**

Higher in patients with RDEB than in those with other types of EB
2. **REDB patients vs. other EB patients**

No significant variation between RDEB and other EB patients
3. **Patients with generalized EB vs. localized EB**

**Antibodies**

Significantly higher in generalized cases than in localized EB cases
SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

3. Patients with generalized EB vs. localized EB

No significant difference was observed between the groups.
Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

4. Comparison of the studied variables in EB patients with high and low BEBS scores

Antibodies

Significantly higher in patients with higher BEBS scores than in those with lower values
Although IL-1β, IL-2, IL-6, TNF-α, TNF-β, and IFN-γ were higher in the EB patients with higher BEBS scores than in those with lower values, only differences in IL-6 resulted statistically significant.
DISCUSSION

Patients with RDEB (i.e., the EB type with the most severe clinical manifestations), those with generalized EB and those with a higher BEBS score showed the highest increase in serum anti-skin antibodies and cytokine concentrations.

Increases of serum anti-skin antibodies were strictly related to the inflammatory response (mainly evidenced by the IL-6 increase) and to the severity of the disease.
CONCLUSIONS

The induction of a chronic inflammatory response could explain, at least in part, the activation of autoimmunity and the deterioration and extensions of the basal EB lesions.

The increase in pro-inflammatory cytokines seems to confirm that EB is a systemic disease, explaining the extracutaneous involvement frequently observed.
Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

Pro-inflammatory cytokines

Severity of clinical manifestations

Activation of immune process: anti-skin and anti-COL7 antibodies

EB: a systemic disease

BIO-THERAPY?
NGS STUDY ON POLYMORPHYSMS OF GENES INVOLVED IN INFLAMMATORY RESPONSE

(Esposito S et al., unpublished data)
FUTURE PERSPECTIVES

These results showed that autoimmunity and inflammatory responses are frequently activated in EB, mainly in severe forms, suggesting the use of immunosuppressive drugs or biologicals active against IL-6 could reduce clinical signs and symptoms of disease.
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