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ROLE OF INFLAMMATION IN EB:

Implication for new therapeutic approaches

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Role of inflammation in EB: implication for new therapeutic approaches

- 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

Role of inflammation in EB: implication for new therapeutic approaches

Immunol Res (2015) 61:63–69
DOI 10.1007/s12026-014-8583-3

CUTTING EDGE IN AUTOIMMUNITY

Epidermolysis bullosa and the partnership with autoimmunity: what should we assimilate?

Susanna Esposito · Sophie Guez · Francesca Manzoni · Annalisa Bosco · Donato Rigante

Published online: 21 November 2014

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

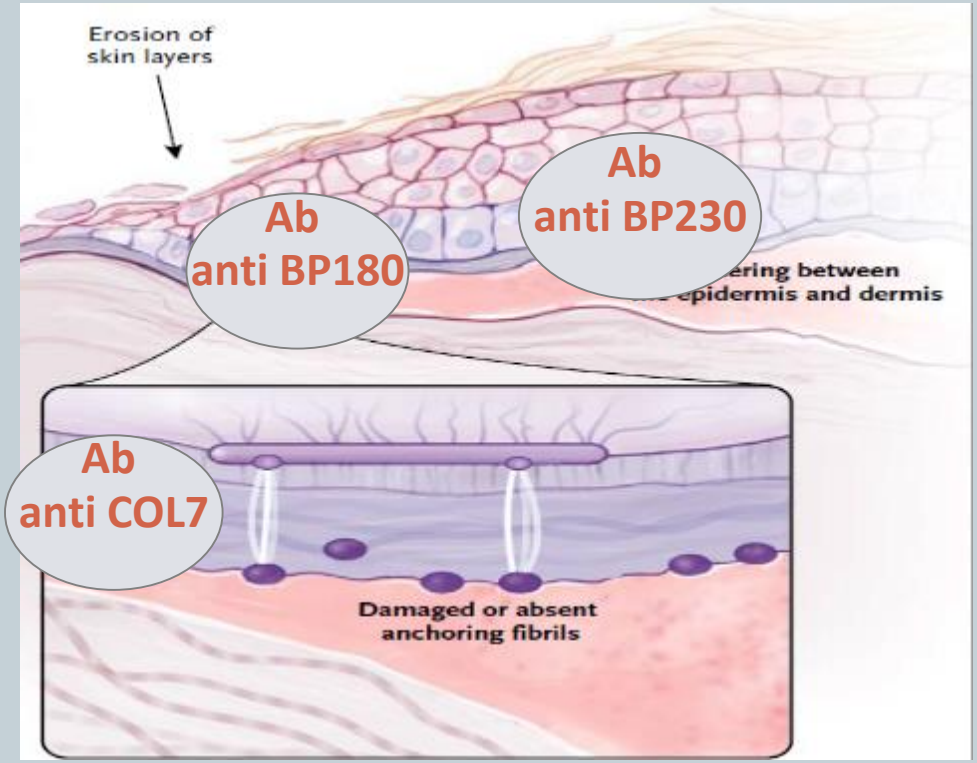
Role of inflammation in EB: implication for new therapeutic approaches

As occurs in autoimmune diseases, environmental factors are likely to be combined with hereditary in triggering disease's manifestations.

Genetic determined tissue damage

↕

Autoimmune process



Role of inflammation in EB: implication for new therapeutic approaches

Proinflammatory Cytokines and Antiskin Autoantibodies in Patients With Inherited Epidermolysis Bullosa

Giuseppina Annicchiarico, MD, Maria Grazia Morgese, PhD, Susanna Esposito, MD, Giuseppe Lopalco, MD, Michele Lattarulo, PhD, Marilina Tampoia, PhD, Domenico Bonamonte, MD, Luigia Brunetti, MD, Antonio Vitale, MD, Giovanni Lapadula, MD, Luca Cantarini, MD, and Florenzo Iannone, MD

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

Tampoia *et al. Orphanet Journal of Rare Diseases* 2013, **8**:132
http://www.ojrd.com/content/8/1/132

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Prevalence of specific anti-skin autoantibodies in a cohort of patients with inherited epidermolysis bullosa

Marilina Tampoia[1*], Domenico Bonamonte[2], Angela Filoni[2], Lucrezia Garofalo[2], Maria Grazia Morgese[3], Luigia Brunetti[4], Chiara Di Giorgio[5] and Giuseppina Annicchiarico[6]

In several patients with EB high levels of anti-skin antibodies are detected, proportional to the severity of the disease

International Journal of
Molecular Sciences

MDPI

Article

Autoimmunity and Cytokine Imbalance in Inherited Epidermolysis Bullosa

Susanna Esposito [1,*], Sophie Guez [1], Annalisa Orenti [1], Gianluca Tadini [1,2], Giulietta Scuvera [1], Laura Corti [2], Alessia Scala [1], Elia Biganzoli [3], Emilio Berti [2] and Nicola Principi [1]

In press

Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

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

Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

Study population

42 EB patients (13 EBS, 22 DEB, 5 JEB, 2 Kindler syndrome)

38 controls

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

Interfernon (IFN) γ

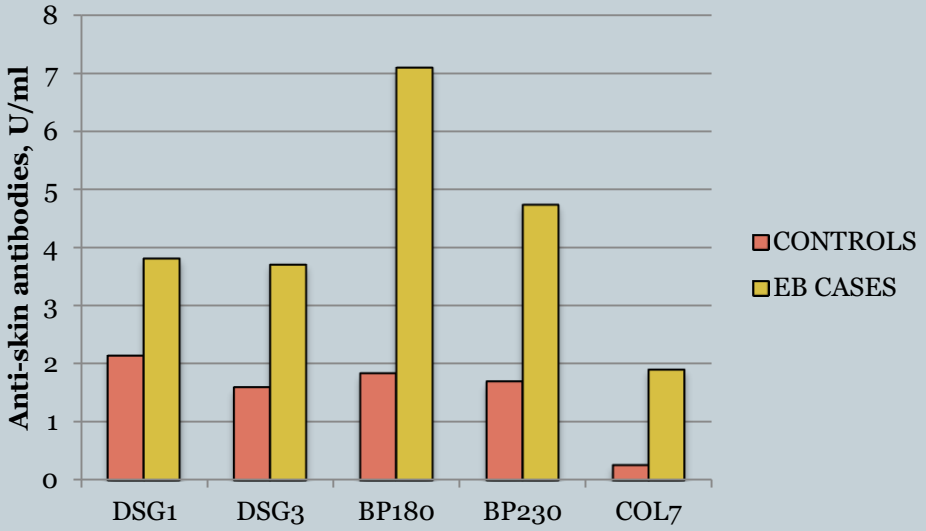
Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

1. EB patients vs. controls

Antibodies

Significantly higher in the EB patients than in the controls



Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

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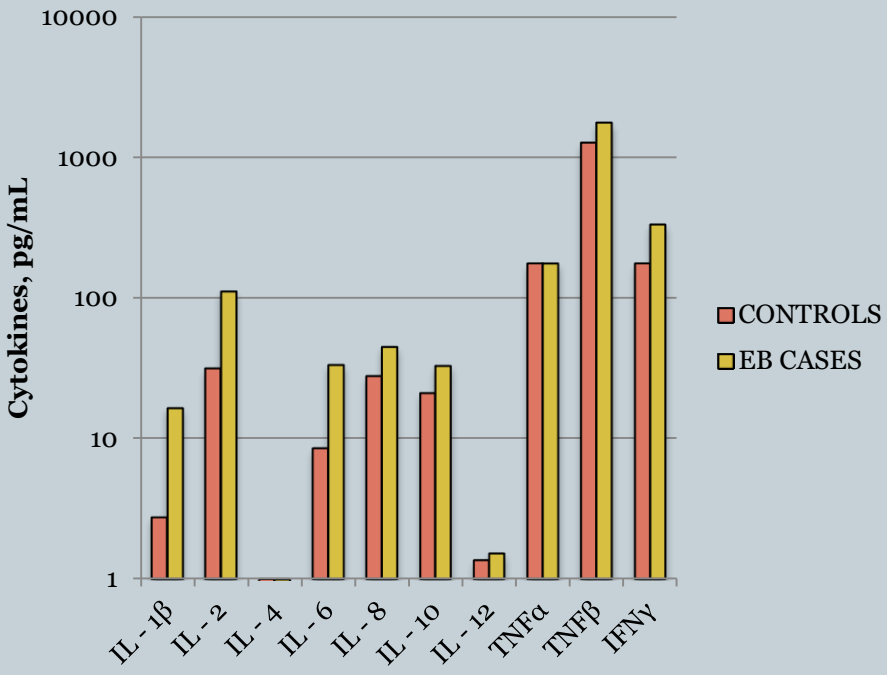


Cytokines

The same trend evidenced for many cytokines, in particular IL-1β, IL-2, IL-6, IL-10, TNF-β, and IFN-γ

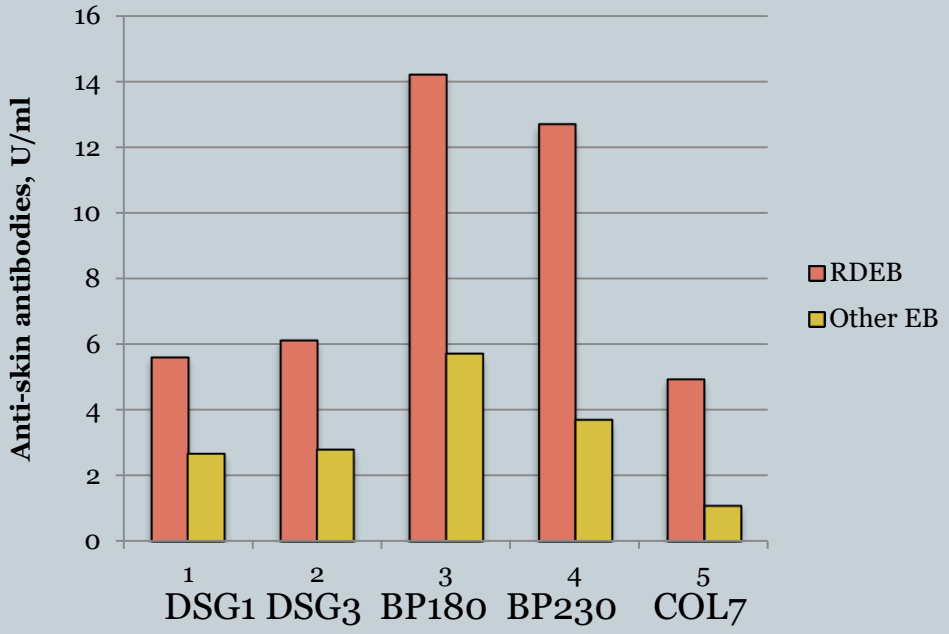
Only IL-4 and TNF-α serum levels did not differ between the groups

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

2. REDB patients vs. other EB patients

Antibodies

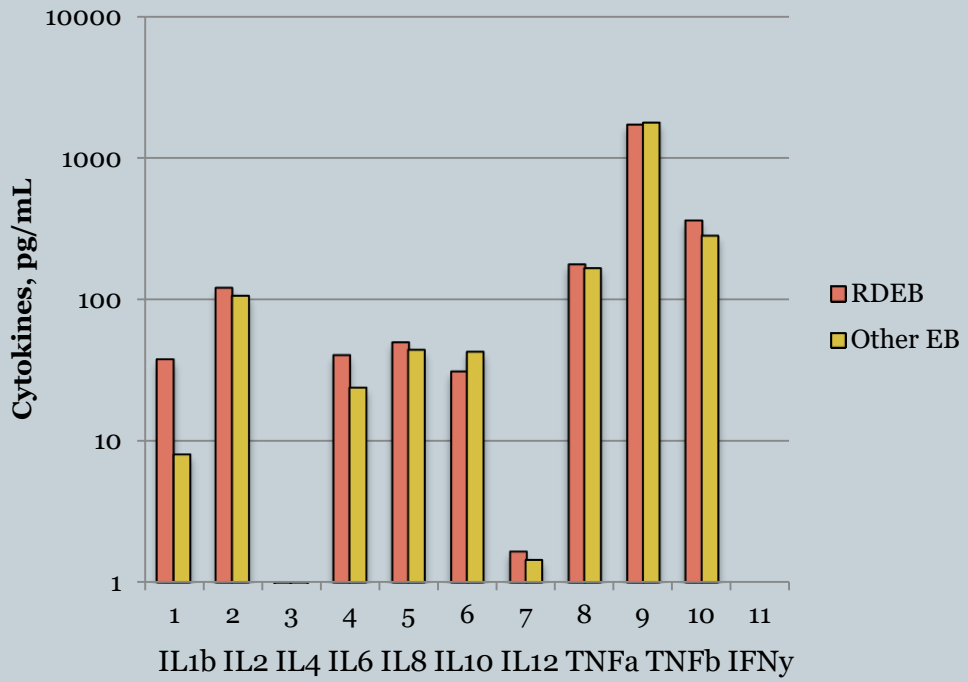
Higher in patients with RDEB than in those with other types of EB



Autoimmunity and cytokine imbalance in inherited epidermolysis bullosa

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

2. REDB patients vs. other EB patients



Cytokines

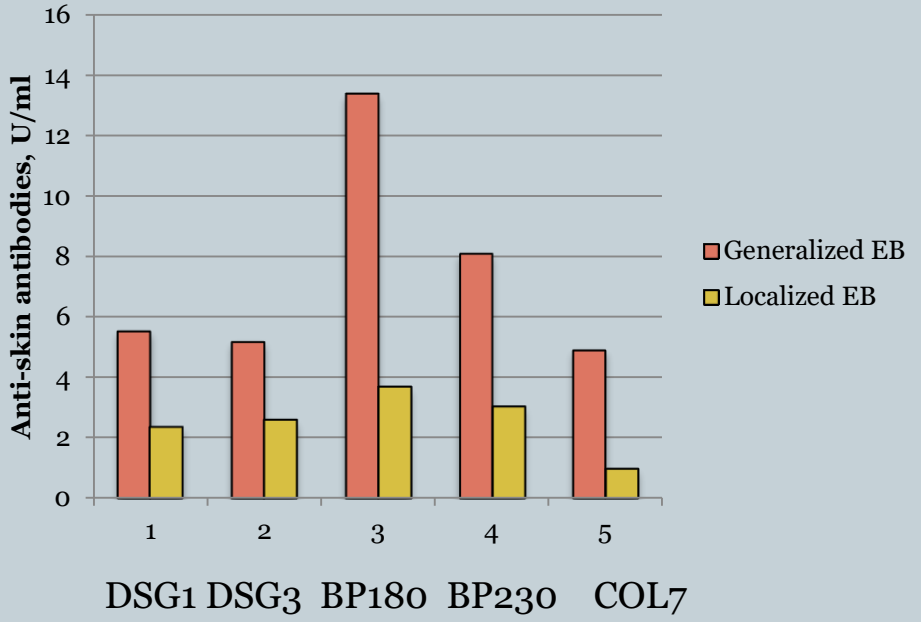
No significant variation between RDEB and other EB patients

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

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

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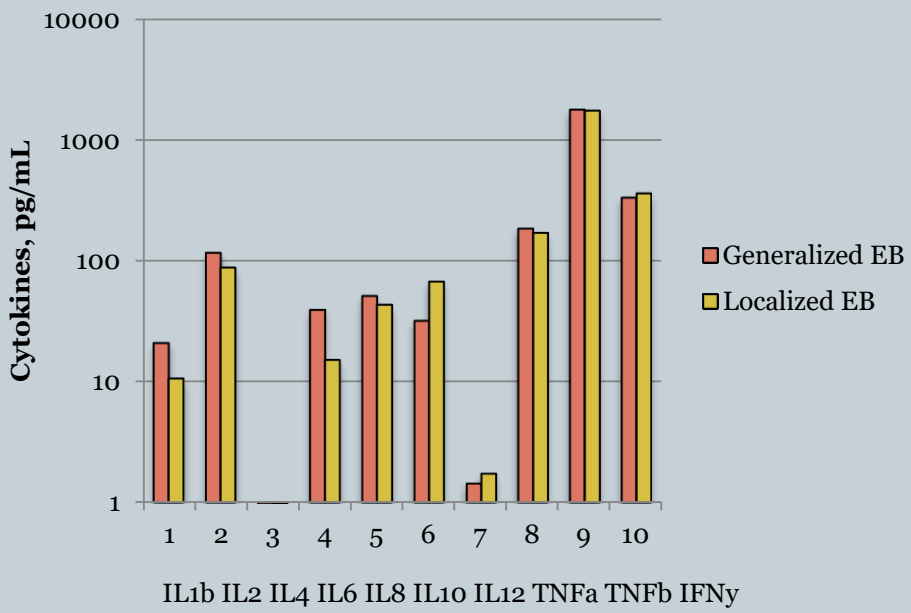


Cytokines

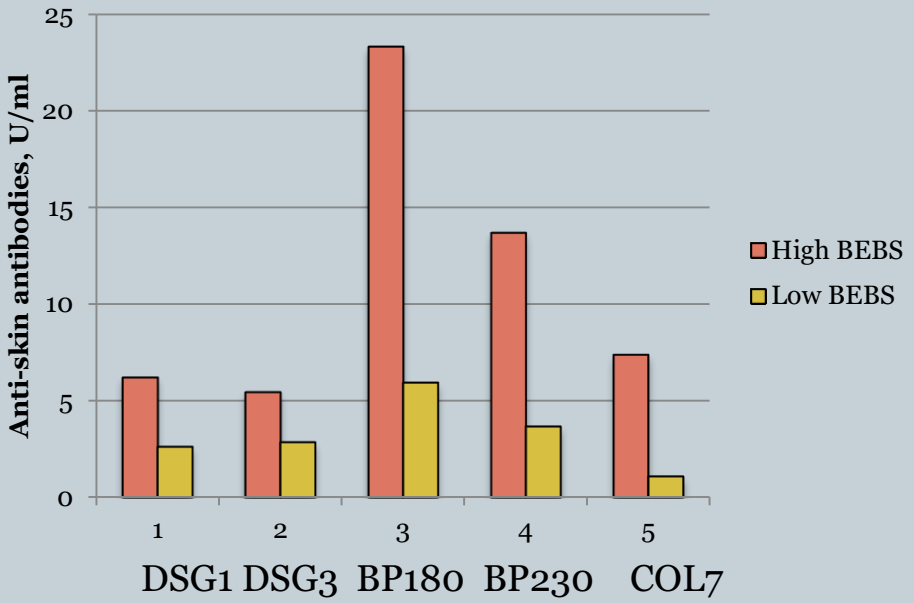
No significant difference was observed between the groups

SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

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

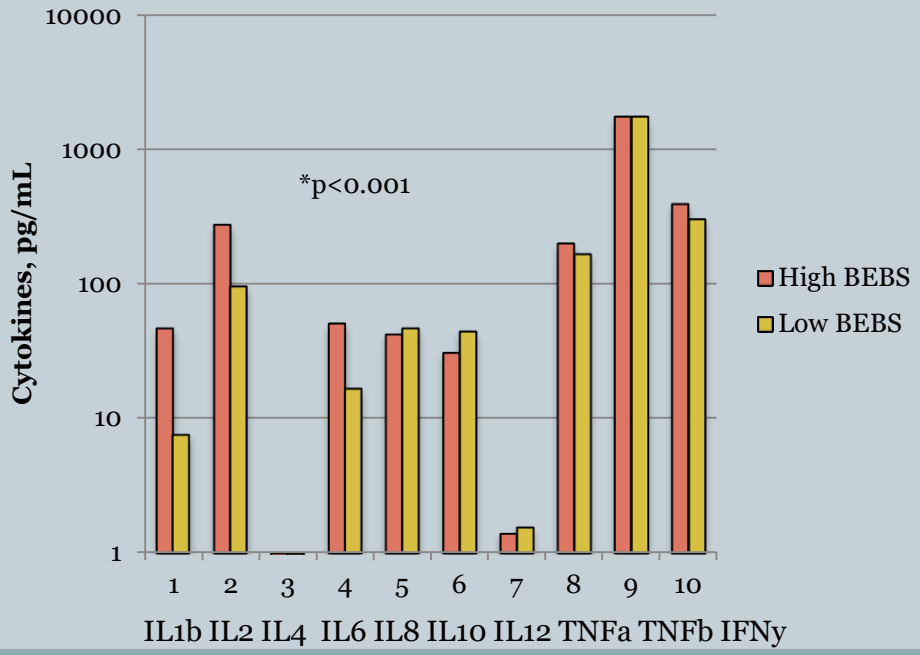
Antibodies

Significantly higher in patients with higher BEBS scores than in those with lower values



SERUM ANTI-SKIN ANTIBODIES AND CYTOKINE CONCENTRATIONS

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



Cytokines

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

Conclusion

Pro-inflammatory cytokines

Severity of clinical manifestations

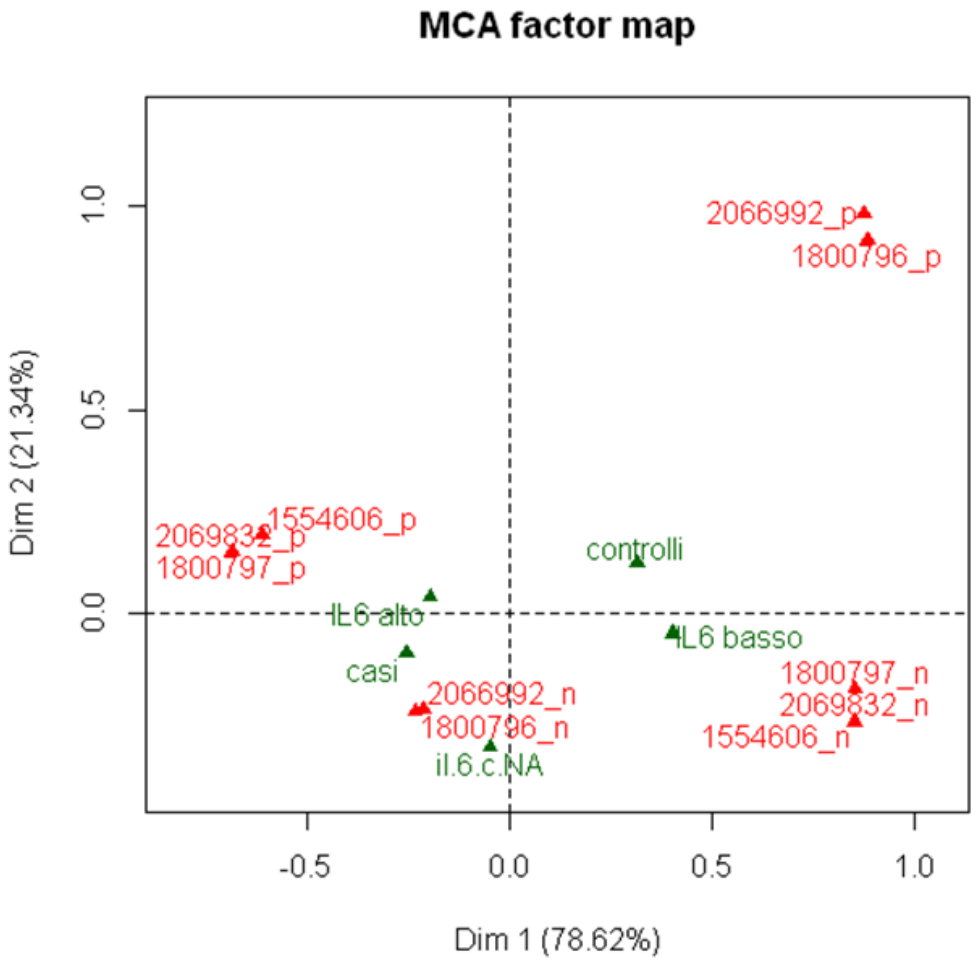
Activation of immune process : anti-skin and anti-COL7 antibodies

EB: a systemic disease

BIO-THERAPY?

NGS STUDY ON POLYMORHYSMS 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 immunosoppressive drugs or biologicals active against IL-6 could reduce clinical signs and symptoms of disease

AKNOWLEDGMENTS

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