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Inflammasome activation and inflammation in Epidermolysis bullosa

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Introduction

Epidermolysis bullosa (EB) comprises a group of rare genetic disorders characterized by skin fragility and blister formation due to mutations in genes encoding for the basement membrane proteins or proteins ensuring basement membrane organization or keratinocyte integrity. Inflammasomes are multiprotein complexes, controlling the activation and release of critical pro-inflammatory cytokines, namely IL-1 β and IL-18, *via* caspase-1. The role of cytokines in orchestrating tissue repair and integrity in EB has been poorly studied.

Objective

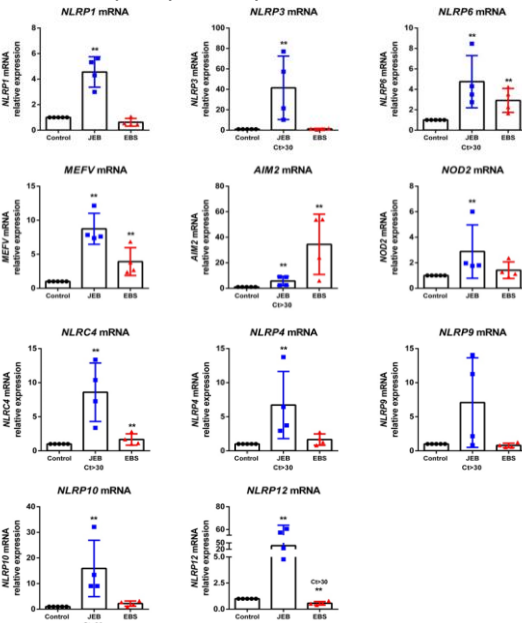
The objective of this study was to investigate the expression and regulation of inflammasome-components and cytokine secretion in keratinocytes of EB patients and controls.

Methods

Primary keratinocytes were derived from biopsies of individuals with 2 different types of EB, specifically junctional epidermolysis bullosa (JEB) (N=4) and epidermolysis bullosa simplex (EBS) (N=4). Normal human epidermal keratinocytes (NHEK) were used as controls. The gene expression of the major inflammasome sensors, members of the caspase family and cytokines was measured using the Mesa Blue qPCR MasterMix Plus for SYBR Assay on a Light Cycler LC480. Cytokine secretion was measured by ELISA.

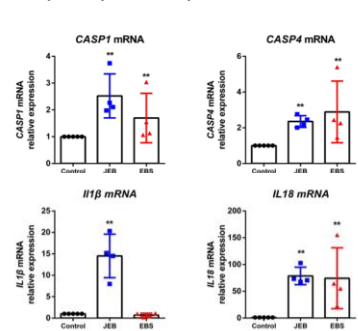
Results

Inflammasome sensors expression in human primary keratinocytes



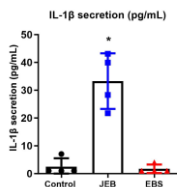
- Elevated mRNA levels of *NLRP1*, *NLRP3*, *NLRP6*, *MEFV*, *NOD2*, *NLR4*, *NLRP4*, *NLRP10*, and *NLRP12* in JEB patient-derived keratinocytes as compared to NHEK.
- The gene expression of *NLRP6*, *MEFV*, *AIM2*, and *NLR4* was increased in EBS patient-derived keratinocytes as compared to NHEK.

Caspase and cytokine expression in human primary keratinocytes



- The gene expression of *CASP1* and *CASP4* was higher in both JEB and EBS patients as compared to NHEK, but did not change significantly between JEB and EBS samples.
- *IL1B* and *IL18* gene expression was significantly higher in JEB patients as compared to controls.

Cytokine secretion in human primary keratinocytes



Data represent the mean \pm SEM of ≥ 3 independent experiments done in human primary keratinocytes of ≥ 4 independent donors.

- IL-1 β secretion was significantly higher in JEB patients as compared to EBS or controls.
- IL-18 secretion was below detection limit for all groups.

Conclusion

In this study, we demonstrated that keratinocytes derived from JEB and EBS patients exhibit increased expression of inflammasome components compared to NHEK suggesting a role of inflammasome(s) in EB pathogenesis. Our data highlight the importance of adhesion of the different skin layers to ensure keratinocyte homeostasis.

As the dysregulation of inflammasome sensors leads to the excessive production of pro-inflammatory cytokines, it could contribute to the chronic inflammation observed in EB.

Further studies on the type of inflammasome(s) implicated in EB and targeted therapeutic interventions to modulate inflammasome activation may hold promise for the development of anti-inflammatory therapies in EB.

Abbreviations: NOD-like Receptors: NLR; interleukin-1 β : IL-1 β ; interleukin-18: IL-18.