A unique mechanism of epithelial detachment in mucous membrane pemphigoid caused by autoantibodies against the C-terminus of COL17

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Introduction

- **Mucous membrane pemphigoid (MMP)** is an autoimmune blistering disorder, which mainly presents as mucosal lesions. Although the pathogenesis of MMP is reported to be related to autoantibodies against the C-terminus of collagen XVII (COL17), the blistering mechanisms behind the oral lesions in MMP are not fully understood.
- We hypothesized that **one of the blistering mechanism in MMP may be associated with the inhibition of protein-protein binding by autoantibodies against the C-terminus of COL17.**
- This study focused on the interaction of COL17 with the extracellular matrix component collagen IV (COL4).

Methods and Results

1) Oral lesions in MMP are less inflammatory than skin lesions in BP (Fig 1).

❖ Histological analysis in Bullous pemphigoid (BP) and MMP

2) mAb targeting C-terminus of COL17 don't co-precipitate COL4 in the oral mucosal keratinocyte (Fig 2).

❖ Immunoprecipitation (IP)

Fig 2. Immunoprecipitation with mAbs TS39-3, C17-C1 or mIgG1 using cell lysates of NHEK and NHOMK.

- ❖ COL17 directly binds to COL4 in both NHEK and NHOMK
- ❖ Only in NHOMK, the binding is disrupted by C17-C1.

Methods and Results

3) The expression levels of COL4A1 and COL4A2 is different between NHEK and NHOMK (Fig 3).

❖ mRNA expression of COL4 in NHEK and NHOMK

Fig 3. mRNA levels of 6 COL4 gene (COL4A1, A2, A3, A4, A5, A6), which encode the distinct chains of COL4 α 1 through COL4 α 6.

❖ The different bindings of COL17 and COL4 may be associated with the isoform expression levels.

4) Autoantibodies against the C-terminus of COL17 disturb the direct binding of COL17 and COL4 (Fig 4).

❖ In vitro binding inhibition assay

Discussion and Conclusion

- ❖ COL17 directly bind to COL4 in both NHOMK and NHEK.
- ❖ The direct binding of COL17 and COL4 is different between NHOMK and NHEK, which attribute to the expression levels of COL4 isoform genes.
- ❖ mAb targeting the C-terminus of COL17 or MMP-IgG disrupts the binding of COL17 and COL4 only in NHOMKs.
- ❖ MMP-IgG targeting the C-terminus of COL17 may play a pathogenic role in the oral mucosal lesions by inhibiting the protein-protein interaction with less inflammation.

References

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