Shedding of collagen XVII accelerates tumor growth and invasion in skin carcinogenesis

Célimène Galiger¹, Stefanie Löffek^{1,2}, Marc Stemmler³, Venugopal Mittapalli¹, Jasmin Kröger¹, Philipp Esser¹, Leena Bruckner-Tuderman¹, Claus-Werner Franzke¹

¹Department of Dermatology, Medical Center University Freiburg, Germany. ²Skin Cancer Unit of the Dermatology Department, University Hospital Essen, Germany, ³Institute of Experimental Medicine I, University of Erlangen-Nürnberg, Germany.

Introduction

Collagen XVII (ColXVII) is an important epithelial anchorage molecule in the skin that is highly upregulated in several epithelial cancers during dysplasia-to-cancer transformation. **One unique feature of collagen XVII is that its collagenous ectodomain is proteolytically released from the cell-surface.**

In this study, we investigated the role of collagen XVII shedding in skin carcinogenesis.

Results

Enhanced collagen XVII expression and shedding in human squamous cell carcinomas.

Collagen XVII and ectodomain selective antibodies revealed co-staining

Collagen XVII expression is linked to proliferation

Collagen XVII co-localizes to invasive podoplanin+ cells

Knockdown of collagen XVII in SCC-25 cells by lentiviral shRNA causes reduced tumor growth and matrix cell invasion.

Weak clonogenic capacity & tumor growth

Reduced invasiveness

Xenograft mouse model

Smaller tumors

Re-expression of collagen XVII in SCC-25 Col17-kd cells rescues tumor growth and cell invasiveness.

Re-expression of non-sheddable collagen XVII in SCC-25 Col17-kd cells does not restore clonogenicity and invasion.

Monoclonal collagen XVII antibodies as shedding inhibitors prevent matrix-independent growth and invasion of SCC cells.

Antibody treatment suppresses invasion

Distinct functions of collagen XVII endodomain and ectodomain.

Endodomain increases tumor growth

Ectodomain induces invasion

Re-expression of collagen XVII endodomain improved cell proliferation.

Conclusion

It seems that particularly the post-translational modification of ColXVII by ectodomain shedding is the major driver of epithelial cancer progression. Since collagen XVII shedding is strongly increased at the invasive front of squamous cell carcinomas, local inhibition of shedding by selective blocking antibodies may offer a method to prevent carcinoma progression.