An autocrine regulatory loop in fibroblasts between the keratinocyte growth factor (KGF) and the extradomain-A fibronectin (EDA$^+$FN) may contribute to psoriasis pathomechanism

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Introduction

In our previous work we showed that the fibronectin splice variant EDA$^+$FN, its receptor the alpha5-integrin, the keratinocyte growth factor (KGF) and its receptor (KGFR) are overexpressed in psoriatic uninvolved skin compared to normal skin. EDA$^+$FN and KGF both stimulate keratinocyte proliferation, moreover KGF is also known to induce alpha5-integrin expression in keratinocytes. In the present work we aimed to examine the regulatory mechanism between KGF, KGFR, EDA$^+$FN and FN1 in human fibroblasts.

Methods

We silenced FN1 with gene specific trilencer-27 siRNA in human fibroblast. We carried out real-time RT-PCR, immunocytochemistry and flow cytometry analysis of EDA$^+$FN and KGFR 24 hours after gene specific silencing of FN1. Secreted KGF protein levels were determined in FN1 silenced human fibroblast samples by ELISA.

Results

FN1 mRNA (n=4) and protein (n=4) expressions decreased by 80% in FN1 silenced human fibroblasts. The EDA$^+$FN splice variant mRNA (n=4) and protein (n=4) expressions were also reduced 24 hours after gene specific silencing of FN1. Knockdown of the FN1 gene in normal human fibroblasts resulted in significantly increased KGFR (FGFR-2 IIIb receptor variant)

protein expressions (n=4), however no changes in the mRNA levels were observed (n=4). The amounts of secreted KGF protein (n=4) were significantly higher in human fibroblasts 24 hours after gene specific silencing of FN1.

Conclusion

These data indicate the existence of a previously unknown autocrine regulatory network in fibroblasts between KGF, KGFR $EDA^{+}FN$ and FN1 that may be relevant to psoriasis pathomechanism.