Higher level of KGF could influence EDA$^+$FN production in fibroblasts through the MAPK cascade in uninvolved psoriatic skin

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Introduction

A growing body of evidence indicate that the healthy looking uninvolved psoriatic skin carries alterations. We have provided data that suggests that the EDA domain fibronectin (EDA$^+$FN) and its receptor, α5 integrin, are key molecules in the altered epidermal response in psoriasis. We also showed that keratinocyte growth factor (KGF, FGF7) and its receptor FGFR2 are overexpressed in the uninvolved psoriatic skin. Therefore, we investigated the putative regulatory link between KGF and EDA$^+$FN and tried to determine signalling mechanisms in EDA$^+$FN and FN1 production.

Methods

Fibroblasts were treated with human recombinant KGF. In blocking experiments, MEK1 (PD 098059), AKT1/2 (Akt inhibitor VIII), STAT1 (Epigallocatechin gallate) and STAT3 (Stattic) inhibitors were used. For FN1 gene silencing in fibroblasts a specific trilencer-27 siRNA was used. Real-time RT-PCR and flow cytometry analysis of EDA$^+$FN and FGFR2 were carried out 24 hours after gene specific silencing of FN1. Secreted KGF protein levels were determined by ELISA.

Results

We carried out RTq-PCR and flow cytometric measurements to analyze EDA$^+$FN and FN1 production 24 hours after applying exogenous KGF to cultured normal human fibroblasts. EDA$^+$FN protein expression increased significantly following exogenous KGF treatment. To examine which major signaling pathways are affected by KGF inhibitory experiments were used. MEK1 inhibition abolished the changes in EDA$^+$FN level triggered by KGF indicating the

involvement of the MAPK cascade. Our data also suggest that $EDA^{+}FN$ and FN1 expressions are suppressed by STAT1 and STAT3. Knockdown experiments targeting the FN1 gene in normal human fibroblasts resulted in a significant increase in FGFR2 protein level, without affecting the mRNA expression. The amount of secreted KGF was not effected by the silencing of FN1.

Conclusions

Our data provide evidence for the existence of novel regulatory connections between the extracellular matrix fibronectin and KGF. Moreover, this autocrine loop is likely to be altered in the uninvolved skin of psoriatic patients, which may contribute to the pathomechanism of the disease.

Előadást kívánok tartani.

Az absztrakt témája: **elméleti**