Transforming growth factor beta and interleukin-13 synergize in the pathogenesis of Crohn’s disease associated intestinal fistulae

Gerhard Rogler, Zurich
Fistulae: A clinical problem in CD patients

Fistulae are frequent!

- 33% after 10 years disease duration
- 52% after 20 years disease duration
- most frequently peri-anal localization (54%)
- frequent cause of surgical interventions (83%)
- 34% recurrent fistulae
During EMT, epithelial cells actively down-regulate cell-cell adhesion systems, lose polarity and acquire a mesenchymal phenotype - with increased migratory capacity.

E-cadherin and β-catenin expression decreases; β6 integrin (restricted to epithelial cells) is re-expressed.

Mediators of EMT: TGFβ, SNAIL1, SNAIL2 (Slug) during carcinogenesis
EMT occurs during fistula formation

Cytokeratin 8
E-Cadherin
β6 Integrin
β-Catenin

Bataille et al., Inflamm Bowel Dis 2008
SNAIL1 is strongly expressed in TCs in and around CD- fistulae

Scharl et al., Inflamm Bowel Dis 2010
SLUG is expressed around fistulae tracts

SLUG is expressed in colonic lamina propria fibroblasts (CLPF), squamous epithelial cells, and in the submucosa in and around CD-associated fistulae.

Scharl et al., Inflamm Bowel Dis 2010
EMT drives fistula formation in CD patients

TGF induces SNAIL1 expression and pushes EMT

TNF increases, whereas TGF suppresses PTPN2 protein in fistula fibroblasts

IL-13 secretion is increased, when PTPN2 levels are suppressed.
TGF-β induces secretion of IL-13 from fistula CLPF

**A**

![Graph showing SNAIL1 mRNA level normalized to β-actin](image)

**B**

![Graph showing SLUG mRNA level normalized to β-actin](image)

**C**

![Graph showing IL-13 secretion in pg/ml](image)

**D**

![Graph showing IL-13 secretion in pg/ml](image)
IL-13 and IL-13Rα1 in fistulae from CD patients

IL-13 in CD fistula

IL-13α receptor in CD fistula
IL-13 induces mRNA of SLUG and β6-integrin IEC

A. SLUG mRNA level normalized to β-actin

B. β6-Integrin mRNA level normalized to β-actin

C. SNAIL1 mRNA level normalized to β-actin

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** = Control

= IL13

30 min          24 h

0,0
0,2
0,4
0,6
0,8
1,0
1,2
1,4
1,6
1,8
Chronic administration of TGFβ, but not of IL-13, induces EMT.
Basal levels of SLUG and β6-integrin are elevated in fistula CLPF

**A**

- **SLUG mRNA level normalized to β-actin**
  - Non-fistula
  - Fistula

**B**

- **β6-Integrin mRNA level normalized to β-actin**
  - Non-fistula
  - Fistula

CLPF from CD patients
Summary

- TGFβ induces SNAIL1 and IL-13 expression in fistula CLPF
- TGFβ induces an EMT-like phenotype of IEC
- IL-13 does not induce EMT in IEC
- IL-13 promotes the expression of genes associated with invasive cell growth (SLUG)

*These findings indicate that TGFβ and IL-13 synergize to induce EMT in IEC and, subsequently, cell invasion of EMT-cells, what finally leads to the development of fistulae during CD course.*
A clinical POC study with an anti-IL-13 antibody in CD peri-anal fistulae has been started (December 2010) (Novartis)
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Thank you for your attention