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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

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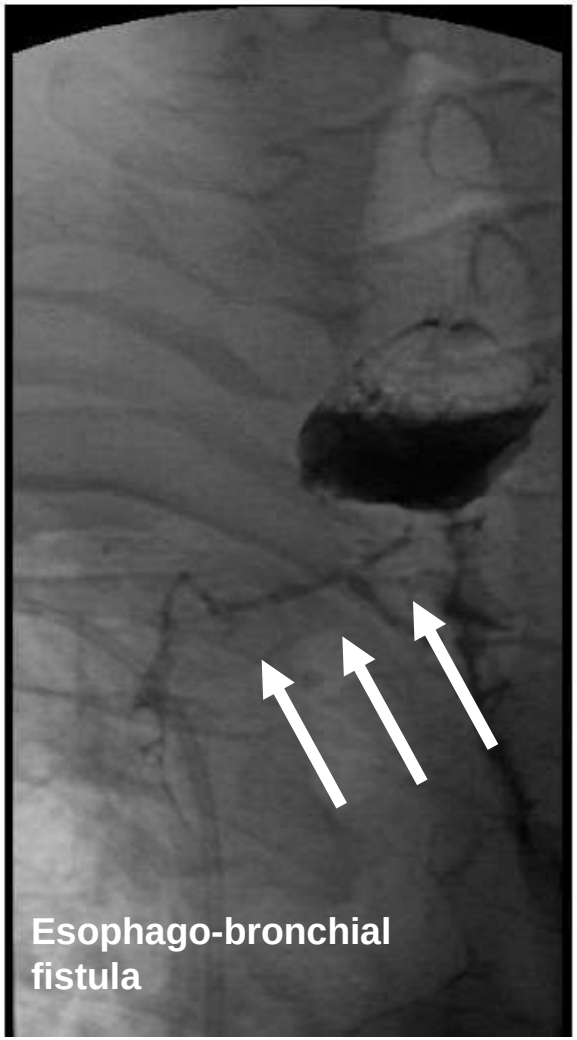
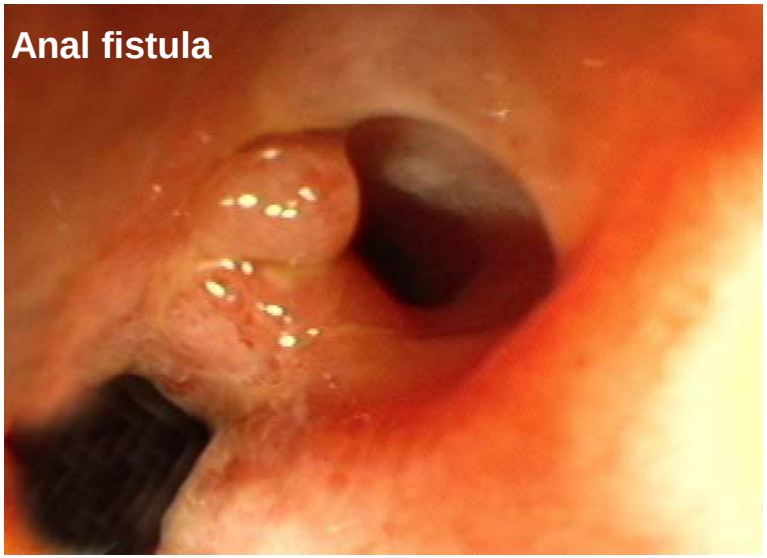
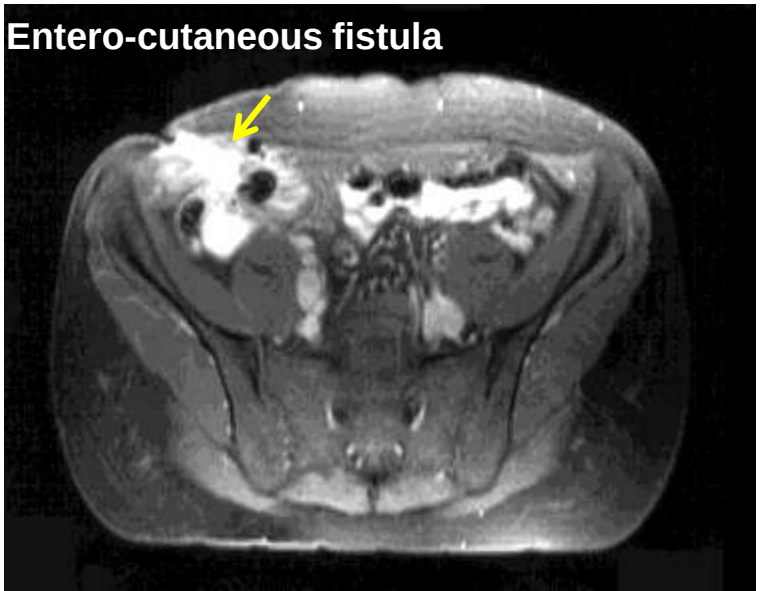


Fistulae are frequent!

- 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





Epithelial-mesenchymal Transition (EMT)

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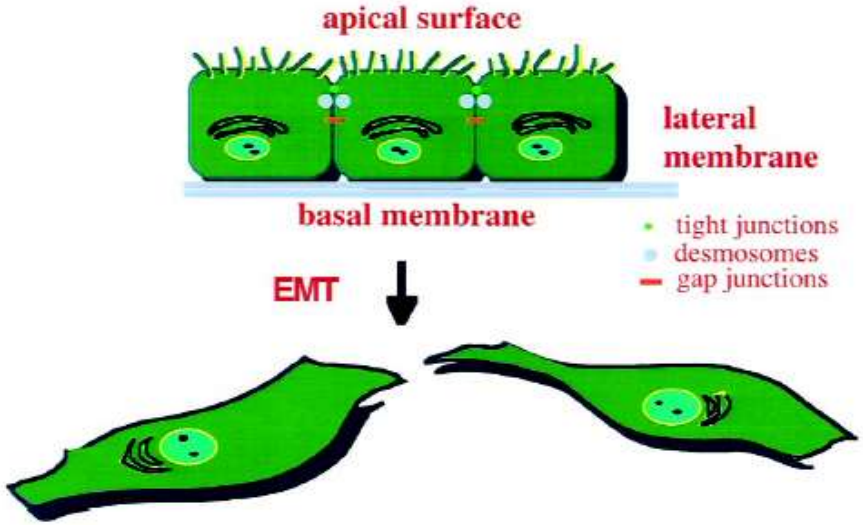
- During EMT, epithelial cells **actively down-regulate cell-cell adhesion systems, lose polarity and acquire a mesenchymal phenotype** - with increased migratory capacity.
- **E-cadherin** and **β-catenin** expression decreases; **β6 integrin** (restricted to epithelial cells) is re-expressed
- **Mediators of EMT**: TGFβ, SNAIL1, SNAIL2 (Slug) during carcinogenesis



EMT occurs during fistula formation

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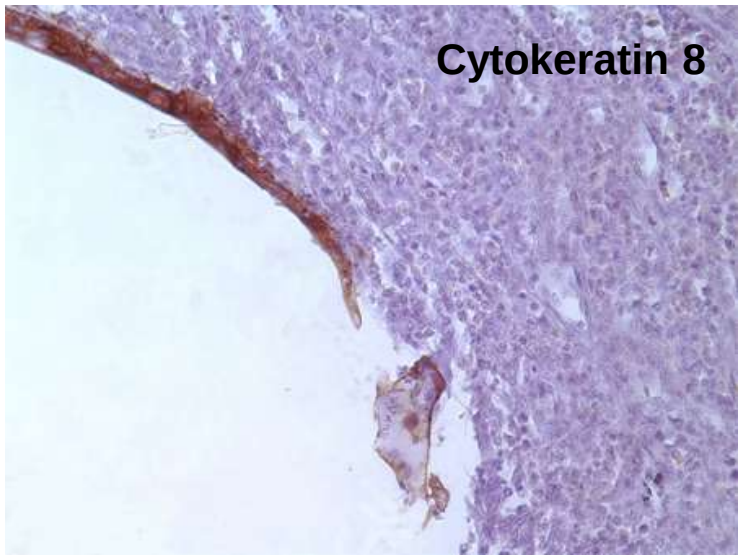

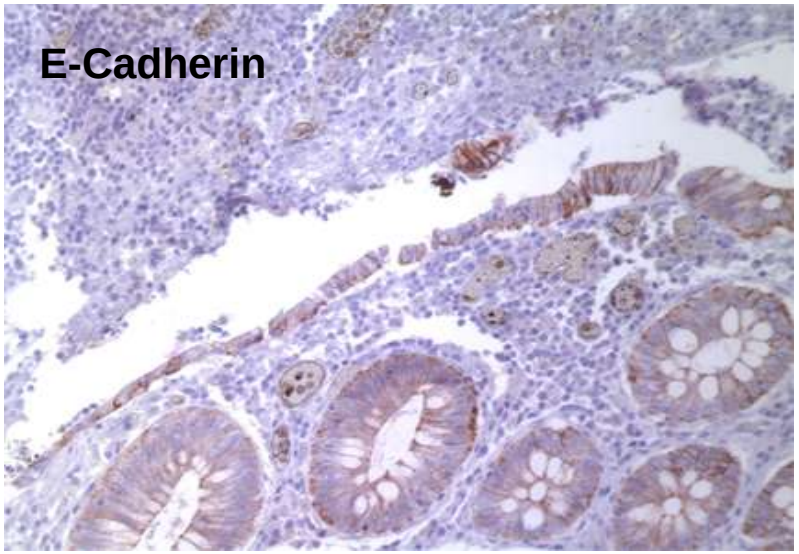

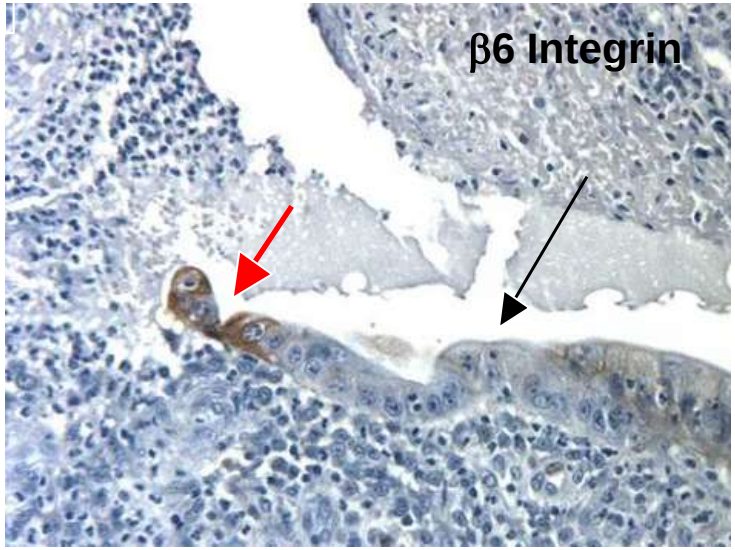

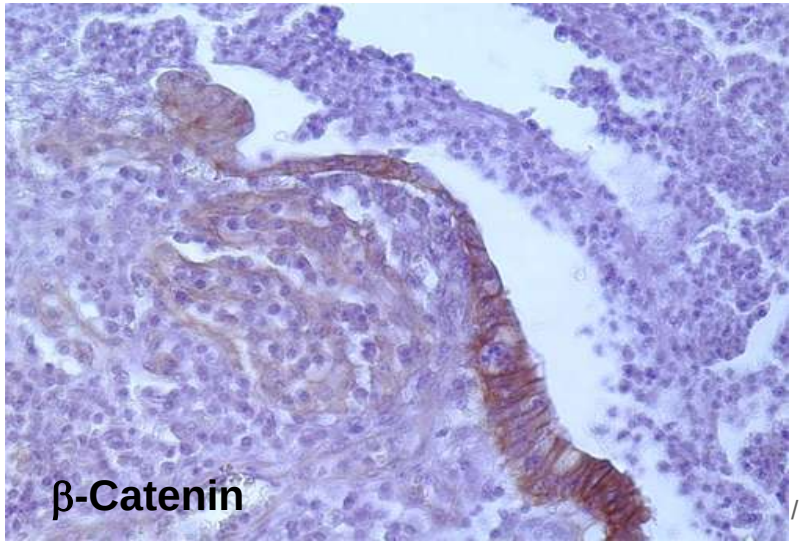

Bataille et al., Inflamm Bowel Dis 2008

SNAIL1 is strongly expressed in TCs in and around CD- fistulae

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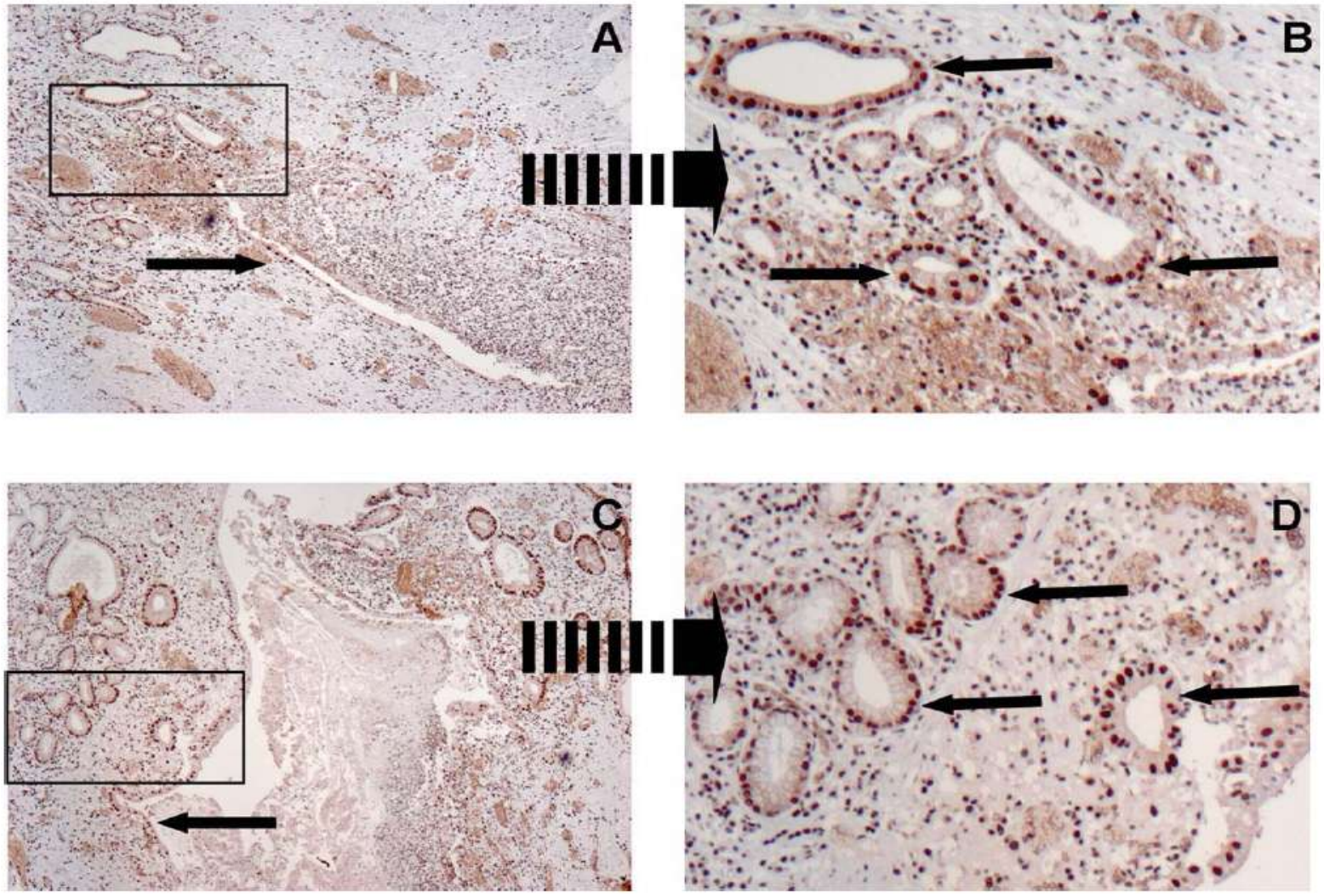

Scharl et al., Inflamm Bowel Dis 2010

SLUG is expressed around fistulae tracts

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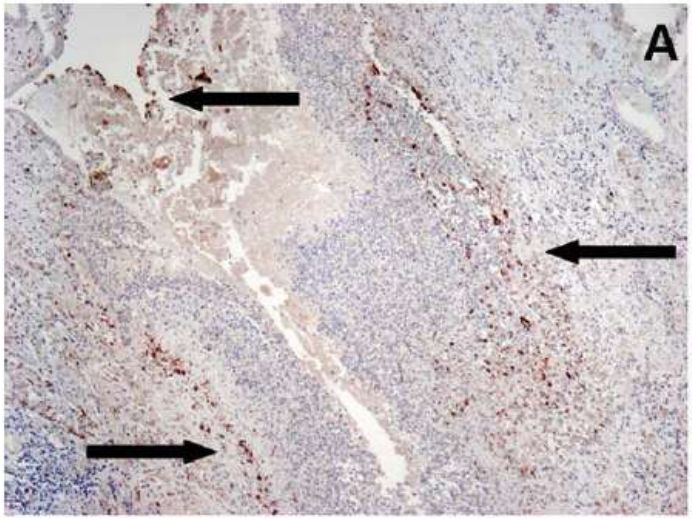
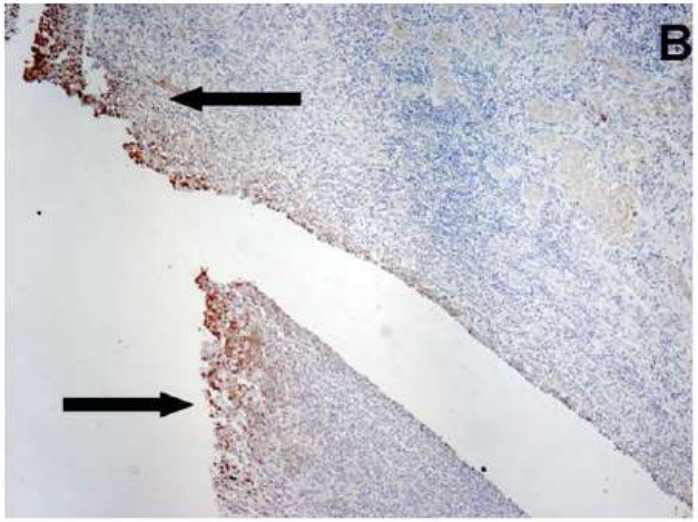
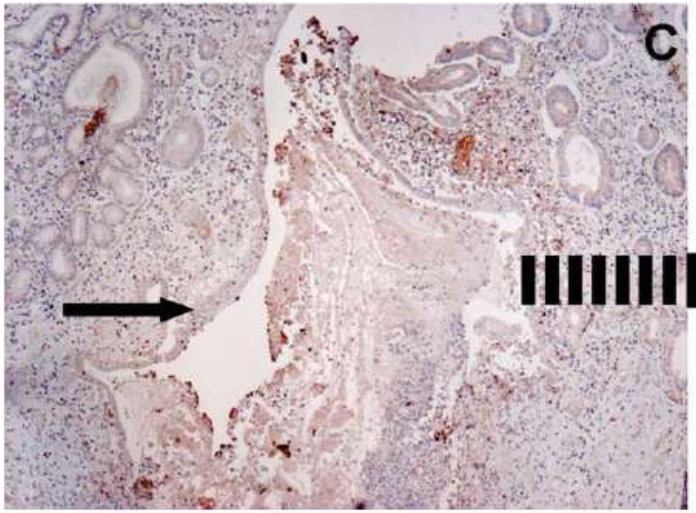
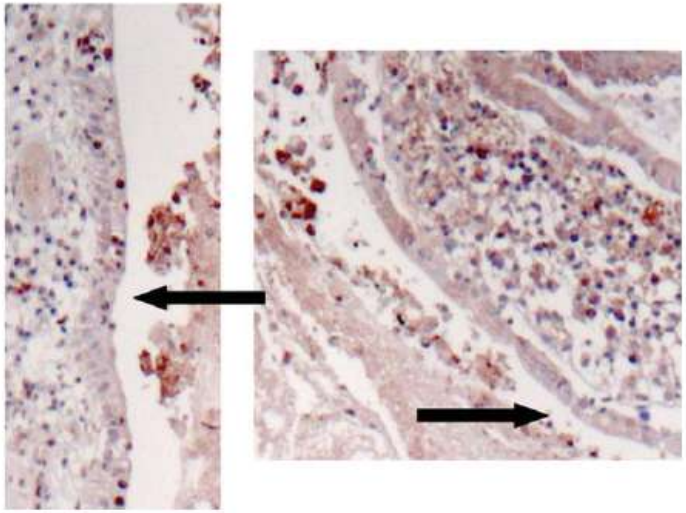
SLUG is expressed in colonic lamina propria fibroblasts (CLPF), squamous epithelial cells, and in the submucosa in and around CD-associated fistulae.









Scharl et al., Inflamm Bowel Dis 2010

Pathways in CD associated EMT and fistula formation

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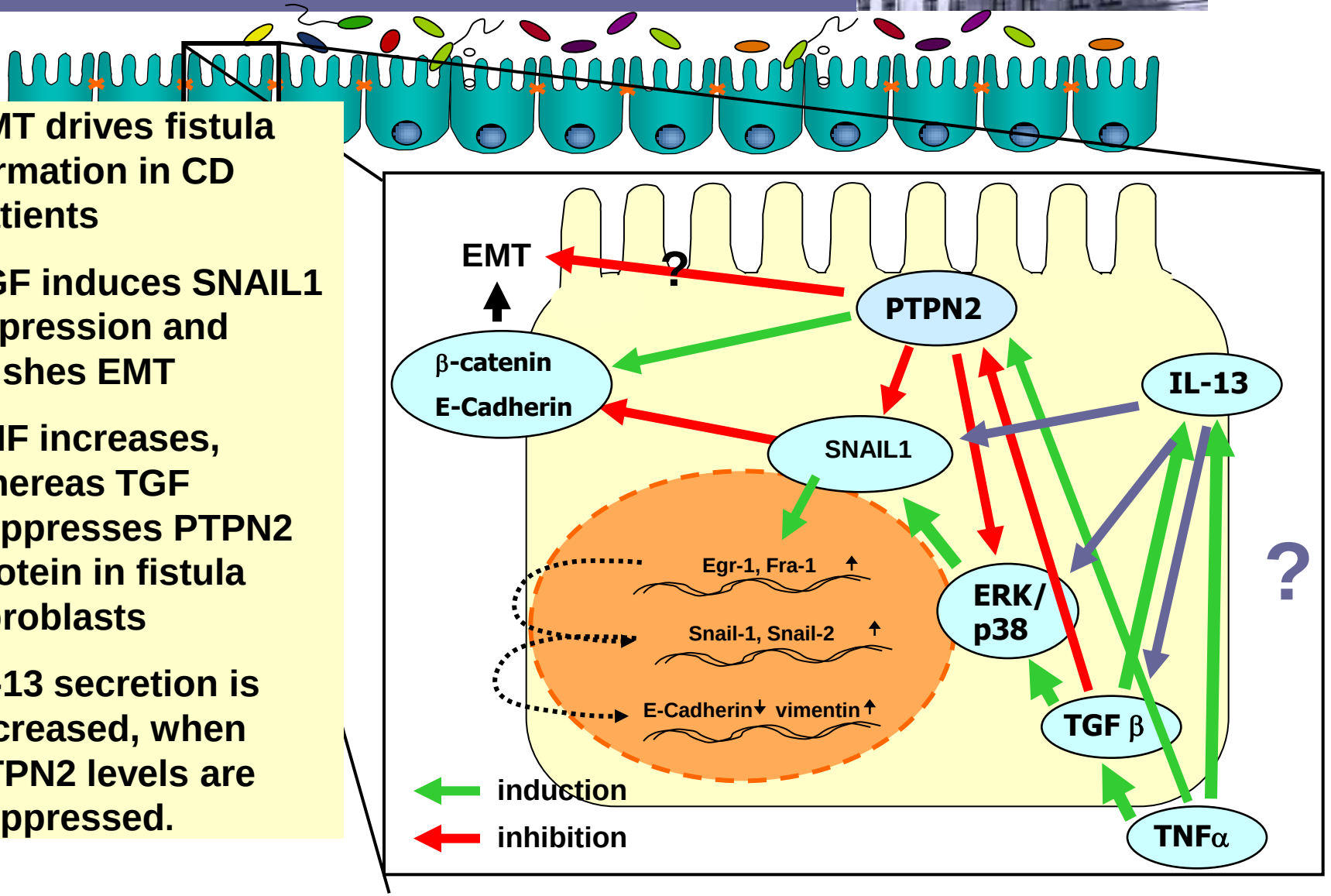
- EMT drives fistula formation in CD patients
- TGF induces SNAIL1 expression and pushes EMT
- TNF increases, whereas TGF suppresses PTPN2 protein in fistula fibroblasts
- IL-13 secretion is increased, when PTPN2 levels are suppressed.



TGF-β induces secretion of IL-13 from fistula CLPF

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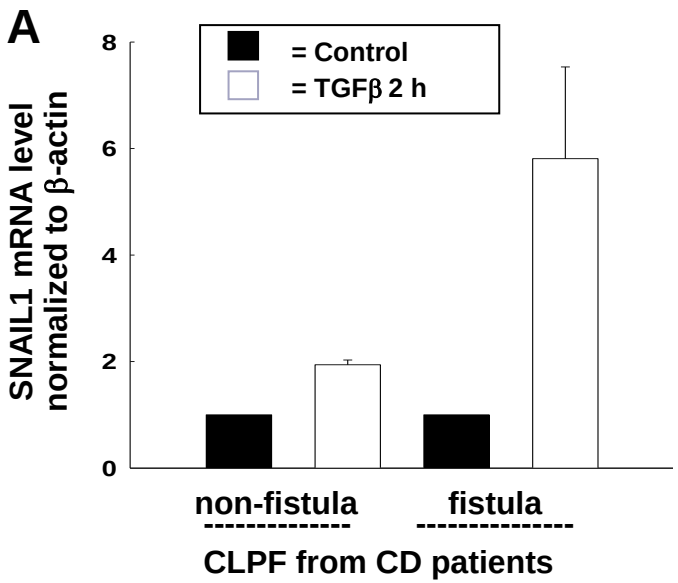

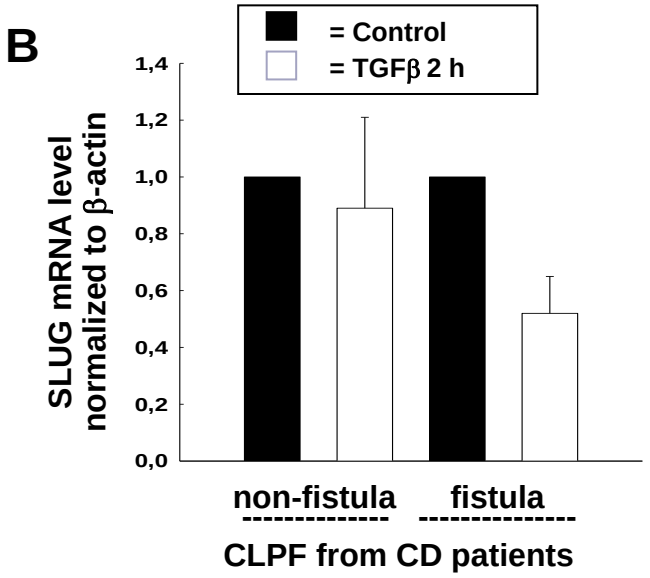

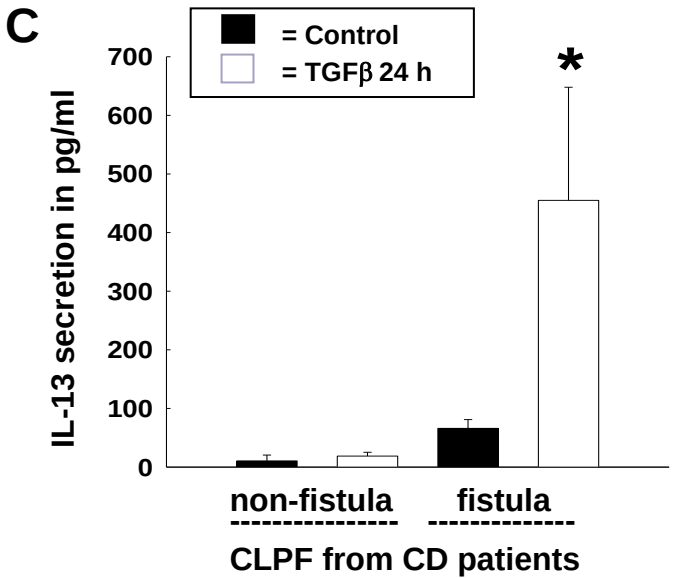

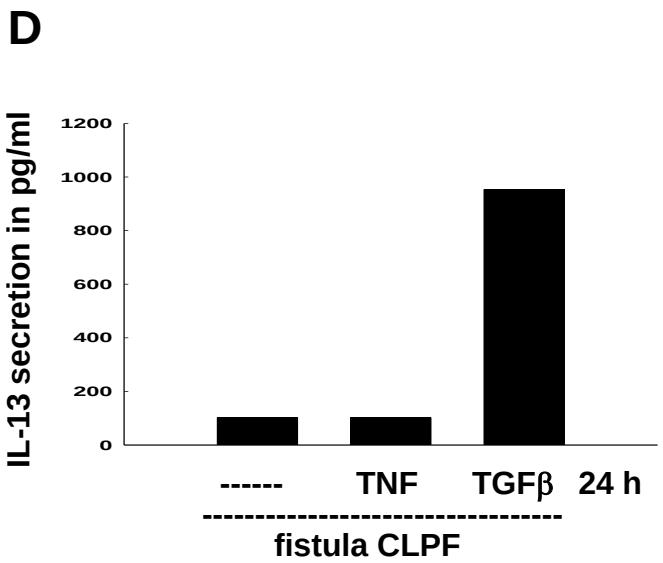

IL-13 and IL-13Rα1 in fistulae from CD patients

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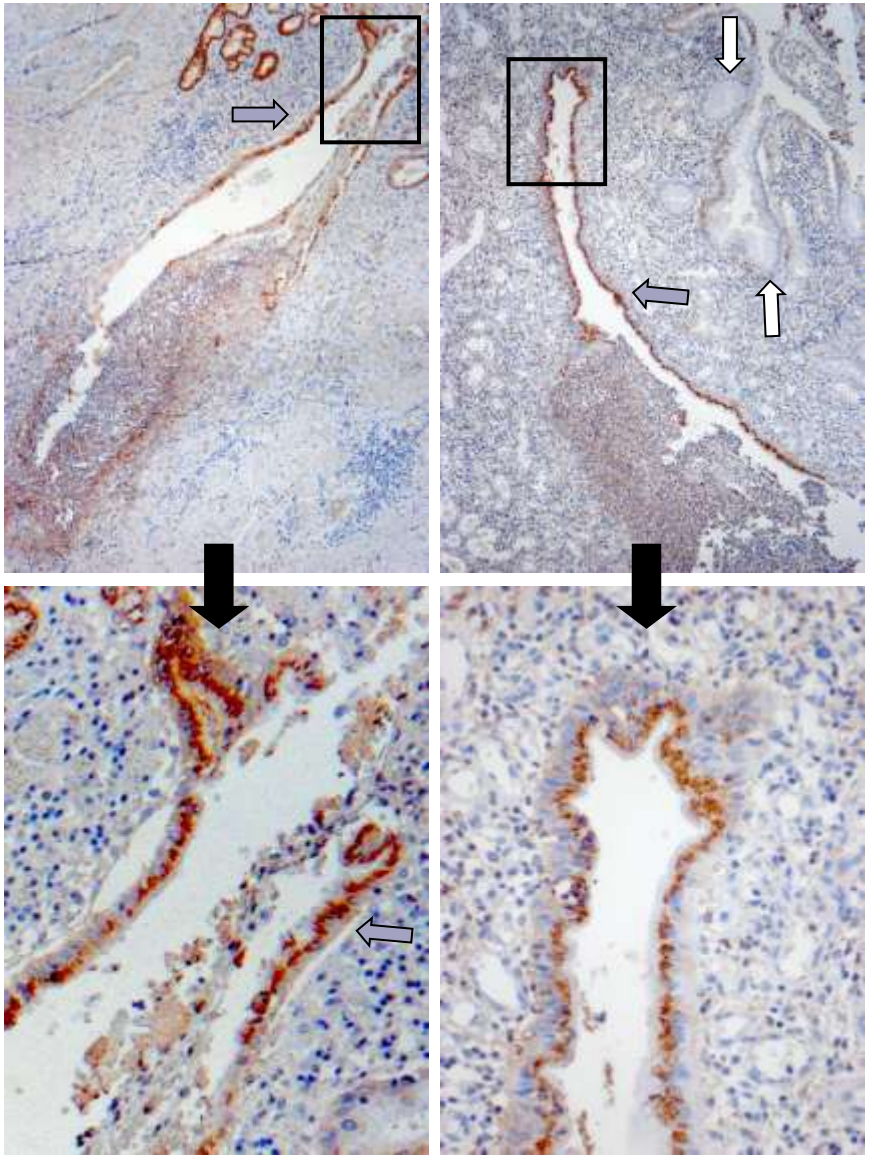
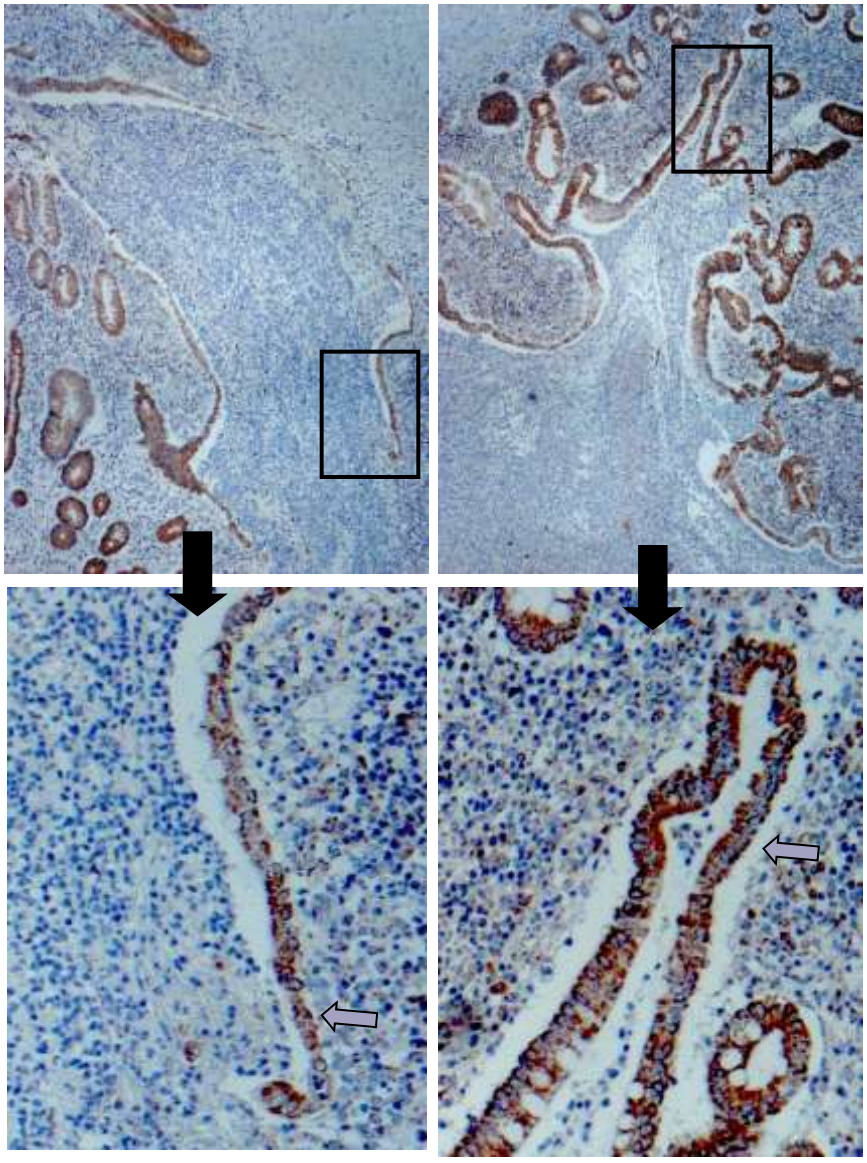
IL-13 in CD fistula



IL-13α receptor in CD fistula



IL-13 induces mRNA of SLUG and β6-integrin IEC

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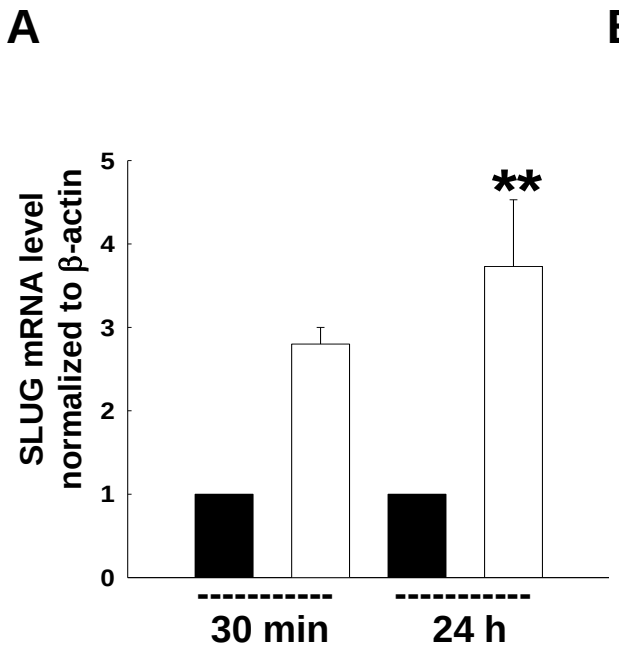

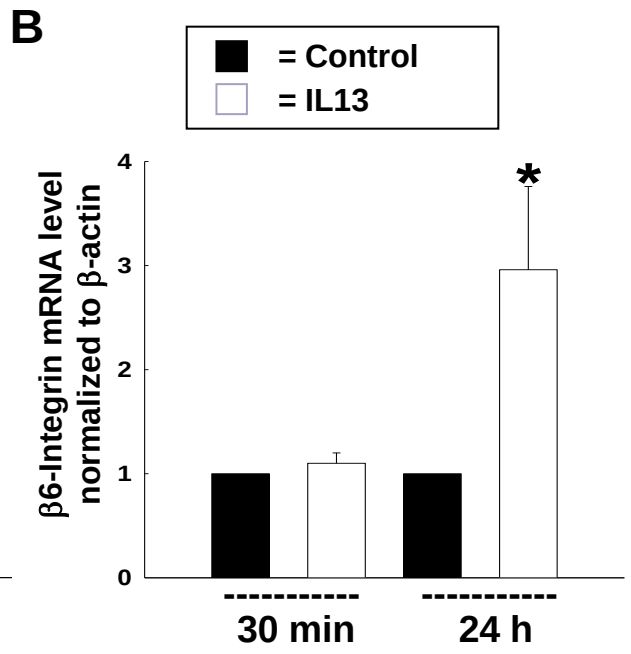

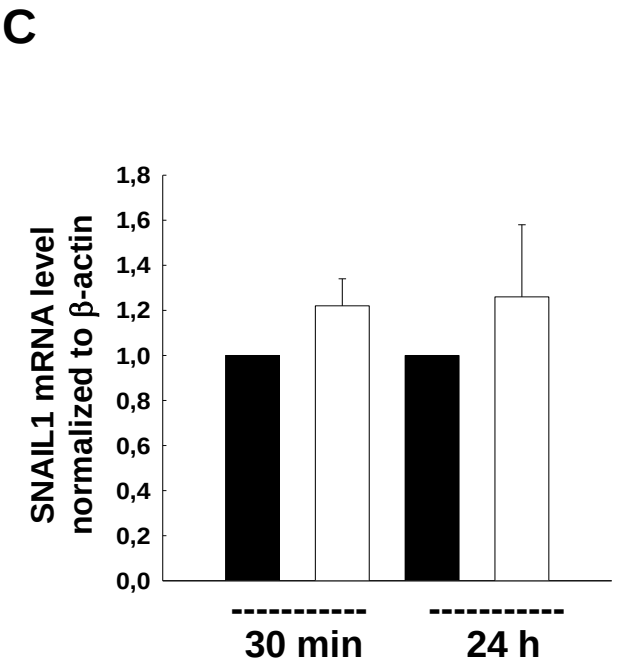

Chronic administration of TGFβ, but not of IL-13, induces EMT

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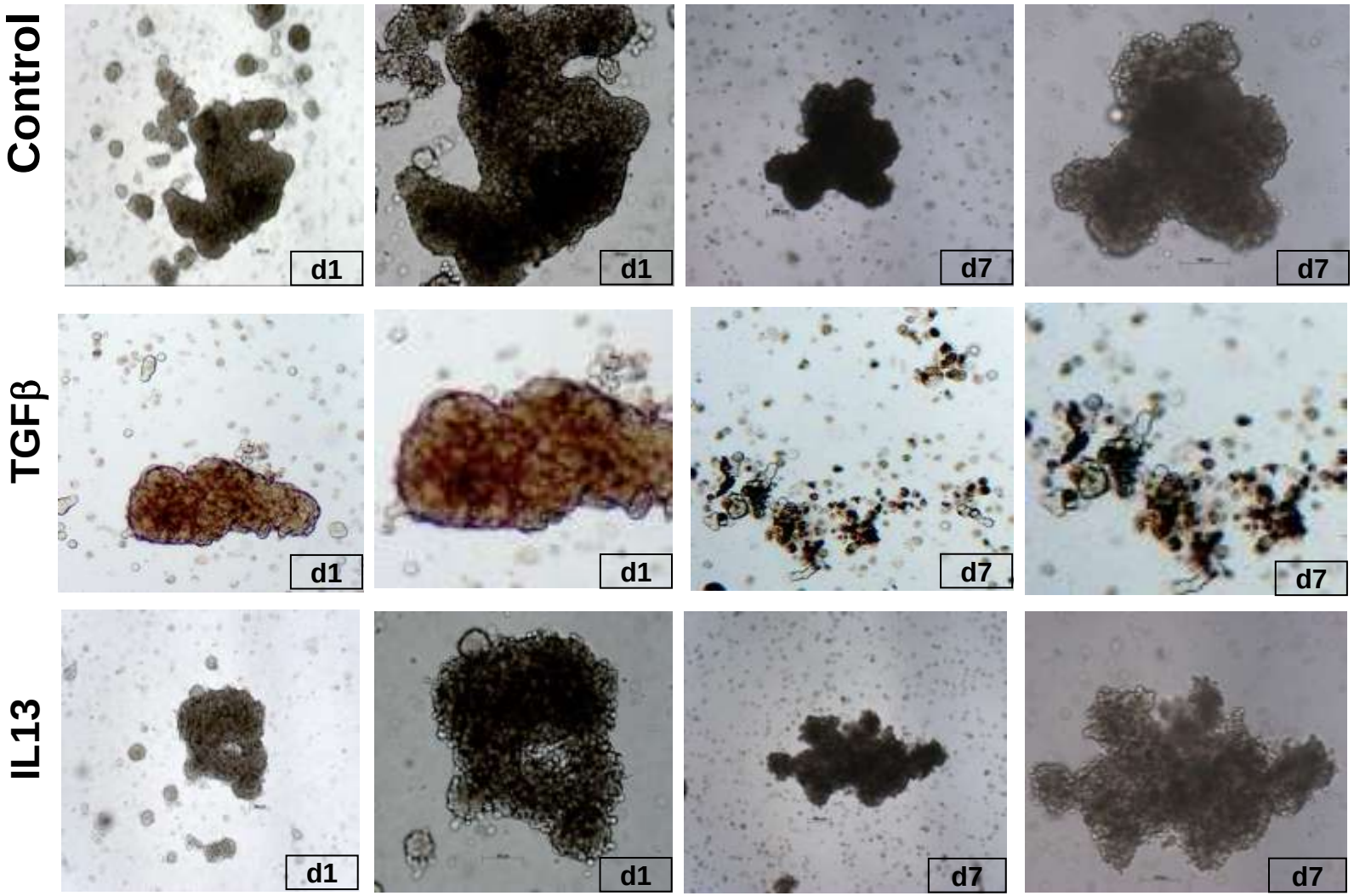

Basal levels of SLUG and β6-integrin are elevated in fistula CLPF

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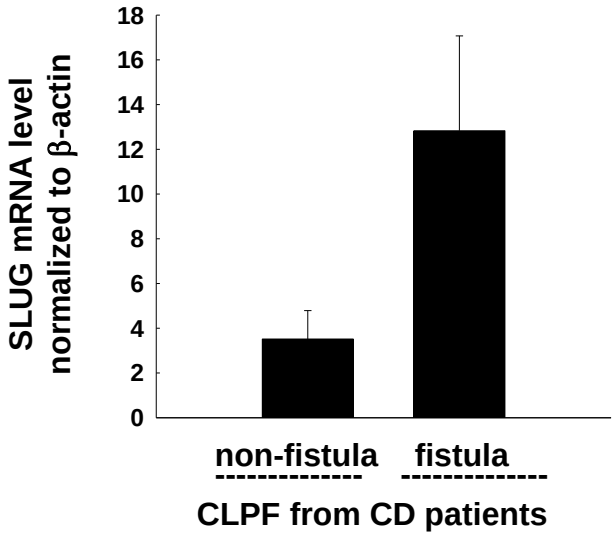
A



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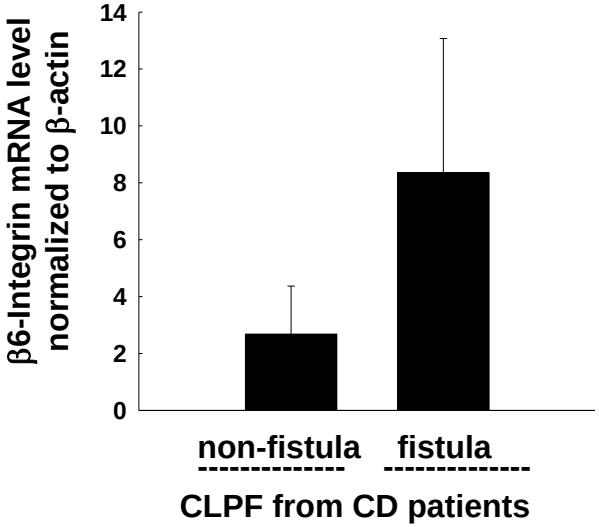

Summary

- **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.***

Outlook

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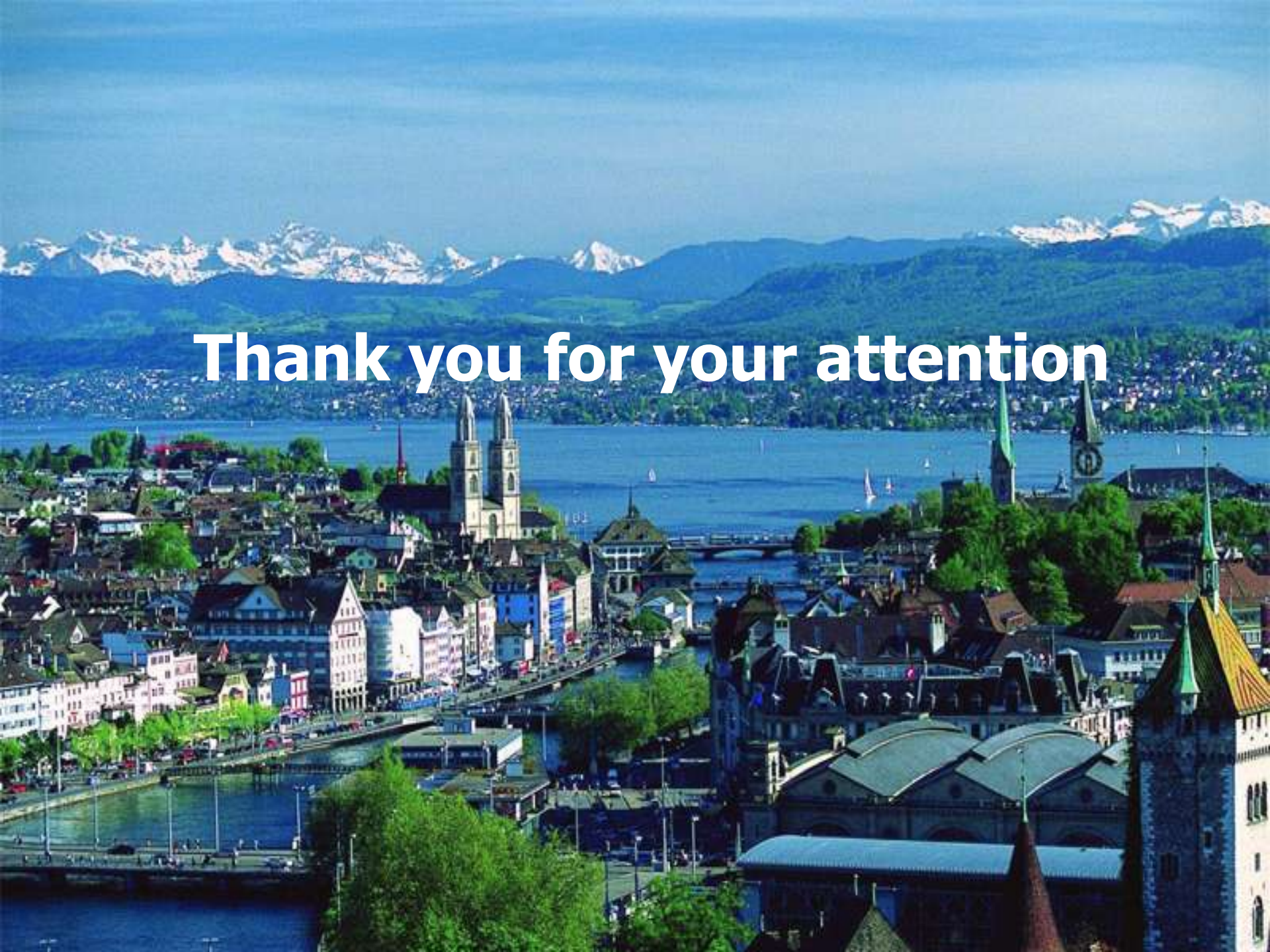
- ***A clinical POC study with an anti-IL-13 antibody in CD peri-anal fistulae has been started (December 2010) (Novartis)***

The "fistula team":

- ***Michael Scharl, MD***
- ***Theresa Pesch***
- ***Silvia Kellermeier***
- ***Sandra Frei***
- ***Ekkehard Jehle, MD***


Thank you for your attention