Drugs that modulate histone acetylation disrupt TGFβ signaling and reduce collagen I expression in models of stricturing Crohn’s disease

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Copenhagen, 08-03-19
Disclosures:

Conflict of interest : None
Intestinal fibrosis in Crohn’s Disease (CD)

- Fibrotic strictures are the main indication for surgery in CD

**Tissue damage** • Microbes, drugs, ischemia and oxidative stress

**Immune cell infiltration** • Secrete cytokines, e.g. TGF-β

**Fibroblast activation** • Increased extracellular matrix production, • Collagen (I, III & V)

Genotype → Environment → Epigenetics

Healthy

Stricturing

Inflamed
Histone acetylation is an important epigenetic mechanism of gene regulation

- Reduced histone-3 acetylation is a feature of stricturing in CD
- Low levels of histone acetylation associated with high collagen I expression
- VPA treatment increases acetylation and reduces collagen expression

Felice et al. Alimentary pharmacology & therapeutics 41 (1), 26-38
Lewis et al. Journal of Crohn's & colitis 11 (suppl_1), S17
Key questions

(i) How does VPA suppress collagen I expression?
(ii) What drives hypoacetylation in stricturing Crohn’s disease patients?
(iii) Can we identify novel, more specific, therapeutic targets that are regulated by histone acetylation?

Methods:

• Genes regulated by VPA in CCD18Co intestinal fibroblasts were identified by illumina HT12 gene expression array
• The effects of VPA on the target pathways were explored by immunohistochemistry (IHC) and Western Blot.
• VPA target genes were analysed in tissue from Stricturing CD patients by qPCR and IHC.
Suppression of COL1A1 is linked to inhibition of TGFβ1 in VPA treated fibroblasts

- Increased COL1A1
- Decreased COL1A1

**CCD-18co intestinal fibroblasts**
- PBS control or Valproic acid 5mM, for 48hrs (n=4)
- Validation: CD biopsies

- COL1A1
- TGFβ1
- HNRNPK
- DPP3
- ALDOA
- HCFC1
- TGFB1
- TOB1
- PITRMI
- SMARCD1
VPA suppresses TGFβ1 induced changes in histone acetylation & gene expression

- TGF-β reduces Histone 3 acetylation / VPA reverse this change
- VPA inhibits TGF-β-induced nuclear accumulation of phospho-SMAD3
- VPA inhibits Collagen I secretion from TGF-β treated fibroblast
- Changes in collagen I are mirrored by changes in TGF-β1|1
TGFβ1 and COL1A1 are increased in strictures

- mRNA profiling of strictured intestine (SCD) relative to non-strictured (NSCD) paired-adjacent areas in the same patient (n=7)

Increased expression of HDAC4 and HDAC7 in strictured intestine

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Working model

- TGF-β signaling induces histone 3 hypoacetylation
- Leads to increased Collagen I and TGF-β1|1 expression
- Is TGF-β1|1 required to maintain a pro-fibrotic phenotype?
Acknowledgments

Blizard institute, London
Prof. Andrew Silver (project supervisor)
Prof. James O Lindsay (project supervisor)

Royal London Hospital
Prof. Roger Feakins (pathologist)
Endoscopy Unit
Core pathology services

Funders
Bart’s and the London Charity