Results: We have established both colonic organoids generated from lesion and non-lesion parts of same UC patient. There is no significant difference of phenotypes such as stem cell and differentiation markers between these organoids. However, cell proliferation of organoids from lesion part was significantly slower than that from non-lesion part in spite of same culture condition. Moreover, oxidative stress of the organoids from lesion part is higher, suggesting that the pathogenesis of UC lesion might be maintained in the organoids from lesion part. Microarray analysis identified 22 genes upregulated in the organoids from lesion part more than 10 times compared with the organoids from non-lesion part. 16 genes downregulated in the organoids from lesion part less than one-tenth were also shown. The expression of some genes was also preserved in surgical specimens resected from 10 patients with UC.
Conclusions: Comparison between organoids from lesion and non-lesion part of same patient might reveal the fundamental pathogenesis in intestinal epithelial cells of UC. The identification of lesion specific genes might also be useful for the elucidation of molecular mechanism and therapeutic target for mucosal healing in UC.

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Gene expression profiles in inflamed colonic biopsies from newly diagnosed Crohn's disease and ulcerative colitis patients differ depending on the age at diagnosis

S. Verstockt[1]*, B. Verstockt[2,3], J. Van Bouwel[4,5], W. Meert[4,5], A. Cortes Calabuig[5], V. Brys[4,5], V. Ballet[2], E. Glorieus[6], M. De Decker[7], G. Van Assche[2,3], P. Hindryckx[6], M. Ferrante[2,3], D. Laukens[6], F. Mana[7], M. De Vos[6], S. Vermeire[2,3], I. Cleynen[1]
[1]*University of Leuven, Department of Human Genetics, Laboratory for Complex Genetics, Leuven, Belgium,* [2]*University Hospitals Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium,* [3]*University of Leuven, Department of Chronic Diseases, Metabolism and Ageing (CHROMETA), Leuven, Belgium,* [4]*University of Leuven, Department of Human Genetics, Leuven, Belgium,* [5]*University Hospitals Leuven, Genomics Core, Leuven, Belgium,* [6]*University Hospital Ghent, Department of Gastroenterology, Ghent, Belgium,* [7]*University Hospital Brussels, Department of Gastroenterology, Brussels, Belgium*

Background: Crohn's disease (CD) and ulcerative colitis (UC) are the most common forms of inflammatory bowel disease (IBD), both of unknown aaetiology. Clinical phenotypes are heterogeneous, partly depending on age at diagnosis. In this study we aimed to define the molecular profile of newly diagnosed IBD patients naïve for biologicals and immunosuppressives, and if this differs depending on the age at diagnosis.
Methods: Inflamed colonic biopsies were obtained from 23 CD (median age 24.0 (16.2–62.8) years; 35% male; 5 L2/18 L3) and 16 UC (median age 31.5 (16.7–69.0) years; 29% male; 7 E2/9 E3) patients within 6 months after diagnosis. All patients were naïve for biologicals and immunosuppressives, and without previous IBD-related surgery. Biopsies from 15 non-IBD controls (median age 35.7 (20.6–68.3) years; 47% male) were used to age-match with each patient group. Single-end RNA sequencing was performed using Illumina HiSeq4000. Normalisation and differential expression was done using DESeq R package. A fold change >2.0 and adjusted $p < 0.05$ were considered biologically significant. Pathways were analysed with IPA.
Results: Comparative analysis identified 632 (516 up, 116 down) differentially expressed genes between CD patients and age-matched controls; and 3796 (2542 up, 1254 down) between UC patients and matched controls; 581 genes were different in both CD and UC. Common upstream regulators of overlapping genes are STAT1, IFNγ, IFNα, and TNF. Pathway analysis showed that Th1/Th2 activation (e.g. STAT1, MHC-II HLAs) was enriched in CD and UC, while phagosome formation (e.g. FCGR2A/B, TLRs) and agranulocyte adhesion/diapedesis (e.g. MMPs) were UC-specific. While in CD there was a fairly small difference between younger (≤30 years, $n = 16$) and older-onset (>30 years, $n = 7$) patients (58 and 110 dysregulated genes, overlap of 21), younger (≤40 years, $n = 11$) UC patients showed more dysregulation than older-onset (>40 years, $n = 5$) UC patients: 3550 vs. 1722 genes, with an overlap of 1441. This seems to also reflect differences in disease severity between younger and older-onset, with 64% of younger UC exhibiting extended disease (E3) compared with 40% in the older group. Genes unique for younger UC are mainly involved in "LPS/IL-1 mediated inhibition of RXR" (eg. TNF, TLR4), while those specific for older UC were enriched for "role of macrophages, fibroblasts, and endothelial cells in rheumatoid arthritis" (eg. VCAM, TLR10).
Conclusions: There is a strong mRNA dysregulation in newly diagnosed CD, and even more in newly diagnosed UC. Younger-onset UC shows a prominent mRNA dysregulation compared with older-onset. This difference most likely reflects differences in disease severity, although this needs to be further established.

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Human neutrophil elastase degrades the therapeutic monoclonal antibodies effective in IBD

K. Kok[1,2]*, R. Curciarello[3], T. Sobande[1], S. Jones[1], G. Docena[3], T. MacDonald[1]
[1]*Blizard Institute, Barts and the London School of Medicine and Dentistry, Centre for Immunobiology, London, UK,* [2]*Barts Health, London, UK,* [3]*Instituto de Estudios Inmunológicos y Fisiopatológicos-IIFP-CONICET-Universidad Nacional de La Plata, La Plata, Argentina*

Background: A significant proportion of inflammatory bowel disease (IBD) patients are primary non-responders to biological therapies. Human Neutrophil Elastase (HNE) is highly expressed in IBD mucosa, especially in ulcerative colitis (UC). The aim of this study was to determine whether HNE degrades biologics, rendering them ineffective, and whether its action can be reversed by its natural inhibitor, Elafin.
Methods: Biologics (Infliximab, Adalumimab, Vedolizumab) were digested using different concentrations of recombinant HNE, in the absence or presence of Elafin, overnight. Neutrophils where isolated from human blood (4 UC patients and two healthy donors) by gradient centrifugation with Na-Dextran solution. Neutrophils where lysed and elastase activity was quantified. Antibody integrity after recombinant or natural HNE digestion was then analysed by western blot, and the functional capacity of the anti-TNF antibodies to neutralise TNF-alpha was tested using recombinant human TNF-alpha and a TNFR reporter cell line.
Results: Recombinant and HNE from blood cells fully degrades all anti-TNF-alpha agents and Vedolizumab in a dose-dependent manner (HNE 0.125–5 µg/ml degrades biologics from 6% to 99.9%, respectively). This activity is significantly inhibited by recombinant Elafin ($p < 0.001$). Treatment with HNE also partially prevented the ability of the biologicals to inhibit TNF-alpha bioactivity (HNE at 10 µg/ml causes 90% reduction of the anti-TNF's neutralising ability, while HNE at 5 µg/ml diminishes 25% of their neutralising activity).
Conclusions: These results may explain some of the reasons for primary non-responsiveness to biological therapies in IBD patients.