Transcriptional signature of ulcerative colitis in remission

C.G. Fenton[2], H. Taman[1,2], J. Florholmen[1], R.H. Paulssen[1,2]

[1]Gastroenterology & Nutrition Research Group and [2]Genomics Support Centre Tromsø (GSCT),
Department of Clinical Medicine, UiT- The Arctic University of Norway

Background

Ulcerative colitis (UC) is a chronic condition characterized by the relapsing inflammation despite previous histological and endoscopic healing[1,2]. The objective of this study was to address if existing transcriptional profiles can improve and support the current definition of UC in remission apart from the today existing endoscopic, histologic and laboratory scoring systems.

Methods

Mucosal biopsies from treatment-naïve UC patients (n=14), healthy controls (n=16) and UC patients in remission (n=14) (Table 1) underwent RNA-Seq using the Next Seq550 instrument from Illumina. Data analyses, relevant statistics, annotations and TNF-α measurements were performed as described previously[3].

Table 1: Patients characteristics

Characteristics	Control (n =16)	Debut UC (n=14)	UC remission (n=14)
Male/Female	11/5	9/5	9/5
Age mean ± SD	52.9 ± 16.9	39.6 ± 15.2	48 ± 28.0
TNF-α Level ± SD	3663 ± 1973	15907 ± 9623	4624 ± 1798
Endo Score mean ± SD	0	1.93 ± 0.27	0
Treatment	none	none	5-ASA*

*5-Amino-salacylic acid

Results

Analyses revealed 927 significantly DEGs in remission when compared to UC and normal samples (Figure 1). PCA showed a clear distinction between remission-, normal and UC samples along the first principal component 1 (PC1) with 45.7 %, and second principal component (PC2) with 9.3 % of the total variance (Figure 2). Cell fractions of monocytes, T cells, neutrophils, B cells/ lymphoid cells and myeloid cells decreased during remission, while the fraction of epithelial cells increased when compared to UC (Figure 3). This is in concordance with the observed inverse regulation of the common up-regulated inflammatory UC genes during remission (Table 2). A circumvent situation is also observed for down-regulated UC genes with genes involved in TGFβ- signalling, transport and drug metabolism (Table 2). Aside from DEGs involved in innate—and adaptive immune responses, genes like neuropeptide YY (PYY) and neurotrophic receptor tyrosine kinases (NTRK1 & NTRK2) showed increased expression during remission (Figure 4).

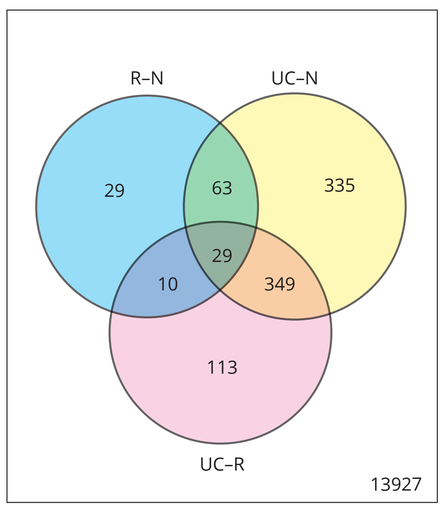

Figure 1. Venn diagram of significantly differentially expressed genes. Only genes with an absolute fold change > 1.0 are considered.

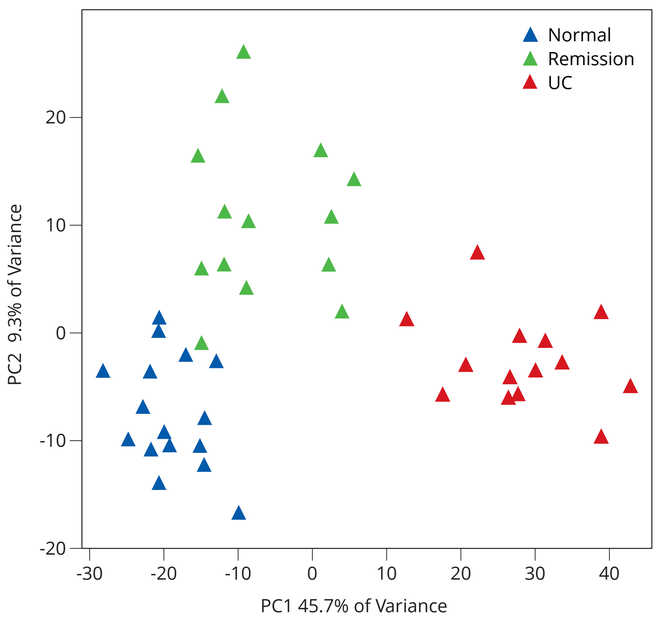

Figure 2. Principal component analysis.

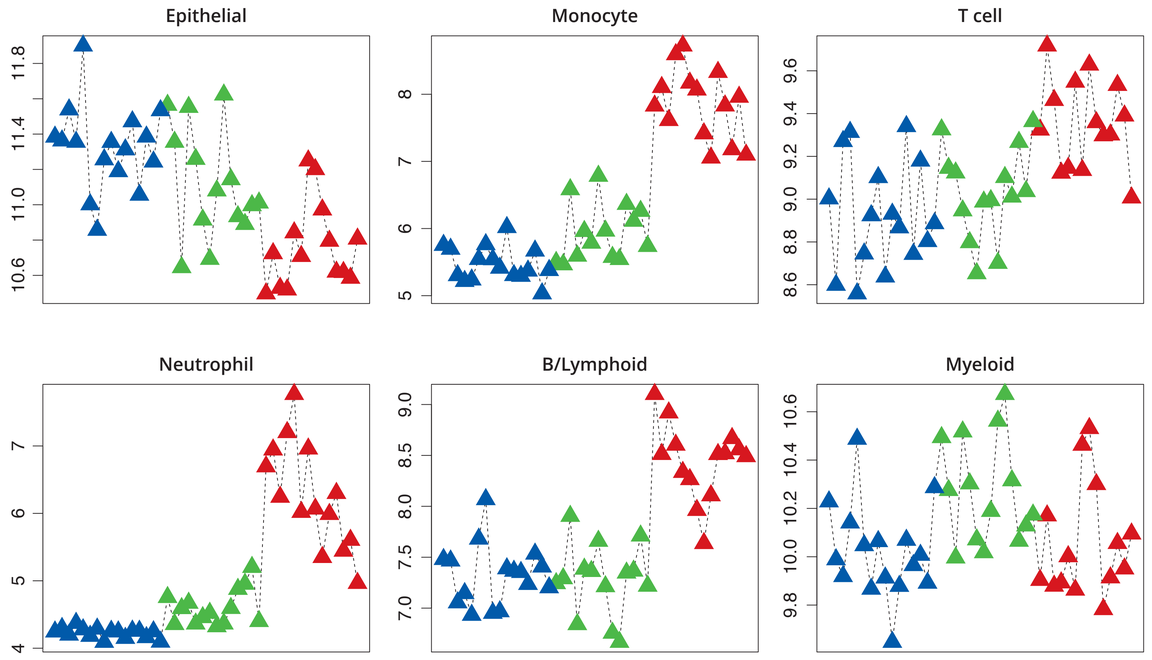

Figure 3. Estimation of cell populations between samples using cell deconvolution methods. ▲ Normal, ▲ Remission, ▲ UC.

Table 2. Selected DEGs common between normal mucosa (N), ulcerative colitis (UC) and remission (R).

Gene Symbol	Log2 FC UC-N	Log2 FC UC-R	Log2 FC R-N	Annotations
DUOXA2	5.52	3.87	1.65	innate immune system
OLFM4	4.01	1.18	2.83	innate immune system
CHI3L1	3.90	2.71	1.19	innate immune system
DEFA5	3.35	1.27	2.08	innate immune system
MMP10	3.17	1.60	1.57	cell adhesion; ECM remodelling
CLDN2	2.60	1.08	1.53	cytoskeletal signalling
S100P	1.41	-1.04	2.45	innate immune system
CYP3A4	-2.82	-1.55	-1.27	drug metabolism
SLC6A19	-3.26	-1.28	-1.98	transport
BMP3	-3.74	-1.37	-2.37	TGF-beta pathway
AQP8	-4.48	-1.93	-2.54	transport

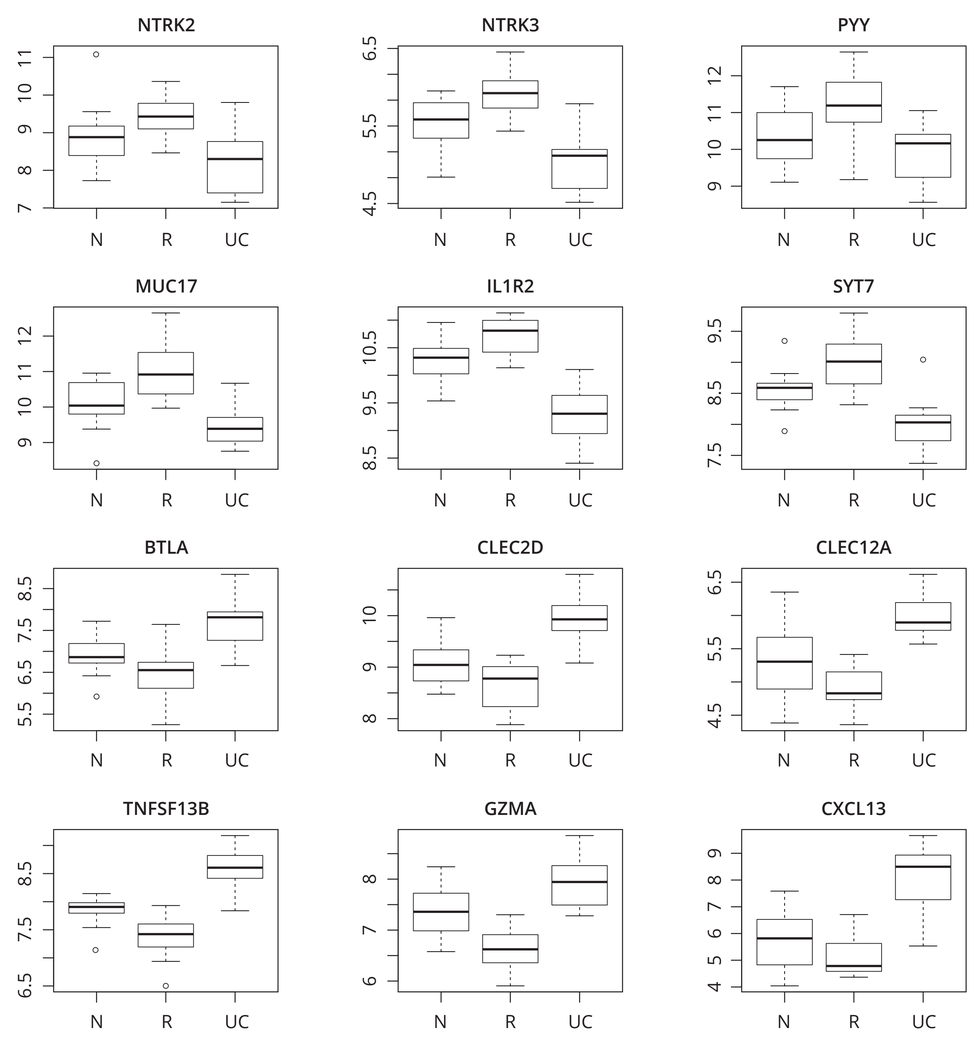

Figure 4. Selection of some relevant non-inflammatory DEGs in UC remission.

Conclusion

Apart from reduced major key inflammatory activities seen for UC, we propose that a gut-brain communication network is involved during remission beside the partial restoration of immunological functions and recovery of local homeostasis in the epithelial mucus layer and lamina propria. In addition, a certain role for the composition of bacterial gut flora may be implied. These results can be useful for the development of treatment strategies for remission and might be useful molecular targets for further investigations aiming to predict relapse of UC patients in the future.

References

1. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: The ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol 2014;12:929-34 e2.
2. Bryant RV, Winer S, Travis SP, Riddell RH. Systematic review: Histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An ioibd initiative. J Crohns Colitis 2014;8:1582-97.
3. Taman H, Fenton CG, Hensel IV, et al. Transcriptomic landscape of treatment - naive ulcerative colitis. J Crohns Colitis 2017:1-10.

Layout/Design: Rod Wolstenholme, Faculty of Health Sciences, UiT The Arctic University of Norway.