Downregulated Mucosal Autophagy, Alpha Kinase-1 and IL-17 Signaling Pathways in Active and Quiescent Ulcerative Colitis

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Introduction

Inflammatory bowel disease (IBD) comprises of Ulcerative Colitis (UC) and Crohn's Disease (CD). It is caused by an inappropriate immune response to intestinal microflora, leading to recurring periods of active bowel inflammation followed by remission.[1] Active IBD heavily impairs psychological and social functioning, causing debilitating abdominal pain, diarrhea and fatigue. Hence, a major clinical challenge in IBD management is to prevent relapse of IBD and achieve mucosal healing.

The study aims to analyse colonic mucosal transcriptional profiles and signalling pathways during active and quiescent IBD, with emphasis on immunological host response of patients. This allows identification of important mechanisms for sustaining deep remission and preventing relapse.

Methods

Study Subjects
47 IBD patients were recruited at five Swedish hospitals. All patients were at least 18 years of age with a confirmed diagnosis of IBD with colonic involvement for at least 3 months. The IBD patients were compared to healthy subjects of at least 18 years of age without gastrointestinal or any chronic disorders.

Colonic Biopsies
Colonic biopsies were collected during colonoscopy. The biopsies from patients with active disease were retrieved from inflamed colonic sites before the start of therapy. Patients in remission and healthy subjects provided biopsies from the sigmoid colon.

Mucosal Gene Expression
RNA from biopsies were extracted and mucosal gene expression was studied using the nCounter Human Host Response panel, which assesses Host Susceptibility, Interferon Response, Innate Immune Cell Activation, Adaptive Immune Response and Homeostasis. Positive scores correspond to upregulation and negative scores correspond to downregulation. A total of 776 genes and 56 immune-related pathways were analysed with OPLS-DA to differentiate these genes and pathways.

Results

1. Patients with active IBD have a distinct colonic mucosal transcriptional profile from healthy subjects

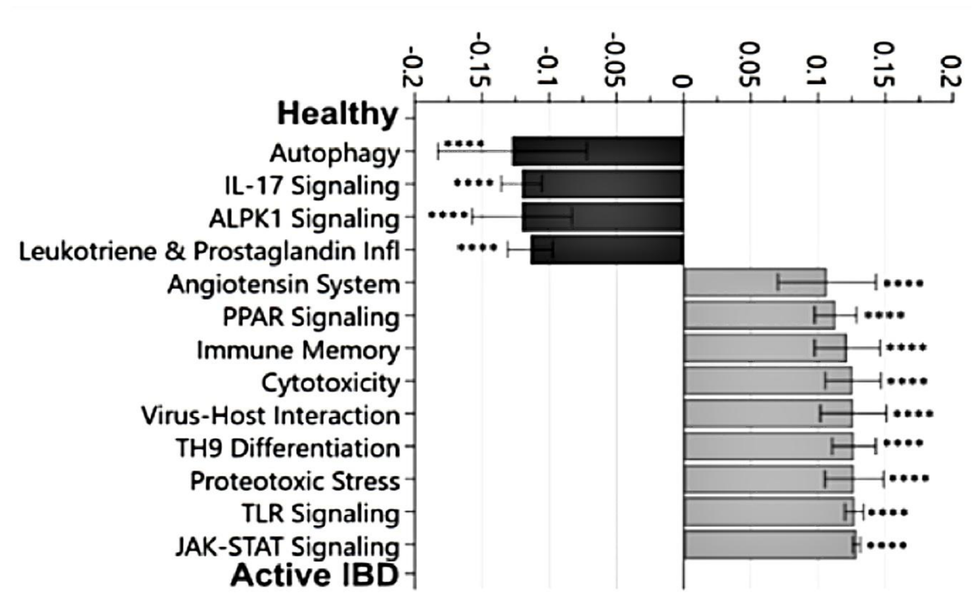

Fig 1. OPLS-DA loading column plot depicting up- and downregulated pathways in IBD vs healthy subjects based on their pathway scores.
4 pathways were noted to be downregulated, while another 52 pathways were upregulated (full graph not shown).

Most pathway scores were increased in active IBD compared to healthy subjects. However, the **alpha kinase-1 (ALPK1), autophagy, IL-17 signalling and leukotriene and prostaglandin inflammation pathways were decreased instead**, further evidenced by the downregulation of specific genes involved in such pathways.

2. Most pathway scores are increased in active UC, except for autophagy which had a decreased score compared with UC remission.

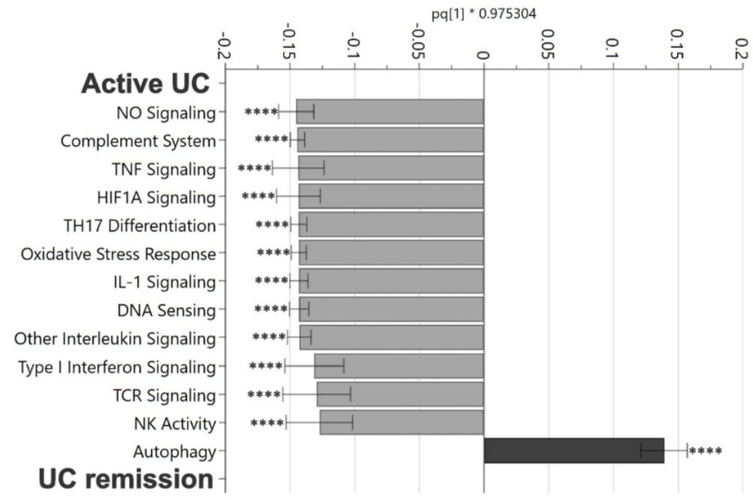

Fig 2. OPLS-DA loading column plot depicting up- and down-regulated pathways in active UC vs UC remission based on their pathway score.
Only 1 pathway was downregulated in active UC, while the other 48 were upregulated.
(full graph not shown)

Comparing active UC to UC remission, most pathway scores are increased in active disease except for **autophagy pathway** which had a **decreased score** compared to remission, suggesting dysfunctional autophagy signalling in active UC.

3. Colonic mucosal gene expression in UC patients in remission differed from healthy subjects with an emphasis on homeostasis

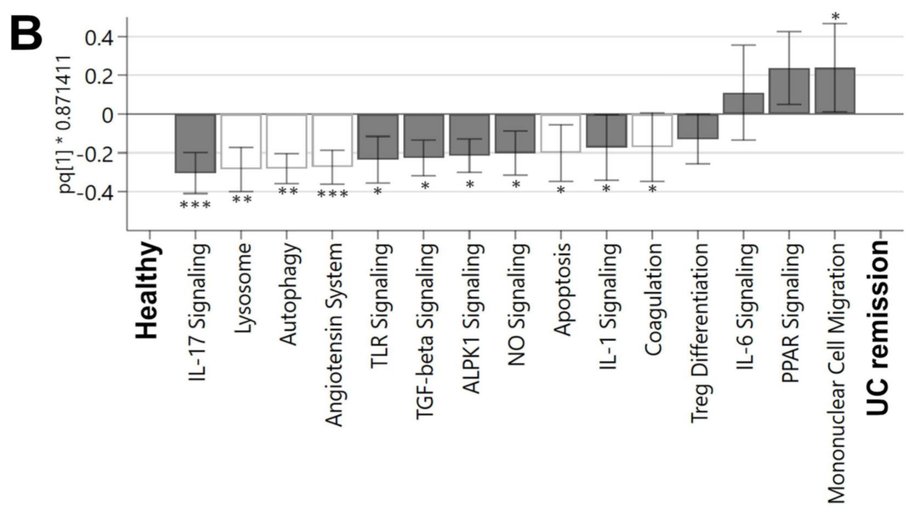

Fig 3. OPLS-DA loading column plot of pathway scores. Pathways shown with white bars belong to the phase of homeostasis.

Comparing patients in UC remission to healthy subjects, **11 pathways had decreased scores, of which 5 pathways were linked to homeostasis** (white bars on Fig. 3), including pathways involving **lysosome, autophagy, angiotensin system, apoptosis, and coagulation.**

Discussion

1. Lower pathway scores of **autophagy, ALPK1, IL-17 and leukotriene/ prostaglandin signalling** were noted in IBD patients with **active disease compared to healthy subjects**. Similar findings were noted in **quiescent UC**, suggesting that these pathways are impaired consistently regardless of disease activity.
2. There is permanent mucosal dysfunctionality related to autophagy, ALPK1, and IL-17 signalling pathways in **both active disease and during periods of remission**, suggesting that dysregulation of these pathways may cause future flares of disease.

Limitations of this study include:
1. Paired analyses and evaluation of within-subject effects were not done as UC patients in remission group were independently included from the active UC group.
2. Restricted information on subjects' comorbidities.

Conclusion

This study indicates that autophagy, alpha kinase-1 and IL-17 signaling pathways are persistently downregulated in UC irrespective of disease activity. Furthermore, UC patients in remission present a unique mucosal environment, potentially preventing patients from reaching and sustaining true homeostasis. These findings may enable better comprehension of the remitting and relapsing pattern of colonic IBD and guide future treatment and prevention of flares.

References

1. McDowell C, Farooq U, Haseeb M. Inflammatory Bowel Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Available from: http://www.ncbi.nlm.nih.gov/books/NBK470312/