P067 Molecular profiling of early Crohn's disease reveals a prominent role for WNT5A

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Background

Crohn's disease (CD) is characterized by a chronic inflammation of the gut, progressing to stricturing and/or penetrating complications in most patients. Effective intervention before the onset of bowel damage, and thus in the early phase of the disease, is required to optimize patient outcomes. We aimed to define the molecular landscape of early CD by using the unique post-operative recurrence (POR) model.

Methods

Ileal mucosal biopsies were obtained during colonoscopy from (1) 25 patients with early recurrence CD (Rutgeerts' score i2b, i3 or i4) within 18 months after ileo-colonic resection with ileo-colonic anastomosis (= POR CD); (2) 19 CD patients within 18 months after diagnosis (= new CD); and (3) 14 active CD patients >3 year after diagnosis and/or >3 year after ileo-colonic anastomosis (= late CD). As comparison, 12 controls were included. Total RNA was used to study mRNA and microRNA (miRNA) expression via Affymetrix Human Gene 1.0 ST and Affymetrix miRNA 2.0 arrays, respectively. A false discovery rate (FDR) <5% and >2-fold change (mRNA) or >1.5-fold change (miRNA) were considered biologically significant. Gene and miRNA expression profiles were integrated using the Ingenuity miRNA Target Filter.

Results

When comparing POR, new and late CD with controls, we observed respectively 353, 608 and 614 significantly differentially expressed gene probe sets. Comparative analyses of the miRNA expression profiles in POR, new and late CD versus controls identified respectively 13, 5 and 1 significantly differential signal(s). Integration of dysregulated genes and miRNAs in POR CD found 64 miRNA-mRNA pairs with negative correlation in expression profiles, five of which experimentally supported in literature: hsa-let-7g-5p is known to target PRDM1 and PTGS2, hsa-miR-30d-5p targets SLC7A11 and WNT5A, and hsa-miR-196a-5p targets ANXA1. To be sure that POR i2b/i3/i4 represents a true baseline model for early CD, we looked at gene expression in ileal biopsies from 3 CD patients with uninflamed post-operative ileum (i0), and 6 CD patients with POR i1. Comparison of i0, and i1 versus controls identified respectively 1 and 123 significantly differentially expressed gene probe sets. WNT5A was the only dysregulated gene in i0, and showed an increased expression with an increasing Rutgeerts' score ($p<0.0001$).

Conclusion

We showed an important mRNA dysregulation in new/late CD, while dysregulated miRNA expression was more pronounced in POR CD. WNT5A, a non-canonical Wnt ligand, seems to have a key role throughout, being the only dysregulated gene in i0 CD patients, showing an increased expression with increasing Rutgeerts' score, and being targeted by one of the dysregulated miRNAs. WNT5A is known to be involved in reparative inflammation.