**Clinical and molecular effects of guanylate cyclase c-activation**

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Abstract for the mid term evaluation report.

In 2012 we published the clinical and molecular characterisation of a novel inherited disease, Familial GUCY2C diarrhea syndrome (FGDS) in the New England Journal of Medicine. We identified 32 individuals in a large family from western Norway with early onset relatively mild diarrhea , susceptibility to Crohn's disease (7 patients) and small bowel obstructions (8 patients). By linkage analysis and high throughput sequencing we identified heterozygosity for a rare missense variant in the *GUCY2C* gene in the patients. *GUCY2C* encodes guanylat cyclase C (GCC), the intestinal receptor for ST toxin from *E.coli* (causing tourist diarrhea) and endogenous ligands uroguanylin and guanylin. Binding of ligands result in increased cellular cyclic GMP, which in turn leads to secretion of chloride, bicarbonate and water into the intestinal lumen. The c.2519G>T variant was shown to have an activating effect on GCC upon binding of ligands, thus explaining the diarrhea in our patients.

The aim of my further PhD project was to elucidate the mechanisms of Crohn´s disease susceptibility in FGDS, and we approached this by investigating genetic low risk variants for Crohn's disease, global gene expression in the terminal ileum, and intestinal microbiota in the FGDS patients compared to healthy controls. Global gene-expression studies on the ileal biopsies from 11 FGDS patients and 16 healthy controls (false discovery rate of 5 %) showed that 6 genes belonging to the group of metallothioneins were downregulated in the patients. The metallothioneins are important for NOD2-related autophagic clearance of bacteria, which is one process involved in development of Crohn's disease. Interestingly, by analysing 140 low risk Crohn's disease loci in 23 FGDS-patients above 30 years, and sequencing of the whole *NOD2* gene, we found an increased number of *NOD2* risk variants in the FGDS patients with Crohn's disease compared to the patients with no signs of inflammation in the gut. These data point to defect autophagy as one possible mechanism for the susceptibility to intestinal inflammation in FGDS patients.

Dysregulation of host-microbe interactions is a key mechanism in Crohn's disease, and alterations in gut microbiota have also been found to alter expression of metallothioneins. We next investigated the intestinal gut flora in fecal samples from 24 FGDS-patients and 12 healthy family members, 99 healthy other controls and 45 patients with IBD. FGDS patients had a significantly different microbiota profile compared to the other groups, with particularly low levels of bifidobacteria. These bacteria have anti-inflammatory effects and are used therapeutically as probiotics. Because the bifidobacteria feed on the mucus lining the intestinal epithelium, a possible explanation for the low abundance of this species could be a disrupted mucus barrier in FGDS patients, and this should be further investigated.