Identification of ectopic olfactory receptor gene in ulcerative colitis patients and functional analysis of OR51E2 using ex vivo culture of colonic organoid in both human and mice

Korea University, Internal medicine, Seoul, South Korea

Background: Olfactory receptors (ORs) are one of the largest gene family of human genome and the GPCRs. Ectopic expression of ORs have been detected not only in the nose, but also various non olfactory organs, including testis, prostate, kidney and GI tracts. Some ORs have been demonstrated to have an effect on cell growth and cancer progression or inhibition. But their exact functions have not yet been fully investigated. Here, we identified OR gene in ulcerative colitis patients using RNA-sequencing analysis and real-time PCR. In order to analyse the functional role of OR gene, we used the organoids from both human and mice colon and DSS colitis model.

Methods: Colon tissues (seven naive ulcerative colitis patients with moderate to severe grade and seven normal patients for control) were obtained from endoscopic biopsy for RNA-sequencing and qPCR. Organoids were generated from normal human colon tissue obtained from endoscopic biopsies and B6J mice colon. For the assessment of functional role of OR gene in colon, we generated colonic organoids from both human and mouse (B6J) and gene expression patterns were analysed after inflammatory cytokines stimulation including TNF-α and IL-6 treatment. For in vivo assay, 3% DSS colitis mice model were used for the OR expression assay.

Results: We identified three candidate OR genes (OR 51E2, OR51E1 and OR56B4) in RNA-sequencing analysis and OR51E2 was significantly highly expressed in naive ulcerative colitis tissue in the validating q PCR assessment. In vivo assessment using DSS colitis model, Olf 78, which is homologous to human OR 51E2, was significantly increased in DSS treated mice colon. We test the expression changes of OR51E2 and a mouse olfactory receptor gene, in both human and mice organoid after treatment with TNF-α (10ng/ml). Organoid culture with low dose TNF-α (10ng/ml) yielded the decreased expression of OR51E2 in human colonic organoid but not in mice organoid.

Conclusions: This study show the possibility that ectopically expressed olfactory receptor, OR51E2 has a role in the pathogenesis of ulcerative colitis. The findings can provide the basis for alternative pathways of IBD development.

Immunophenotyping of peripheral whole blood from 743 IBD patients identifies patterns of association between immune cell populations and T-cell subsets with disease occurrence, severity and medication use

R. Kosoy1,2, S. Kim-Schulze1, A. Rahman1–4, L. Peters1, A. E-Ald1, J. Perrigouè5, A. Castillo4, J. Rogers1, A. Areja1, A. Hurley1,2, M. Merad3, J.F. Colombel1, M. Dubinsky1, J.R. Friedman1, C. Broderick1, S. Plevy1, E. Schadr1, B. Sands1, A. Kasarskis1, C. Argmann1–2, M. Suarez-Farinas1,2,3
1Icahn School of Medicine at Mount Sinai, Genetics and Genomics Sciences, New York, USA, 2Icahn Institute for Genomics and Multiscale Biology, New York, USA, 3Icahn School of Medicine at Mount Sinai, Hematology and Medical Oncology, New York, USA, 4Icahn School of Medicine at Mount Sinai, Human Immunology Institute, New York, USA, 5Janssen R&D, Spring House, PA, USA

Background: Inflammatory bowel disease (IBD) is a complex disorder with unique genetic and immunologic features. Characterisation of circulating immune cells in IBD and their association with clinical disease phenotypes is incomplete. Thus, we investigated FACS based measures of immune cells for association with IBD clinical features.

Methods: We profiled the frequency of immune cells in whole blood of 428 CD, 315 UC and 180 non-IBD control patients undergoing endoscopy at Mount Sinai Hospital. Flow cytometry with 19 markers in two panels measured distribution of 10 main immune cell types and 13 T-cell subsets (Figure 1). Data analysis used multivariable mixed-effect models incorporating demographic, clinical and technical variables, with FDR-adjustment for multiple testing.

Results: Compared with controls, CD patients had more neutrophils and less B-, T- and NK-cells, but in UC patients the changes were mainly within T-cell subsets: higher Th2, lower CD45RA- CD4/CD8, and Th1Th17 T cells (Figure 1). Major changes were also observed between CD and UC. Focusing on the link between the peripheral immune cells and intestinal manifestations, we tested for associations with endoscopic measures. Within CD patients, endoscopic disease severity scores were associated with more neutrophils and fewer B- and T cells, while in UC it was associated with more a CD14+ monocytes. We also investigated the effect of medications in IBD patients, with major changes associated with anti-TNFα (infliximab/ adalimumab) and mercaptopurine (6-MP) (Figure 2A). Affected cell types included B-, NK-, T-CD45RA- CD4/CD8, and Th1Th17 cells, sometimes in the opposite direction. Interestingly, the same immune cells were associated with anti-TNFα use and endoscopic CD severity but with opposite direction. Investigation of concomitant use of anti-TNFα and 6-MP identified significant interactions, such as the reduction of Th1Th17 cells with 6-MP reversed with concomitant anti-TNFα use (Figure 2B). In a subset analysis we observed different effects by infliximab or adalimumab in CD vs. UC, including infliximab decreasing neutrophils in UC only, and adalimumab in CD only.

Conclusions: The largest study of peripheral blood immune compartments thus far in IBD revealed major changes, differentiating UC from CD, and highlighting complex effects of medication use.

Proinflammatory cytokines and bile salts inhibit the cellular uptake of butyrate by Caco-2 cells

M. Couto1,2,3, N. Andrade1,2, A. Correia-Branco1,2, F. Magro4,5, F. Martel1,2
1Unit of Biochemistry, Faculty of Medicine, University of Porto, Department of Biomedicine, Porto, Portugal, 2IS, Instituto de Investigación e Inovação em Saúde, University of Porto, Porto, Portugal, 3Centro Hospitalar Tondela-Viseu, E.P.E., Department of General Surgery, Viseu, Portugal, 4Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Department of Biomedicine, Porto, Portugal, 5Centro Hospitalar São João, E.P.E., Department of Gastroenterology, Porto, Portugal