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Frédéric Baribaud

Janssen R&D, USA

Molecular surrogates of histologic activity in Crohn's disease

Objective markers of disease severity in inflammatory bowel disease that support clinical decision-making are still needed. We hypothesized that novel objective markers of tissue inflammation are best identified at the site of disease with a tissue-level assessment of disease activity. Biopsy samples were obtained from participants in the UNITI trials of ustekinumab in moderate-to-severe Crohn's disease. Pairs of adjacent biopsies were taken from the rectum, splenic flexure and ileum. One biopsy from each pair was assessed by global histology disease activity score (GHAS) while the other was submitted for microarray analysis. Partial least squares regression and random forest were used to identify biomarkers associated with histological severity and robustness of the resulting models was assessed using cross-validation. A single multivariate model comprising 16 genes was identified that predicted histological activities in rectum or splenic flexure biopsies. This model was characterized by R2=0.78 for the training set, and R2=0.59, 0.54 and 0.32 on external validation sets. A separate 14-gene model capturing histological activity in ileal biopsies was characterized by R2=0.5 for the training set and R2=0.45 in the external validation set. In general, both models contained genes related to tissue degradation, barrier function and immune regulation, including CXCL11 (I-TAC). Both models retained performance in external validation datasets from UNITI-2 but exhibited lower performance. Our analysis supports the ability of biopsy transcriptomics combined with machine learning approaches, to capture disease-relevant variability in Crohn's disease and more importantly, supports the use of similar approaches to identify additional surrogate markers.

Biography

Frédéric Baribaud holds a PhD from the University of Lausanne and has conducted his Post-doctoral studies at the University of Pennsylvania. He has worked at Incyte Corporation in a discovery role on target validation and as a Compound Team Co-Lead for small molecular inhibitors. For the past ten years, he has been working at Janssen R&D in Imunology Biomarkers on various inflammatory diseases. In his current role as Scientific Director he is focusing on obtaining disease rational for targets and patient segmentation for inflammatory bowel diseases.

fbaribau@its.jnj.com