
DOP Session 7: Genetics, Omics & Clinical trials

Abstract citation ID: jjad212.0096**DOP56****Fibrosis-related transcriptome unveils a distinctive matrix remodelling pattern in penetrating but not in stricturing ileal Crohn's Disease**H. Tavares de Sousa^{1,2}, M. Ferreira^{3,4,5}, I. Gullo^{4,5,6,7}, A.M. Rocha^{4,5}, C. Oliveira^{4,5}, F. Carneiro^{4,5,6,7}, F. Magro^{8,9,10}

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Background: Fibrosis underlies most of CD complications requiring surgery, such as intestinal strictures and penetrating events. We previously demonstrated there were no histopathological differences on transmural fibrosis and fibromuscular changes between penetrating and stricturing ileal CD. This study aimed to investigate and compare the fibrosis-related transcriptomic profiles of penetrating and stricturing ileal CD.

Methods: Using Nanostring technology and comparative bioinformatics, we analysed the expression of 787 genes covering the core pathways and processes involved in fibrosis, in 34 ileal surgical specimens, 11 B2 and 23 B3, the latter encompassing 12 with associated stricture(s) (B3s) and 11 without (B3o). Each patients' tissue was retrieved from three FFPE 20mm-sections. Quality control of extracted RNA was performed according to Nanostring parameters and principal component analysis (PCA) graph for the distribution analysis. For the selection of the differentially expressed genes (DEGs) we adopted a *P*-adjusted <0.05 and a Fold Change ≤ -1.5 or ≥ 1.5 . Statistical analysis adopted level of significance at 5%.

Results: We included 34 patients, in a well-balanced sample for age (at diagnosis and at surgery), gender, CD localization, perianal disease and therapy. Inflammation and fibrosis histopathological scoring were similar (median of 3 and 1, respectively), in the three groups. No DEGs differentiated B3s and B3o subgroups, which were grouped as B3. The B2 and B3 groups showed a very good clustering on the gene heatmap, which uncovered 30 DEGs between the 2 groups, all being upregulated in B3 and, conversely, downregulated in B2 patients – Figure. More than half of the upregulated genes have been established or partially involved in CD fibrogenesis (yellow-box and line, respectively), while 8 DEGs have been implicated in fibrosis in other organs (brown-line box) and 3 others having an anti-fibrotic role in other tissues (green-line box). Importantly, the vast majority of the most significantly active biologic processes and pathways in the B3 group were related to response to TGF β and matrix organization, production and degradation, unveiling a continuous process of tissue healing and destruction distinctive of this aggressive phenotype.

Conclusion: Despite the histopathological similarities of fibrosis between stricturing and penetrating ileal CD, their fibrosis-related transcriptomic profiles are distinct. Penetrating CD was remarkable for the activation of all the unveiled DEGs and of biologic pathways concerning permanent matrix production and degradation. Hence, although fibrosis underlies both penetrating and stricturing CD, therapeutic targets may differ even in end-of-stage disease.

Figure(s)/Table(s): see next page

