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Inflammatory Environment-Induced Transcriptomic Alterations in Crohn’s Disease Adipose Stem Cells
D. Montfort-Ferré1, A. Boronat-Toscano1, J.F. Sánchez-Herrero1, A. Caro1, M. Menacho1, I. Vañó-Segarra1, M. Martí1, B. Espina1, R. Pluvinet1, L. Cabrinety4, C. Abadia4, M. Ejárque1, C. Nuñez-Roa1, E. Maymo-Masip1, L. Sumoy2, J. Vendrell1, S. Fernández-Veledo1, C. Serena1
1Health Institute Pere Virgili IISPV, Hospital Joan XXIII of Tarragona- Universitat Rovira i Virgili URV., Tarragona, Spain
2Germans Trias i Pujol Research Institute IGTP, High Content Genomics and Bioinformatics, Badalona, Spain
3Hospital Joan XXIII of Tarragona, Surgery Service, Tarragona, Spain
4Hospital Joan XXIII of Tarragona, Gastroenterology Service, Tarragona, Spain
5Hospital Vall d’Hebron of Barcelona, Surgery Service, Barcelona, Spain

Background: Crohn’s disease (CD) is characterised by expansion of mesenteric adipose tissue, called creeping fat, which seems to be directly related to disease activity. Adipose stem cells (ASCs) isolated from the creeping fat of CD patients exhibit dysfunction, featuring impaired adipogenesis and an intensely pro-inflammatory phenotype. This study aims to explore the transcriptome of ASCs isolated from active and inactive CD subjects in comparison with healthy subjects, seeking key markers of this dysregulation.

Methods: Patients were recruited at Hospital Joan XXIII of Tarragona and Hospital Vall d’Hebron of Barcelona in accordance with the principles of the Helsinki Declaration. Transcriptome profiling was performed in ASCs isolated from adipose-tissue biopsies of visceral origin: CF and hMES in Crohn subjects (n=7, each) and hMES in inactive CD patients (n=7) and healthy control subjects (n=7). Groups were matched by age, gender, and BMI. Finally, we examined the pathways involving the differentially expressed gene (DEGs) in ASCs isolated from patients with CD with different clinical activity by gene set enrichment analysis (GSEA).

Results: Patients with CD across different clinical activity stages exhibited similar transcriptome patterns, indicating persistent ASC dysregulation even during remission state (Fig 1A). ASCs isolated from both creeping fat and mesenteric adipose tissue distant from intestinal damage displayed similar dysregulation, implying a global dysregulation of all mesenteric fat in CD. Specifically, transcriptomic analysis identified significant dysregulation of the NK2 Homeobox 3 (NKX2-3) gene in ASCs from active CD patients. Although higher NKX2-3 expression has been associated with B cells and intestinal tissues in CD, our study is the first to link elevated expression of this gene also to creeping fat. Pathway enrichment analysis revealed significant enrichment in oxidative stress and immune response pathways in active CD (Fig 1B). Furthermore, our findings indicated also an elevated NKX2-3 expression in ASCs of inactive CD compared to controls, with oxidative stress pathway up-regulation (Fig 1C). Notably, no significant DEGs were found between ASCs from active and inactive CD groups (Fig 1D), suggesting a similar profile in both states.

Conclusion: Our study reveals profound ASC dysregulation in CD, in both active and inactive phases. Elevated NKX2-3 expression, previously associated with increased risk of complications in IBD, is now demonstrated in the mesenteric adipose tissue, persisting even in inactive CD patients.

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Figure(s)/Table(s): see next page
Figure 1: Transcriptomic profiling of ASCs reveals that CD is associated with an up-regulation of immune response and stress-related genes. (A) Venn diagram of the relationship among differentially expressed genes (DEGs) in ASCs from control, active CD and inactive CD groups. (B) In the left panel, a volcano plot shows differential gene expression between ASCs isolated from control (hMES n=7) and active CD (CF n=7; hMES n=7). Significant genes with adjusted p-value <0.05 are in red. The right of the X axis indicates the gene expression elevated in ASCs from active CD, and the left of the X axis indicates the gene expression elevated in control-ASCs. The gen set enrichment analysis (GSEA) is shown in the right panel. Red circles highlight the pathways up-regulated in active CD and blue circles highlight pathways down-regulated in active CD. (C) Volcano plot showing differentially gene expression between ASCs isolated from control (hMES n=7) and inactive CD (hMES n=7). The normalised enrichment score (NES from GSEA) is shown in the right panel. Red circles indicate the pathways up-regulated in inactive CD and blue circles indicate the down-regulated pathways in inactive CD. (D) Volcano plot showing differential gene expression between ASCs isolated from active CD (CF n=7; hMES n=7) and inactive CD (hMES n=7) groups.