CHARACTERIZATION OF THE TRANSCRIPTOMIC PROFILE OF PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCS) OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA (FH) TREATED WITH LOW-DENSITY LIPOPROTEIN-APHERESIS (LDL-A)

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BACKGROUND

LDL-A is a potentially valuable treatment applied to conventional therapy-resistant hypercholesterolemic patients with coronary artery disease and peripheral artery disease. Selective cholesterol removal obtained with LDL-A is also able to induce an increase of cytoprotective and antioxidant signals, as well as a rise in anti-inflammatory cytokines levels. Several clinical studies suggest that LDL-apheresis may reduce the recurrence of cardiovascular events and may improve the microcirculation, but the precise molecular mechanisms underlying this enhancement are still unknown. The aim of the study was to identify, through a high-throughput approach, the modulation of PBMCs gene expression profile induced by LDL-A.

METHODS

The gene expression profile was evaluated in PBMCs isolated from 5 FH patients before and after LDL-A treatment, using SurePrint G3 Human Gene Expression 60K Microarray Kit (Agilent Technologies). The results were evaluated by statistical (unpaired t test, correction for multiple testing Benjamini-Hochberg) and functional pathway analysis (Ingenuity Pathway Analysis, IPA).

RESULTS

Using a fold-change (FC) ≥2 as the threshold we demonstrated that LDL-A modulates the expression of two hundred and forty genes in PBMCs (Figure 1-2). The most interesting canonical pathways were: Granulocyte and Agranulocyte Adhesion and Diapedesis, Communication between Innate and Adaptive Immune Cells, Natural Killer Cell Signaling and Atherosclerosis Signaling (Figure 3-4). Many pro-inflammatory cytokines involved in the development and progression of the atherosclerotic process were significantly down-regulated: Interleukin 1 (IL-1, FC=-5,054), involved in the pathogenesis of different auto-inflammatory syndromes; chemokine ligand 8 (CXCL8, FC=-10,502) associated with the promotion of neutrophil chemotaxis and degranulation and with inflammation, and other pro-inflammatory chemokine, including chemokine ligand 1 (CXCL1, FC=-2,605), chemokine ligand 2 (CXCL2, FC-3,658), chemokine ligand 3 (CXCL3, FC=-2,282), chemokine ligand 4 (CXCL4, FC=-2,36) (Table 1).

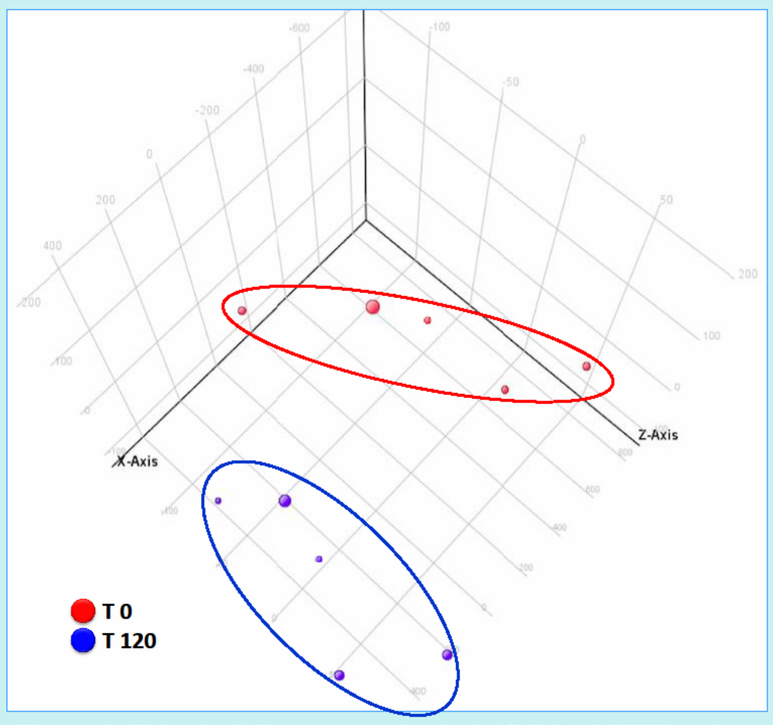

Figure 1. ***Principal Component Analysis (PCA)*** **of 5 FH patients BEFORE (T0) and AFTER (T120) LDL-A treatment**

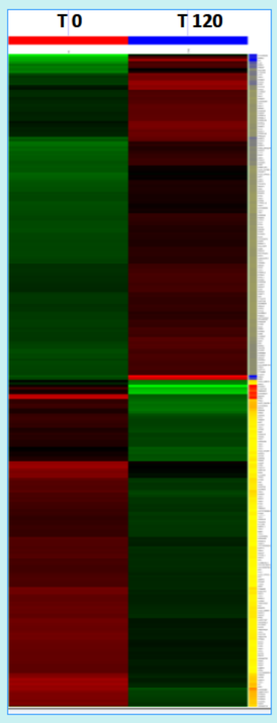

Figure 2. ***Heat Map*** **of the 240 genes Differentially expressed BEFORE (T0) and AFTER (T120) LDL-apheresis.**

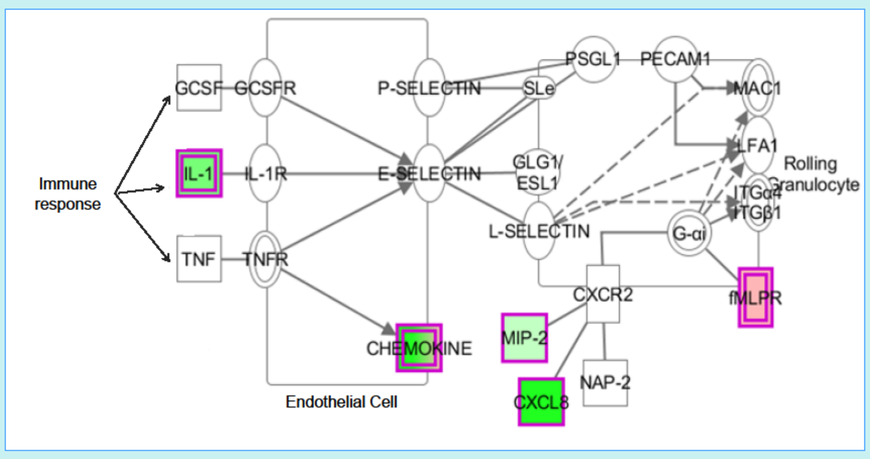

Figure 3. ***Endothelial involvement***

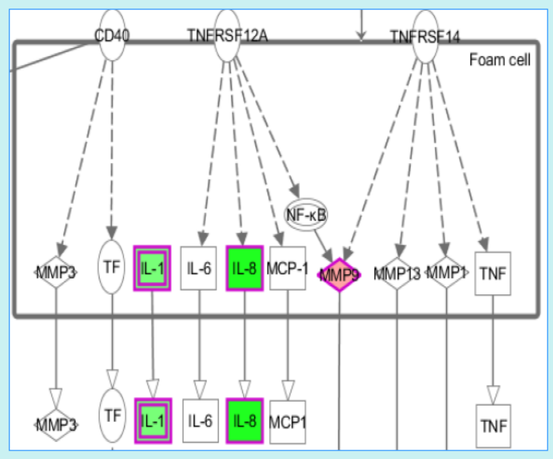

Figure 4. ***Atherosclerosis signaling***

Table 1: most of the pro-inflammatory cytokines down-regulate AFTER apheresis treatment

Symbol	*Entrez Gene Name*	*Fold Change*
CXCL8	chemokine (C-X-C motif) ligand 8	-10,502
IL1B	interleukin 1, beta	-5,054
CXCL2	chemokine (C-X-C motif) ligand 2	-3,658
CCL3L3	chemokine (C-C motif) ligand 3-like 3	-2,645
CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	-2,605
CCL3	chemokine (C-C motif) ligand 3	-2,530
CCL4	chemokine (C-C motif) ligand 4	-2,361
CXCL3	chemokine (C-X-C motif) ligand 3	-2,282

CONCLUSIONS

Our data suggest that LDL-apheresis may contribute to cardiovascular risk reduction through the modulation of different pathways involved in the progression of atherosclerotic disease and improvement of microcirculation. This observation might open new perspectives in the prevention of cardiovascular risk in patients with FH.

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