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Introduction: fingolimod (FTY) is a second-line drug approved for Relapsing Remitting Multiple Sclerosis. It is known to prevent lymphocyte egress outside lymph nodes, reducing peripheral lymphocytes counts. We investigated transcriptional changes induced by the drug in B and T lymphocytes in order to better elucidate its mechanism of action at the molecular and pathway levels.

Materials and Methods: 24 RRMS patients were sampled at baseline and after 6 months of FTY treatment. CD3+ T cells and CD20+ B cells were sorted with MACS MicroBeads system and RNA sequencing performed using Illumina NextSeq500 platform. Differentially expressed genes (DEGs) were identified for each cell type and genes modulated by FTY (fold change [FC]>2 or FC<0.5 and false discovery rate [FDR]<5%) were considered for a pathway analysis based on KEGG database. Subpaths activation state was also tested using MinePath tool. We performed network analysis on cell-specific interactomes, followed by centrality-based analysis to elicit key genes.

Results: a marked up-regulation was observed in both T and B lymphocytes (313 up- and 240 down-regulated genes in T cells; 400 up- and 104 down-regulated genes in B cells). Most of the DEGs resulted implicated in cell migration or immune-related functions, largely confirming results from previous microarray-based studies: among them *CX3CR1* was strongly up-regulated ($p_{adjusted}=6.4x10^{-26}$, FC=5.96) and *CCR7* was down-regulated in both cell types ($p_{adjusted}=5.4x10^{-31}$, FC=0.18). Pathway and subpaths analyses confirmed an involvement of processes related with immune function and cell migration. Network analysis elicited hub genes like *CD44* involved in cell migration and several down-regulated hubs related with ribosome function.

Conclusions: Our data suggest that FTY induces major transcriptional changes in genes with immune and cell migration functions associated with a down-regulation of several central hubs related with ribosome function; this modulation is shared between T and B lymphocytes.