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Myeloproliferative disorders

TRANSCRIPTOMIC ANALYSIS OF CD34⁺ CELLS IN MYELOFIBROSIS HIGHLIGHTS THEIR ROLE IN EXTRACELLULAR MATRIX DYSREGULATION AND MARROW FIBROSIS

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Myelofibrosis (MF) is the most aggressive Philadelphia-negative myeloproliferative neoplasms, characterized by progressive bone marrow (BM) fibrosis and reduced survival. The pathogenesis of BM fibrosis remains still controversial.

The role of CD34+ stem/progenitor cells as potential drivers of the fibrotic process has never been explored so far, although a growing body of literature shows that they overexpress proinflammatory cytokines in MF with higher fibrosis grade.

To provide insights in this context, we performed RNASeq analysis on immunomagnetically isolated CD34+ cells from MF pts (prePMF, overtPMF, secondary-MF) to identify transcriptome differences according to: disease subtype, degree of BM fibrosis (MF-F ≤1 vs. >1) and therapy with JAK-inhibitors (therapy naïve, MF-TN vs. MF-JAKi). CD34+ cells from healthy donors (HD) served as controls.

Sequencing was performed using Novogene total RNASeq solution on Illumina NextSeq 500/550 platform on a Mid-Output kit V2.5 (300 cycles). Pathway enrichment analysis was performed using GeneOntology and KEGG. Genes were considered differentially expressed when presented at least >2-fold change and p value <0.05. To identify the most impactful pathways, a gene ratio cut-off of 0.02 was set as reference.

The analysis shows that integrins and coagulation factors are significantly upregulated in MF-TN pts in comparison to HD. Among these, integrin α11 is downregulated in response to JAKi.

Intriguingly, when comparing overtPMF vs. prePMF, the analysis identified a positive regulation of supramolecular fiber organization, ossification and BMP (bone morphogenetic proteins) pathways (Fig1A). These results were confirmed by comparing MF-F > 1 vs. ≤ 1. Notably, pathways dedicated to ossification and extracellular matrix, included collagen-content and structural constituents, resulted differentially expressed in JAKi vs. MF-TN, together with those involved in signalling receptor regulation (e.g. MAPK cascade) (Figure 1B).

Consistently, *COL2A1* (collagen), *CEACAM1* and *CEACAM6* (angiogenesis's regulators), *NCKAP1* (focal adhesion modulator), *BMP8B*, and *BMP2* resulted strongly upregulated in MF-F >1 when compared with MF-F ≤1. Interestingly, *CEACAM1* and *BMP2* resulted downregulated by JAKi.

By Comparing PMF with secondary-MF, FHOD1, a regulator of actin microtubules involved in cell's structure, resulted downregulated, while it is upregulated by JAKi therapy.

Our analysis reveals for the first time that pathways associated with wound healing, osteogenesis, and extracellular matrix remodeling are differentially expressed in malignant CD34⁺ cells, correlating with the extent of BM fibrosis. Notably, JAKi therapy modulates the expression of several of these genes involved in tissue remodeling and angiogenesis, suggesting a broader impact on disease biology beyond cytokine signaling suppression.

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