Poster 15: Metabolic reprogramming of bone marrow stromal cells in chronic lymphocytic leukemia

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In chronic lymphocytic leukemia (CLL), tumor cell survival depends on a multitude of supportive signals delivered by the surrounding immune and stromal cells in the lymph nodes and the bone marrow. CLL cells are also able to educate the surrounding cells to set up a protective environment which highlights the importance of the crosstalk between the tumor cells and the microenvironment.

To gain insight into how CLL cells modify stromal cells, we analyzed the transcriptome and the proteome of a bone marrow mesenchymal stromal cell line, HS5, as a surrogate of the microenvironment in co-culture with the CLL cell line MEC for 24h in transwell to avoid direct contact. RNA-seq identified a total of 99 significantly upregulated and 111 significantly downregulated genes in HS5 cells co-cultured with MECI cells compared to HS5 cells alone (>2 fold, adjusted p<0.05). Interestingly, oxygen homeostasis regulators (EN02, CYR61, SOD2, NAMPT) were significantly up-regulated. GSEA revealed a significant enrichment of the glycolysis process (NES=l.9, FDR <0.001). Analysis of the proteomic data identified upregulation of metabolism members including the reductases AKRIBI and PLOD!, and two mitochondrial proteins involved in the respiratory chain: the acetyl CoA-dehydrogenase MCAD and the subunit of the NADH dehydrogenase NDUFA10. In line with these results, clustering and pathway analysis of the proteomic data showed a protein signature related to the oxidation-reduction process. Altogether, these results suggest that CLL cells produce soluble factors that specifically modify the gene expression profile of stromal cells and induce metabolic reprogramming related to a mitochondrial phenotype.

To confirm these findings, we assessed the cellular oxygen consumption rate (OCR) and the extra-cellular acidification rate (ECAR) using the Seahorse Assay to quantify the mitochondrial respiration and the glycolysis respectively, in the HS5 cells cultured with conditioned media (CM) issued from primary CLL cells (n=3). The result showed a significant increase of the maximal respiration (p=0.01), of the spare respiratory capacity (p=0.03) and of the glycolysis capacity (p=0.03) in the HS5 cells upon exposure to CLL CM. In agreement with increased glycolysis, glucose uptake and ATP production were enhanced in HS5 cells cultured with the CM issued from CLL cells.

Altogether, these results demonstrate that CLL cells increase the production of energy in surrounding stromal cells by enhancement of the glycolysis and by promoting mitochondrial-based oxidative phosphorylation. This bioenergetic shift induced by CLL cells could enhance stromal cells fitness, which therefore will benefit to tumoral cell survival. We are currently investigating how this crosstalk interferes with the effect ofBCR pathway inhibitors or BH3-mimetics. Targeting this axis may represent a therapeutic strategy of interest.