W19: Comprehensive metabolomic analysis identifies deregulated metabolic pathways associated with immune dysfunction in Waldenstrom Macroglobulinemia

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Altered energy demand of malignant cells and metabolic reprogramming of immune cells within tumor microenvironment is a hallmark of cancer. In Waldenstrom Macroglobulinemia (WM), continuous monoclonal IgM synthesis by infiltrative lymphoplamacytic cells within highly dynamic and metabolically active bone marrow (BM) microenvironment, suggests that metabolic pathways are key contributors to the malignant progression in WM. Our group has previously reported that levels of certain cytokine are altered in WM BM microenvironment and such an alteration is associated with increased survival and IgM secretion by WM. Given that the altered cytokine composition could induce a metabolic switch in immune cell function, the goal of this study was to identify deregulated metabolic pathways in both malignant and BM microenvironment cells with an ultimate aim to identify biomarkers that can be targeted therapeutically in WM.

WM patients samples including BM plasma (n=28), peripheral blood serum (n=94) and BM cells (n=34) and also equivalent normal counterparts were collected and used for analysis. Comprehensive targeted metabolomics analysis was performed using Capillary Electrophoresis Time-of-Flight Mass spectrometry (CE-TOFMS), CE-triple quadrupole mass spectrometry (CE-qQqMS) and Liquid Chromatography (LC-TOFMS). Seahorse XFe96 analyzer was used to determine mitochondrial metabolic function. BM cells from control and WM patients samples were used to detect myeloid derived suppressor cells (MDSC) using flow cytometry.

Principal Component Analysis (PCA) and Hierarchal Clustering Analysis (HCA) identified two distinct clusters for disease and normal samples. Metabolites belonging to amino acid, fatty acid, central carbon and purine metabolic pathways showed significant differences between disease and control samples. Analysis of mitochondrial function using the cells obtained form WM or normal samples confirmed the data obtained by CE-TOFMS, CE-qQqMS and LC-TOFMS. Reduced levels of amino acids, including arginine and cysteine, were shown to be also associated with increased populations of both monocytic and granulocytic MDSCs, with high Arginase1 activity.

In summary, our data identifies an altered metabolic phenotype in both malignant and BM microenvironment cells in WM, and indicates that interference with the metabolic processes could be a potential therapeutic strategy for patients with WM.