Molecular Clusters and Tumor-Immune Drivers of IgM Monoclonal Gammopathies

Introduction: IgM MGUS and Waldenstrom Macroglobulinemia (WM) represent a disease spectrum with highly varied therapeutic management ranging from observation to chemoimmunotherapy. The current classification relies solely on clinical features and does not explain the heterogeneity that exists within each of these conditions. Further investigation is warranted to shed light on the biology that may account for the clinical differences.

Experimental Design: We used bone marrow (BM) $CD19^{+}CD138^{+}$ sorted cells and matched BM supernatant from 32 patients (7 MGUS, 25 WM) to perform a multi-omics study including whole exome sequencing, RNA-seq, proteomics, metabolomics and mass cytometry (CyTOF).

Results: We identified three clusters with distinct pathway activation, immune content, metabolic and clinical features. Cluster 1 (C1) included only WM patients and was characterized by silencing of genes involved in cell cycle and immune response, enrichment of mitochondrial metabolism, infiltration of senescent T effector memory cells and aggressive clinical behavior. Alterations of *TNFAIP3* were distinct events of this cluster. C2 comprised both MGUS and WM patients with upregulation of inflammatory response and glycolysis, increase of T follicular helper cells, and indolent clinical behavior. C3 also included both MGUS and WM patients and exhibited intermediate features with combined proliferation and inflammation.

Conclusion: We have identified three distinct molecular clusters, suggesting a potential biologic classification that may have therapeutic implications.