Chromatin Accessibility Landscape and Regulatory Networks of IgM monoclonal Gammopathies

IgM monoclonal gammopathies are characterized by a clonal expansion of abnormal memory B cells and plasma cells harboring the somatic mutation MYD88 L265P, while acquisition of mutations in CXCR4 or copy number alterations (CNAs) are considered second clonal hits. Here, we conducted a comprehensive study to analyze the transcriptomic changes that arise during the expansion of different B cell subclones and linked this information with the accessible genome, allowing the characterization of regulatory mechanisms in IgM MGUS and Waldenström Macroglobulinemia (WM). We performed VDJ and 5' RNA sequencing of bone marrow single cells and observed specific transcriptional signatures by analyzing differential expressed genes on B cell clones. We then transferred the transcriptomic information to single cell ATAC sequencing data to characterize the chromatin states in each B cell subclone. Moreover, we inferred CNAs from the hyperexpanded B cell clones and confirmed these results with bulk whole genome sequencing from sorted CD19+ cells. We demonstrate tumor specific transcriptional signatures and programs in IgM monoclonal gammopathies.