

Waldenström macroglobulinemia (WM) is characterized by the expansion of clonal lymphoplasmacytic cells; the MYD88L265P somatic mutation is found in >90% of patients, but malignant B cells may still display intra-clonal heterogeneity. To assess clonal heterogeneity in WM, we generated and performed single-cell RNA sequencing of CD19+ sorted cells from five patients with MYD88 L265P and two patients with MYD88 WT genotype as well as two healthy donors. We identified distinct transcriptional patterns in the clonal subpopulations not only between the two genetically distinct WM subgroups but also among MYD88 L265P patients, which affected the B cell composition in the different subgroups. Comparison of clonal and normal/polyclonal B cells within each patient sample enabled the identification of patient-specific transcriptional changes. We identified gene signatures active in a subset of MYD88L265P patients, while other signatures were active in MYD88 WT patients. Finally, gene expression analysis showed common transcriptional features between patients compared to the healthy control but also differentially expressed genes between MYD88 L265P and MYD88 WT patients involved in distinct pathways, including NFκB, BCL2, and BTK. Overall, our data highlight the intra-tumor clonal heterogeneity in WM with potential prognostic and therapeutic implications.