Clonal architecture and evolutionary history of WM at the single-cell level

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Waldenström's macroglobulinemia (WM) is characterized by recurrent somatic mutations in *MYD88* (>95% of patients) and *CXCR4* (>30% of patients) genes, as well as deletions involving chromosome 6q (del6q, ~50% of patients), among other alterations. The sequence of these events, their distribution within individual tumor cells, and the changes in the mutational landscape over the course of the disease remain unclear.

To investigate the subclonal architecture and co-dependency patterns of alterations in WM, we performed single-cell mutational and protein profiling on samples from eight patients, collected either at diagnosis or during disease progression.

Results showed that in asymptomatic WM at diagnosis, *MYD88* L265P was the predominant clonal alteration, with any additional events being secondary and subclonal to *MYD88*. In symptomatic WM, clonal diversity was more evident, uncovering combinations of alterations that synergized to promote clonal expansion and dominance. At disease progression, a dominant clone was observed, sometimes accompanied by less complex minor clones, suggesting a clonal selection process. The combined analysis of the immunophenotype and genotype showed slight phenotypic differences between mutated and non-mutated cells within each cell population.

These findings provide a comprehensive view of tumor clonality in WM and illustrate how clonal complexity evolves and impacts disease progression.