

Single-cell transcriptome analysis reveals stem cell-like subsets in the progression of
Waldenström's macroglobulinemia

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Abstract

Waldenström's macroglobulinemia (WM) is an uncommon lymphoproliferative disorder, and the precise cellular landscape and the mechanisms of progression from IgM monoclonal gammopathy of undetermined significance (MGUS) to WM remain unclear. We performed single-cell RNA sequencing of CD19⁺ and CD19⁻CD38⁺ cells from healthy donors, IgM MGUS and WM patients. We found that samples from IgM MGUS and WM patients were composed of fewer early B-cell subsets and more T cells and NK cells than those from healthy controls. Compared with those of IgM MGUS patients, mature B cells of WM patients showed upregulation of PIM1, DUSP22, HES1, NEAT1, RGS1, RGS16, and GADD45B. We also identified a subpopulation of CD3⁺CD19⁺ cells in IgM MGUS and WM patients, and trajectory analysis suggested that this subpopulation might be a stem cell-like subset. Further targeted gene sequencing of CD3⁺CD19⁺ and CD3⁻CD19⁺ cells proved that MYD88 might be the early events in tumorigenesis according to variant allele fraction analysis. Additional

subclonal hits such as CXCR4 and MAP2K1 mutations could be acquired during tumor progression. CXCL signaling, CCL signaling, IL2 signaling and TGF β signaling pathways were involved in communication between CD3⁺CD19⁺ cells and other immune cells. Our findings reveal the composition of CD38⁺ immune microenvironment together with B cells and plasma cells in IgM MGUS and WM patients and provide comprehensive insights into mechanisms of progression from IgM MGUS to WM. The rare CD3⁺CD19⁺ cells might be cells with “stemness” feature.