

Differential diagnosis between IgM monoclonal gammopathies of benign vs clinical significance based on high-sensitive detection of circulating tumor cells (CTCs) and *MYD88*^{L265P}

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Waldenström's macroglobulinemia (WM) precursor conditions have been poorly characterized and risk models have limited predictive value. Thus, we aimed at data-driven development of new methods for minimally-invasive monitoring and prognostication of WM precursor conditions.

New markers for improved CTC detection were investigated after scRNA/BCR-seq of FACSorted bone marrow B cells and plasma cells (PC) from 5 healthy adults, 9 cases with IgM-MGUS and asymptomatic WM (AWM), and 10 WM patients. Owing to the well-known phenotypic plasticity of tumor cells, patient-specific predominant B-cell receptors (BCR) were identified prior holistic and unbiased analysis of clonotypic transcriptomes.

CTCs and other minimally-invasive biomarkers were investigated in the NoMoreMGUS study, which aims at developing new diagnostic criteria that eliminates the term "undetermined" and classifies monoclonal gammopathies into benign vs clinical significance. This multicenter study of 5,000 MGUS monitored yearly during 5 years, includes 252 cases with IgM-MGUS analyzed herein. Median follow-up was 25 months.

scRNA/BCR-seq yielded paired BCR and transcriptomes from 86,457 cells. Patient-specific predominant BCR were detected in 1.8%, 39.2% and 22.1% of B-cell precursors, mature B lymphocytes and PC from IgM-MGUS/AWM patients. The respective frequencies in WM were 5.3%, 82.5% and 59.9%. These results unveiled the presence of clonotypic B-cell precursors in precursor and symptomatic stages.

When compared to the normal counterpart of healthy adults, clonotypic B-cell precursors, mature B lymphocytes and PC from IgM-MGUS/AWM patients showed 624, 818 and 402 differentially expressed genes. A total of 28 genes coding surface protein markers with potential utility for flow cytometry were similarly dysregulated in IgM-MGUS/AWM and WM, which provides additional evidence of phenotypic similarity between premalignant and malignant clones.

Altered transcriptional phenotypes were mined to identify new markers (e.g., CD62L) that were embedded into a single spectral flow cytometry combination for high-sensitive detection of CTCs in IgM-MGUS patients enrolled in NoMoreMGUS. CTCs were detected in 82/252 (33%) cases; the median percentage was 0.42% (interquartile range [IQR], 0.13%-1.56%). Patients with detectable CTCs had significantly higher risk of progression to AWM/WM (HR:10.4, $p=.03$), particularly those with >1% CTCs (HR:15.8, $p=.001$).

Because of the unexpected presence of clonotypic B-cell precursors in IgM-MGUS patients, presence of *MYD88*^{L265P} was investigated using the ultra-sensitive and highly specific rolling circle amplification (superRCA) technology. *MYD88*^{L265P} was detectable in 206/252 (82%) IgM-MGUS patients, with a median mutant allele frequency (MAF) of 0.08% (IQR, 0.02%–0.29). A cutoff of 0.5% MAF identified patients having significantly higher risk of progression to AWM/WM (HR:10.6, $p=.006$).

High-sensitive detection of CTCs and *MYD88*^{L265P} showed superior prognostic discrimination compared to conventional risk factors such as M-protein concentration, hemoglobin, creatinine and β 2microglobulin. Concordance between *MYD88*^{L265P} and CTC detection was 43.4%, suggesting complementary biological information. Whereas 22% of IgM-MGUS pts having both >1% CTCs and >0.5% MAF progressed to AWM/WM, only 0.9% of those with one or none risk factors progressed ($p<.001$).

Data-driven development of new flow cytometry panels defined CTCs as a key risk-factor in IgM-MGUS. Together with high-sensitive detection of *MYD88*^{L265P}, these minimally-invasive biomarkers may contribute to a biologically-driven classification of IgM monoclonal gammopathies with none vs malignant significance.

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