

A multi-omics-based diagnostic model distinguishes Waldenstrom macroglobulinemia from marginal zone lymphoma

Shanshan Zhang¹, Cuilian Zhang¹, Youhai Yuan¹, Siyao Wu¹, Dongqin Zhu², Lina Shi², Zhiyang Zhang¹, Hanzhen Zhang¹, Yang Shao², Xutao Guo¹, Yongqiang Wei¹, Ru Feng¹ and Xiaolei Wei¹

1. Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China.
2. Medical Department, Nanjing Geneseeq Technology Inc., Nanjing, China.

Background

Distinguishing lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/MM) from marginal zone lymphoma (MZL) remains a frequent diagnostic challenge. Although MYD88 mutation testing is central to WM diagnosis, MYD88-wild-type WM and MYD88-mutated non-WM cases require additional molecular support. We therefore investigated whether integrated genomic, transcriptomic, and clinical features could improve molecular discrimination between WM and MZL.

Methods

We studied 44 patients, including 25 with WM and 19 with MZL. Targeted panel sequencing was performed using available tissue, plasma, and/or bone marrow samples. Bone marrow whole-exome sequencing (WES) and RNA sequencing were available for 37 patients (23 WM and 14 MZL). We compared somatic mutations, copy-number alterations (CNAs), mutational signatures, differentially expressed genes, pathway enrichment, and RNA-inferred immune-cell composition. Concordance between paired plasma and bone marrow mutation detection was assessed. A molecular-clinical diagnostic model was developed using mutation features and serum IgM level, with leave-one-out cross-validation (LOOCV).

Results

Panel sequencing showed high detection rates in plasma and bone marrow, and paired plasma-bone marrow mutation detection showed an overall concordance of 83.7% (226/270). WM exhibited a MYD88-centered genomic architecture, frequent CXCR4 co-alteration, enrichment of NF-kappaB pathway lesions, recurrent 1q21.3 gain, and 6q loss. MZL showed a more dispersed driver pattern, with CARD11 and SETD2 enriched in this cohort and distinct CNA signals involving 1p22.3, 2q, and 19q. Global mutation-type distribution did not differ significantly between groups ($p=0.116$), indicating that disease separation was driven primarily by gene- and pathway-level organization rather than by broad mutation-class differences.

Transcriptomic profiling further separated WM from MZL. WM was characterized by upregulation of ribosome biogenesis, RNA processing, translation elongation and termination, nonsense-mediated mRNA decay, and protein synthesis pathways, consistent with a plasma cell-like, IgM-secreting program. MZL showed relatively higher expression of genes related to cellular signaling and adhesion. RNA deconvolution suggested distinct marrow immune ecologies, with WM enriched for plasma B-cell, T follicular helper cell, eosinophil, M2 macrophage, activated mast cell, and regulatory T-cell signals.

Using binary mutation features together with serum IgM, a compact model incorporating MYD88, CARD11, SETD2, and IgM achieved an LOOCV area under the receiver operating characteristic curve of 0.931, outperforming single-feature approaches.

Conclusions

Integrated multi-omics profiling identifies biologically coherent and diagnostically useful differences between WM and MZL. A compact MYD88/CARD11/SETD2-plus-IgM model may provide a practical adjunct for difficult WM differential diagnosis, particularly when MYD88 status alone is insufficient. External validation in larger, subtype-annotated cohorts is warranted.

Keyword

Waldenstrom macroglobulinemia; lymphoplasmacytic lymphoma; marginal zone lymphoma; multi-omics; MYD88; molecular diagnosis; RNA sequencing; whole-exome sequencing

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