

ABSTRACT

Mantle cell lymphoma (MCL) remains one of the most challenging B-cell lymphomas, known for frequent relapses and poor outcomes in high-risk subgroups. Information about the clonal development of MCL and the genomic landscape of relapsed patients with MCL is still scarce, and such patients are in urgent need of more sophisticated therapies. Additionally, a group of aggressive non-Hodgkin lymphomas (NHLs) still lacks sufficiently effective preclinical models, and their complex characterization is of utmost importance for developing reliable experimental models.

Our whole-exome sequencing study of 25 paired diagnostic and relapse samples from MCL patients treated with standard immunochemotherapy revealed significant clonal evolution during disease progression. Resistant subclones, which were enriched for harmful genetic lesions such as *TP53* and *CDKN2A* inactivation, were likely present at diagnosis and were selected by therapy. At relapse, these clones exhibited increased genetic diversity, characterized by a higher mutation load, more extensive and numerous copy number alterations, and notably higher variant allele frequencies of *TP53* mutations. We also identified new relapse-associated candidate drivers, including *LRP1B*, *KMT2D*, *SP140*, *NOTCH1/2*, *PIK3CA*, and *GNA14*, which highlights the complexity of clonal dynamics and points to potential biological mediators of resistance. These results also underscore the limited effectiveness of chemotherapy in patients with *TP53* and *CDKN2A* inactivation and support early consideration of innovative treatments, such as genetically engineered T-cell immunotherapies, for this high-risk group.

In parallel, we performed a detailed characterization of 15 newly developed patient-derived xenograft (PDX) models of aggressive lymphomas, including MCL, Diffuse Large B-cell Lymphoma, Burkitt lymphoma, and T-cell lymphomas. Whole-exome sequencing confirmed that PDX models accurately preserved the genetic profiles of the original lymphomas, maintaining both mutational patterns and copy number variations. However, detailed histopathological analyses revealed consistent phenotypic differences. PDX tumors showed more aggressive morphology, higher proliferation rates, and a significant reduction in tumor microenvironment (TME) complexity. Notably, human non-malignant immune cells were absent, murine macrophages did not infiltrate the tumors, and vascularization was limited to murine vessels with significantly decreased microvessel density and area compared to the original biopsies. These differences highlight that, while PDXs are highly relevant translational tools, they portray tumors with reduced dependence on human TME components and should be

interpreted with caution in studies focusing on angiogenesis, immune responses, or therapies that depend on the microenvironment.

Taken together, these two complementary studies enhance our understanding of MCL pathogenesis and offer crucial insights for translational lymphoma research. They show how chemotherapy influences clonal evolution by selecting for genetically complex, therapy-resistant subclones, highlighting the need to incorporate new therapeutic strategies into initial treatment plans. Additionally, they demonstrate that PDX models are valuable yet imperfect tools that retain the key genetic features of aggressive lymphomas, albeit in a different microenvironmental context, highlighting both their advantages and limitations for preclinical and clinical studies. Overall, this work offers novel insights into the pathophysiology of MCL and provides a strong foundation for enhancing risk stratification in MCL. Additionally, it increases the translational relevance of experimental models, ultimately supporting the development of more effective treatments for aggressive lymphomas.

Keywords: aggressive lymphomas, mantle cell lymphoma, genomic landscape, clonal development, patient-derived xenografts