P1282 DISEASE-SPECIFIC U1 SPLICEOSOMAL RNA MUTATIONS IN MATURE B-CELL NEOPLASMS

**Topic:** 20. Lymphoma Biology & Translational Research

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Background: Recurrent mutations in the third base of U1 spliceosomal RNA responsible for marked splicing and expression abnormalities have been described in chronic lymphocytic leukemia (CLL) and some solid tumors (Shuai et al. Nature, 2019; Suzuki et al. Nature, 2019). However, the clinical significance of these mutations in large CLL cohorts and their presence in other B-cell neoplasms is unknown.

Aims:

To provide a comprehensive map of U1 mutations across a wide spectrum of mature B-cell neoplasms and to assess their transcriptional and clinical implications.

Methods: We first performed an unbiased characterization of U1 mutations in 762 mature B-cell neoplasms analyzed by whole-genome sequencing (WGS) and complemented with RNA-seq data. This WGS cohort comprised 399 CLL, 155 diffuse large B-cell lymphomas (DLBCL), 110 Burkitt lymphomas (BL), 61 mantle cell lymphomas (MCL), and 37 follicular lymphomas (FL). WGS data were analyzed using a bioinformatic pipeline designed to call mutations in any of the 11 canonical U1 genes found in the human genome. Second, we expanded the characterization of recurrent U1 mutations in 1,670 CLL patients from two independent cohorts.

Results:

Our WGS analyses uncovered that the majority of U1 mutations were present between positions 3 and 10 of the gene, the region responsible for 5’ splice site recognition via base-pairing. In line with this, 10.5% CLL, 17.4% DLBCL, and 15.5% BL cases carried mutations in this region, which contrast with only 3.3% MCL and 5.4% FL cases. We observed substantial differences in the mutated sites of CLL, DLBCL, and BL. In CLL, the most frequently mutated site was the position 3 with 7.3% of the whole WGS cohort carrying the previously identified A>C mutation (g.3A>C). In addition, we also identified a novel C>T mutation at position 9 (g.9C>T) in 2% of CLL cases, which was associated with splicing abnormalities both in primary cases and transduced CLL cell lines. In DLBCL, the most frequent mutation was a novel C>T mutation at position 4 (g.4C>T) found in 8.4% of cases. This g.4C>T mutation showed a non-significant enrichment in germinal center B-cell like (GCB) (12.8%) compared to activated B-cell (3.8%) DLBCL (p=0.12). In GCB-DLBCL, this mutation was associated with 1,902 differentially spliced introns and 397 differentially expressed genes. In BL, the most frequent mutation was an A>G mutation at position 7 (g.7A>G), which was found in 10.9% of cases. Of note, this mutation was detected in 29.5% EBV-negative BL while only in 1.4% EBV-positive BL (p<0.001). The g.7A>G mutation was associated with 6,970 introns differentially spliced in EBV-negative BL.

In the extended CLL cohorts, the g.3A>C was enriched in unmutated IGHV (7.4%) and naïve-like (10.9%) subtypes of the disease, whereas the g.9C>T was more often detected in mutated IGHV/memory-like CLL (2%). These two mutations did not significantly co-occur with several CLL driver alterations of prognostic relevance and retained independent prognostic value for time to first treatment in multivariable models.

Summary/Conclusion:

This study expands our understanding of the biologic and clinical consequences of U1 mutations in CLL and reveals novel U1 mutations in DLBCL and BL. U1 mutations and their downstream effects were specific of different entities and subtypes with distinct mutations shaping the transcriptome of CLL (g.3A>C and g.9C>T), DLBCL (g.4C>T) and BL (g.7A>G). Based on its downstream effects, mutation prevalence among distinct B-cell neoplasms, and prognostic value in CLL, U1 represents a new pan-B-cell malignancy driver gene.