P1299 LOSS OF TYROSINE PHOSPHATASE SHP1 SENSITIZES DLBCL TO IBRUTINIB: A CANDIDATE PREDICTIVE BIOMARKER

Topic: 20. Lymphoma Biology & Translational Research

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Background: B-cell receptor (BCR) signaling plays a key role in B-cell non-Hodgkin lymphoma (NHL). Protein tyrosine kinases such as LYN, SYK and BTK are essential in the activation of BCR leading to B-cell survival, proliferation and differentiation. SHP1 is a cytosolic protein tyrosine phosphatase functioning as a negative regulator of the BCR signaling cascade. It dephosphorylates and counteracts the activities of the tyrosine kinases, including CD79A/CD79B, SYK and BLNK. Ibrutinib is a selective BTK inhibitor that has been approved for the treatment of many B-cell malignancies, but not yet for diffuse large B-cell lymphoma.

DLBCL is the most common type of aggressive NHL. Based on cell-of-origin, DLBCL is subclassified into Germinal Center B cell-like (GCB) and activated B-cell like (ABC) DLBCL where chronic active BCR signaling plays a particularly important role in the pathogenesis of the ABC-DLBCL. However, only a subset of ABC-DLBCL respond well to ibrutinib-containing regimen (Wilson et al., 2021, Cancer Cell 39, 1643–1653). New predictive biomarkers are needed to identify patients who likely benefit from ibrutinib.

Aims: We aim to test the hypothesis that SHP1 may play a role in defining the level of the activity of the BCR pathway and impact on the response to ibrutinib.

Methods: A variety of methods was used to demonstrate the roles of SHP1 loss in DLBCL cell lines and primary tumors, including meta-analysis, immunohistochemistry on tissue microarray, promotor methylation, and genetic editing with CRISPR-Cas9 and lenti-viral transduction.

Results: We first reviewed 17 published literatures on SHP1 in NHL using a meta-analysis. The analysis of the SHP1 protein expression by immunohistochemistry revealed that lack of SHP1 expression is strongly associated with NHL including DLBCL. Likewise, the analysis of the methylation studies revealed a strong association between SHP1 promoter hypermethylation and NHL.

To further understand the range of variability of SHP1 expression in subtypes of DLBCL tumors, we constructed a tissue microarray with a large number of primary DLBCL tumors and cell lines. We found a wide range of variability and no substantial difference between the GCB and non-GCB subtypes regarding the extent of SHP1 expression.

We identified a strong reverse linear correlation between SHP1 protein expression and promoter methylation (r = 0.85, P=0.0002) suggesting that promoter hypermethylation may be responsible for reduced SHP1 expression in DLBCL cells. SHP1 was knocked out in both BCR-dependent GCB and ABC cell lines using CRISPR-Cas9 system. The phosphorylation of early BCR components, BTK, SYK and LYN, were increased in the SHP1 knockout clones suggesting that SHP1 depletion causes increased proximal BCR signaling activity. Moreover, the knock out clones demonstrated increased sensitivity to ibrutinib. We further showed that re-introduction of SHP1 vector to the knockout clones via stable lentiviral transduction restored normal sensitivity of cells to ibrutinib.

Summary/Conclusion: Our results show that SHP1 expression is suppressed in a substantial fraction of DLBCL tumors regardless of cell-of-origin subclassifications. Using genetic approaches, we demonstrated that loss of SHP1 increases BCR signaling activity and sensitizes tumor cells to the inhibition by ibrutinib. Our results suggest that loss
of SHP1 may be used as an alternative biomarker to cell-of-origin to identify patients who potentially benefit from ibrutinib treatment.