Mutated MYD88 Cross-talk to BCR Signaling through Activating SYK in Waldenström’s Macroglobulinemia

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Background

Mutations in the Toll-like receptors (TLRs) signaling pathways are highly prevalent in Waldenström’s Macroglobulinemia (WM) and ABC DLBCL, wherein mutated MYD88 triggers NF-κB pro-survival signaling through BTK/IRAK. Activation of B-cell receptor (BCR) signaling can also be triggered by activating mutations in CD79A/B in ABC DLBCL, though are rare in WM (5-8%). Despite these findings, there is evidence for BCR activation in WM (Argyropoulos et al., Leukemia 2016). We hypothesized that crosstalk between TLRs and BCR might account for aberrant BCR signaling in WM and ABC DLBCL.

Methods

PhosFLow studies on MYD88 and BCR signaling components, including SYK (pY525-pY526) and other BCR signaling components were performed in MYD88 mutated WM and ABC-DLBCL cells compared to wild-type MYD88 expressing control cells. Knockdown or overexpression of MYD88 by lentiviral transduction in both MYD88 mutated and wild type cell lines. Western blot and phospho-flow studies were used to detect protein expression and phosphorylation in these cells. Co-immunoprecipitation assay and Confocal Microscopy were used to detect the involvement of SYK in the Myddosome complex. Cell survival following treatment with SYK inhibitors was assessed by Annexin V/PI staining or CellTiter-Glo® Cell Viability Assays.

Results

SYK is directly activated by mutated MYD88 in WM cells

Activated SYK supports MYD88 mutated WM cell growth and survival through the activation of downstream STAT3 signaling.

Conclusion

Our findings demonstrate that in addition to activation of the TLRs pathways, mutated MYD88 activates the BCR component SYK. These findings provide the rationale for combined therapeutics targeting the TLRs and BCR pathways in MYD88 mutated WM and possibly other mutated MYD88 driven B-cell malignancies including ABC-DLBCL.