Direct targeting of MYD88 homodimerization in Waldenstrom's Macroglobulinemia

Xia Liu, Lian Xu, Yang Cao, Zachary R. Hunter, Guang Yang, Jiaji Chen, Christopher J. Patterson, Nickolas Tsakmaklis, Sandra Kanan, Jorge J. Castillo, and Steven P. Treon. Bing Center for Waldenstrom's Macroglobulinemia, Dana Farber Cancer Institute, Harvard Medical School, Boston MA, USA.

MYD88 (L265P) is present > 90% of WM patients, and confers oncogenic activity in Waldenstrom's Macroglobulinemia (WM) and other lymphomas, including ABC subtype of DLBCL. MYD88 L265P can activate multiple downstream signaling pathways including those dependent on IRAKs and BTK leading to NF-κB activation which supports malignant cell growth and survival. MyD88 homodimerization is required to initiate the Myddosome signaling complex and trigger these downstream signaling pathways. Our previous work demonstrated that WM cell growth and survival could be reduced by inhibiting MYD88 homodimerization in MYD88-L265P expressing WM cell lines and in WM patient bone marrow lymphoplasmacytic cells. This provided us the rationale to directly target MyD88 homodimerization in WM. We therefore sought to disrupt the scaffold function of MyD88 through induced expression of MyD88 mini-peptides mimicking regions critical for homodimerization. We designed lentiviral vectors to over-express GFP tagged mini-peptides to disrupt the Myddosome signaling complex in WM cell lines. The over-expression of a MyD88 mini-peptide comprising a crucial residue for MyD88 homodimerization induced apoptosis and reduced cell survival in BCWM.1 cells by Annexin V staining and AlamarBlue® assays. PhosFlow studies demonstrated that the over-expression of $MyD88_{181-202}$ mini-peptide reduced the phosphorylation of BTK, IRAKs and NF-kB-p65. Flow cytometric analysis also showed increased active caspase 3 in MyD88 mini-peptide expressing cells. These studies demonstrate the cell survival can be reduced by disrupting the scaffold function of MyD88-L265P in WM cells, and provide a framework for the development of inhibitors directly targeting MyD88 homodimerization in WM.