Targeting Myddosome Self-assembly in Waldenström's Macroglobulinemia

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Background

MYD88 mutations are present in over 95% of patients with Waldenström’s Macroglobulinemia (WM) (N Engl J Med, 373:584-86), and promote Myddosome self-assembly that triggers NF-kB dependent survival through BTK and IRAK1:IRAK4 (Blood, 122(7):1222-32). While current therapeutic strategies are aimed at blocking these downstream kinases, peptidomimetics that interfere with Myddosome self-assembly may offer a more targeted approach for blocking aberrant MYD88 signaling.

Methods

We expressed mini-peptides of MYD88 Toll/Interleukin-1 Receptor (TIR) or Death Domain (DD) sequences (indicated on figure below) in GFP fusion protein by lentiviral transduction in mutated MYD88 WM and wild-type MYD88 control cells with an inducible vector. Phospho-flow analysis was used to evaluate changes in pBTK, pIRAK1:IRAK4, and pNF-kB, and determined cell growth and survival by AlamarBlue® Assay, Annexin V staining.

Results

Transduction of TIR or DD mini-peptides in mutated MYD88 WM cells but not wild-type MYD88 control cells reduced tumor cell growth and survival.

Transduction of MYD88 mini-peptides in mutated MYD88 WM cells but not wild-type MYD88 control cells reduced NFkB activation.

Conclusion

The findings demonstrate differences in BTK versus IRAK1:IRAK4 directed NF-kB signaling in response to Myddosome self-assembly in MYD88 mutated WM cells. The feasibility of directly targeting MYD88 homodimerization to block aberrant MYD88 signaling was also recognized, and suitable peptide sequences for the development of peptidomimetics that interfere with Myddosome self-assembly and signaling were identified. The findings provide a framework for direct targeting of the Myddosome in MYD88 mutated WM disease.