Expression of oncogenic Myd88 in B cells leads to the development of ABC-DLBCL in vivo

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The adaptor protein MYD88 is critical for relaying activation of Toll-like receptor signaling to NF-κB activation. MYD88 mutations, particularly the p.L265P mutation, have been described in numerous distinct B-cell malignancies, including Waldenstrom´s Macroglobulinemia and diffuse large B-cell lymphoma (DLBCL). Here, we generated a novel mouse model in which Cre-mediated recombination, specifically in B cells, leads to the conditional expression of Myd88(p.L252P) (the orthologous position of the human MYD88 p.L265P mutation) from the endogenous locus. These mice, when crossed to $Cd19^{Cre}$ mice, develop a lymphoproliferative disease and occasional transformation into clonal lymphomas. The clonal disease displays the morphologic and immunophenotypical characteristics of ABC-DLBCL. Lymphomagenesis can be accelerated by crossing in a further novel allele, which mediates conditional overexpression of BCL2. Cross-validation experiments in human DLBCL samples revealed that both MYD88 and CD79B mutations are substantially enriched in ABC-DLBCL compared with germinal center B-cell DLBCL. Furthermore, analyses of human DLBCL genome sequencing data confirmed that BCL2 amplifications frequently co-occurred with MYD88 mutations, further validating our approach. Finally, in silico experiments revealed that MYD88-mutant ABC-DLBCL cells in particular display an actionable addiction to BCL2. Altogether, we generated a novel autochthonous mouse model of ABC-DLBCL that could be used as a preclinical platform for the development and validation of novel therapeutic approaches for the treatment of ABC-DLBCL.