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Panobinostat acts synergistically with ibrutinib in diffuse large B cell lymphoma cells with MyD88 L625P mutation

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Diffuse large B cell lymphoma (DLBCL) frequently harbors genetic alterations that activate the B cell receptor (BCR) and TLR pathways, which converge to activate NF- κ B. While selective inhibition of BTK with ibrutinib causes clinical responses in relapsed DLBCL patients, most responses are partial and of a short duration. We demonstrated that *MyD88* silencing enhanced ibrutinib efficacy in DLBCL cells harboring MyD88 L265P mutations. Chemical downregulation of MyD88 expression with HDAC inhibitors also synergized with ibrutinib. We demonstrate that HDAC inhibitor regulation of MyD88 expression is mediated by STAT3. In turn, STAT3 silencing caused a decrease in MyD88 mRNA and protein levels, and enhanced the ibrutinib antilymphoma effect in MyD88 mutant DLBCL cells. Induced mutations in the STAT3 binding site in the MyD88 promoter region was associated with a decrease in MyD88 transcriptional activity. We also demonstrate that treatment with the HDAC inhibitor panobinostat decreased phosphorylated STAT3 binding to the MyD88 promoter. Accordingly, combined treatment with panobinostat and ibrutinib resulted in enhanced inhibition of NF- κ B activity and caused regression of DLBCL xenografts. Our data provide a mechanistic rationale for combining HDAC inhibitors and ibrutinib for the treatment of DLBCL.

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