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PTEN status and Akt phosphorylation: Implications for the rituximab-resistance in B-cell lymphoma

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Rituximab has been widely used in clinical practice for the treatment of B-cell malignancies, but the majority of patients retreated with rituximab will eventually relapse with variable degrees of resistant disease. There is an urgent need to explore the mechanisms of resistance to rituximab in non–Hodgkin's lymphoma (NHL), and to develop therapeutic strategies to overcome resistance. Herein, we successfully set up three types of rituximab-resistant B lymphoma cell lines with different malignancy grade, and demonstrate that phosphatase and tensin homolog (PTEN) is low expressed in the rituximab-resistant cell lines. Furthermore, we report that reduced PTEN expression correlated with resistance to rituximab and inhibited tumor cell apoptosis through activation of Akt phosphorylation. Restoration of PTEN expression resulted in re-sensitization of resistant cells to rituximab through modulation of apoptosis by suppressing the p-Akt in the PI3K/Akt signaling pathway. Overall, our findings demonstrate a novel mechanism of rituximab-resistance by the involvement of PTEN status and Akt phosphorylation in three different types of rituximab-resistant B lymphoma cell lines, which may be new predictive markers for response to rituximab and provide new insights for reversing rituximab resistance in B-cell lymphoma.

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Understanding the epigenetic response in resistant cancer cells to romidepsin therapy

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The histone deacetylase inhibitor (HDACi) romidepsin has shown therapeutic potential in the treatment of peripheral and cutaneous T cell lymphoma although resistance to this novel therapeutic agent often develops. Multiple mechanisms of resistance to HDACis have been identified *in vitro*, but how this class of epigenetic inhibitors manipulates the epigenome and whether this is altered to cause development of tolerance in cancer cells has not been studied. Previous work in the department into HDACi resistance has identified candidate epigenetic genes, including HDAC8 and KDM5A, whose mRNA expression pattern is perturbed in response to HDACi treatment in multiple romidepsin resistant cell lines. However, whether these alterations in mRNA levels reflect protein expression and functional changes remains unclear. Using the CTCL cell line HuT78 and its romidepsin resistant counterpart (RHuT78), it was shown that both HDAC8 and the KDM5A protein expression are altered differently between the wild type and the resistant cell line upon treatment with romidepsin. Furthermore, by combining romidepsin treatment with the DNA methyltransferase inhibitor 5-azacytidine and inducing an apoptotic response in RHuT78 cells, the expression changes of HDAC8 and KDM5A could be transformed back to that seen in the parental HuT78 cell line. These results suggest that both HDAC8 and KDM5A may contribute towards defining resistant responses to HDACis and are therefore worthy for further study into potential therapeutic targets for inhibition to overcome resistance to romidepsin.

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