Epigenetic reprogramming of diffuse large B-cell lymphoma cell lines: a drug screening to investigate drug resistance

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Abstract

T Diffuse large B-cell lymphomas (DLBCLs) are the most common type of non-Hodgkin lymphomas (30-40% of the cases). The current therapy consists on a regimen of R-CHOP, a mixture of rituximab (a CD20 monoclonal antibody) and four chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine and prednisone). Despite such therapy being effective on 70-80% of DLBCL patients, the remaining 20-30% develop an even more aggressive relapsed tumor.

The mechanisms behind resistance to R-CHOP therapy are not well understood, but alterations affecting the epigenome are among the main hallmarks of drug resistance in several cancers, including DLBCL. New drug combinatioons including compounds targeting the epigenome need thus to be systematically tested in order to overcome drug resistance and improve patient care.

In this study we have systematically screened a comprehensive collection of 60 epigenetic inhibitors to identify compounds able to sensitize R-CHOP resistant DLBCL cell lines. Each compound is tested for optimal dosage and pretreatment time (1, 3 and 9 days) followed by treatment with Rituximab and Doxorubicin, the main contributors to the R-CHOP therapy.

We identified a set of HDAC, HMT and BRD inhibitors able to revert the drug-resistant phenotypes of our cell lines. We are currently in the process of validating our findings and further investigating their mechanisms of action.