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605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Cinobufagin Induces Apoptosis of DLBCL Cells By Targeting the Inhibition of G6PD Activity

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Background: Globally, there are 150,000 new cases of diffuse large B-cell lymphoma (DLBCL) each year, accounting for approximately 30% of all non-Hodgkin lymphoma cases. Although most patients can be cured with R-CHOP immunochemotherapy, 30-40% of patients progress or relapse after treatment. Therefore, there is an urgent need to find new treatments to improve the survival rate of this group of patients. Natural small molecule drugs have unique advantages as anticancer agents due to their low toxicity and multiple targets. This project aims to explore potentially effective natural compounds as new therapeutic strategies for DLBCL.
Methods: Search for suitable natural compounds through GEO database, CMAP server and bioinformatics analysis. The effects of natural compounds on the biological function of DLBCL cells were studied by IC50 assay, apoptosis assay, cell cycle assay and subcutaneous transplanted tumor model. RNA sequencing, metabolomics detection, SEA server and 3D molecular simulation docking analysis were used to explore the drug target. The drug mechanism was verified by G6PD activity assay, EdU incorporation assay, NADPH assay and ROS assay.
Results: We used GEO and CMAP databases to identify 20 natural compounds that target DLBCL prognostic genes. Cinobufagin, a natural bufodienol isolated from toad venom, became the main object of this study because of its low IC50 value. Flow cytometry analysis showed that cinobufagin can effectively induce G2 arrest and apoptosis of DLBCL cells. In addition, cinobufagin significantly inhibited the growth of tumor tissue in a mouse model of heterotopic subcutaneous tumor transplantation. The results of transcriptome sequencing suggested that cinobufagin treatment inhibited multiple metabolism-related pathways. Metabolomic analysis showed a decrease in nucleoside metabolite content and inhibition of niacinamide synthesis. Through SEA server and 3D molecular docking simulation analysis, it was found that glucose-6-phosphate dehydrogenase (G6PD) may be a potential target of cinobufagin. G6PD activity assay showed that cinobufagin could inhibit the catalytic ability of G6PD. EdU incorporation experiments showed that cinobufagin inhibited DNA synthesis in DLBCL cells. In addition, cinobufagin also promoted the up-regulation of NADP+/NADPH ratio and the increase of ROS. The addition of ROS scavengers and nucleotides partially reversed the apoptosis-inducing ability of cinobufagin.
Conclusion:G6PD is a target of cinobufagin. By inhibiting the enzyme activity of G6PD, cinobufagin can inhibit DNA synthesis and the production of reducing NADPH, thereby inducing apoptosis of DLBCL cells. This suggests that Cinobufagin has potential application as a new drug for the treatment of DLBCL.

Disclosures No relevant conflicts of interest to declare.

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