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Combinational Therapeutic Targeting of BRD4 and CDK7 Synergistically Induces Anticancer Effects in Hepatocellular Carcinoma

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Abstract : Objectives: In hepatocellular carcinoma (HCC), oncogenes are continuously and robustly transcribed due to aberrant expression of essential components of the trans-acting super-enhancers (SE) complex. Preclinical and clinical trials are now being conducted on small-molecule inhibitors that target core-transcriptional components, including as transcriptional bromodomain protein 4 (BRD4) and cyclin-dependent kinase 7 (CDK7), in a number of malignant tumors. This study aims to explore whether co-overexpression of BRD4 and CDK7 is a potential marker of worse prognosis and a combined therapeutic target in HCC. Methods: The expression pattern of BRD4 and CDK7 and their correlation with prognosis in HCC were analyzed by RNA sequencing data and survival data of HCC patients from TCGA and GEO datasets. The protein levels of BRD4 and CDK7 were determined by immunohistochemistry (IHC), and survival data of patients were analyzed using the Kaplan-Meier method. The mRNA expression levels of genes in HCC cell lines were evaluated by quantitative PCR (q-PCR). CCK-8 and colony formation assays were conducted to assess cell proliferation of HCC upon treatment with BRD4 inhibitor JQ1 or/and CDK7 inhibitor THZ1. Results: It was shown that BRD4 and CDK7 were often overexpressed in HCCs and were associated with poor prognosis of HCC by analyzing the TCGA and GEO datasets. BRD4 or CDK7 overexpression was related to a lower survival rate. It's interesting to note that co-overexpression of CDK7 and BRD4 was a worse prognostic factor in HCC. Treatment with JQ1 or THZ1 alone had an inhibitory effect on cell proliferation; however, when JQ1 and THZ1 were combined, there was a more notable suppression of cell growth. At the same time, the combined use of JQ1 and THZ1 synergistically suppresses the expression of HCC driver genes. Conclusion: Our research revealed that BRD4 and CDK7 coupled can be a useful biomarker in HCC prognosis and the combination of JQ1 and THZ1 can be a promising therapeutic therapy against HCC.

Keywords : BRD4, CDK7, cell proliferation, combined inhibition
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