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603.LYMPHOID ONCOGENESIS: BASIC

TRIM28 Regulates DHCR7-Mediated Cholesterol Biosynthesis to Promote Survival in B Cell Lymphoma

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Background: TRIM28, a member of the tripartite motif-containing (TRIM) protein family, is a critical regulator of gene expression, DNA damage response and protein degradation, but little is known about its role in lipid metabolism. Dysregulation of cholesterol metabolism has been implicated in the pathogenesis of diffuse large B-cell lymphoma (DLBCL). However, the role of TRIM28 in lymphomagenesis and its clinical relevance remain unclear.
Methods: We searched public databases to characterize the gene expression pattern, clinical parameters, and survival data of TRIM28 in B-cell lymphoma, and immunohistochemistry (IHC) was used to confirm TRIM28 expression. Then, we knocked down TRIM28 by lentiviral shRNA transduction in several B-cell lymphoma lines to determine the effect of TRIM28-KD on cell proliferation, cell cycle progression, apoptosis and drug resistance. In addition, a lymphoma xenograft mouse model was established to test whether TRIM28-KD inhibits lymphoma growth in vivo. Using RNA-seq, we aim to identify novel transcriptional targets and elucidate the mechanisms by which TRIM28 promotes survival in B-cell lymphoma.
Results: Analysis of bioinformatic datasets and clinical samples indicated that TRIM28 expression was significantly upregulated in B-cell lymphoma compared to normal tissues, and high expression of TRIM28 was closely associated with disease progression and poor prognosis in patients with B-cell lymphoma. Knockdown of TRIM28 inhibited lymphoma cell proliferation, induced cell cycle arrest at G0/G1, increased cell apoptosis, and enhanced the sensitivity of lymphoma cells to chemotherapeutic agents. Moreover, TRIM28-KD significantly suppressed lymphoma and prolonged mouse survival in DLBCL xenograft models. The RNA-seq with TRIM28-KD vs. control revealed differentially expressed genes, many of which were enriched in lipid metabolism-related pathways. DHCR7, a critical terminal enzyme in cholesterol biosynthesis, was identified as a potential transcriptional target of TRIM28. TRIM28-KD inhibited DHCR7 expression, which was associated with reduced total cholesterol levels. DHCR7-KD impaired cell proliferation, whereas overexpression of DHCR7 rescued the phenotypes of TRIM28-KD in lymphoma cells.
Conclusions: TRIM28 drives lymphomagenesis through upregulating DHCR7-mediated cholesterol biosynthesis, which may serve as a novel therapeutic target for B-cell lymphoma.

Disclosures No relevant conflicts of interest to declare.

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