(PF1095) DIOSCIN INHIBITS DIFFUSE LARGE B-CELL LYMPHOMA BY MODULATING ACACA-DEPENDENT HISTONE H3K27 ACETYLATION AND INDUCING MITOPHAGY

Topic: 21. Lymphoma biology & translational research

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Background

Diffuse large B-cell lymphoma (DLBCL) is characterized by high heterogeneity and poor prognosis. Dioscin is a natural steroidal saponin from traditional Chinese medicine with known antitumor properties and clinical applications in liver and cardiovascular disorders.

Aims

This study aims to elucidate the effects of dioscin in DLBCL development and its regulatory mechanism on downstream targets and histone acetylation in DLBCL.

Methods

The FDA anti-tumor drug library (n=1746) was used to screen effective anti-DLBCL compounds and potential synergistic agents. In-vitro assays, including cell proliferation, cell cycle, and apoptosis, were performed to evaluate anti-lymphoma effects, and xenograft DLBCL mouse models were established to assess in-vivo efficacy. Drug affinity responsive target stability (DARTS)-based mass spectrum, molecular docking, RNA-seq, confocal immunofluorescence, and ChIP-seq were used to explore the potential mechanism.

Results

To explore novel therapeutic strategies for DLBCL, drug screening was performed based on the FDA anti-tumor drug library (n=1746), and dioscin was identified as an effective anti-DLBCL compound. Subsequently, dioscin treatment was found to significantly inhibit cell proliferation in DLBCL cells in a time- and dose-dependent manner, increase the proportion of cells in the G0/G1 phase, and promote cell apoptosis. Moreover, in DLBCL xenograft models, dioscin markedly suppressed tumor growth rates, weight, and tumor volume compared with the control group.

To further elucidate the direct target of dioscin in DLBCL, we combined DARTS-based mass spectrometry and molecular docking, and identified acetyl-CoA carboxylase α (ACACA), a key enzyme involved in fatty acid synthesis, as a potential dioscin-binding protein. Further DARTS validation confirmed the interaction between dioscin and ACACA. Importantly, ACACA was highly expressed in DLBCL tissues, which was significantly associated with poor prognosis in DLBCL patients. Functional experiments showed that targeting ACACA inhibited cell proliferation and induced cell cycle arrest and apoptosis in DLBCL.

To investigate the downstream mechanism, RNA-seq analysis revealed that both dioscin treatment and ACACA targeting were associated with activation of the mitophagy pathway. Further experiments showed that dioscin and ACACA knockdown increased mitochondrial dysfunction and promoted PINK1-Parkin-dependent mitophagy in DLBCL cells. Mechanistically, dioscin and ACACA regulated intracellular acetyl-CoA levels and enhanced histone acetylation, particularly H3K27ac. Integrative analysis of RNA-seq and ChIP-seq data identified HK2, a known PINK1-interacting protein, as a key downstream target of ACACA. ACACA-mediated H3K27ac enrichment at the HK2 promoter promoted its transcription. Consistently, treatment with the HK2 inhibitor BNBZ partially reversed the pro-mitophagy and anti-proliferative effects induced by ACACA knockdown and dioscin treatment. Furthermore, in-vitro and in-vivo experiments revealed that dioscin exhibited synergistic anti-lymphoma effects when combined with chidamide, a selective histone deacetylase inhibitor, and combination treatment markedly enhanced H3K27ac levels.

Summary/Conclusion

In summary, our findings showed that dioscin suppressed DLBCL progression by targeting ACACA and inducing mitophagy via H3K27ac, highlighting its potential as a novel therapeutic strategy for DLBCL treatment