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Dihydrotanshinone I Inhibits the Proliferation and Growth of Oxaliplatin-Resistant Human HCT116 Colorectal Cancer Cells

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Abstract: Oxaliplatin (OXA) is a first-line chemotherapeutic drug for the treatment of colorectal cancer (CRC), but acquired drug resistance becomes the main cause of treatment failure. Increasing evidence has shown that some natural components may serve as chemoresistant sensitizers. In this study, we discovered Dihydrotanshinone I (DHTS) through virtual screening using a ligand-based method, and explored its inhibitory effects and the mechanism on OXA-resistant CRC in vitro and in vivo. The results showed that DHTS could effectively inhibit the proliferation of HCT116 and HCT116/OXA resistant cells. DHTS-induced cell apoptosis blocked cell cycle in S and G_2/M phases, and enhanced DNA damage of HCT116/OXA cells in a concentration-dependent manner. DHTS also exhibited the obvious inhibition of tumor growth in the HCT116/OXA xenograft model. Mechanistically, DHTS could downregulate the expression of Src homology 2 structural domain protein tyrosine phosphatase (SHP2) and Wnt/β-catenin, as well as conventional drug resistance and apoptosis-related proteins such as multidrug resistance associated proteins (MRP1), P-glycoprotein (P-gp), Bcl-2, and Bcl-xL. Thus, DHTS markedly induces cell apoptosis and inhibits tumor growth in OXA-resistant HCT116 CRC mice models, which can be used as a novel lead compound against OXA-resistant CRC.

Keywords: Dihydrotanshinone I; CRC; oxaliplatin-resistant; virtual screening; SHP2

Citation: Wang, M.; Xiang, Y.; Wang, R.; Zhang, L.; Zhang, H.; Chen, H.; Luan, X.; Chen, L. Dihydrotanshinone I Inhibits the Proliferation and Growth of Oxaliplatin-Resistant Human HCT116 Colorectal Cancer Cells. *Molecules* **2022**, *27*, 7774. https://doi.org/10.3390/molecules27227774

Academic Editors: Fernando de Carvalho da Silva, Vitor Francisco Ferreira and Luana Da Silva Magalhães Forezi

Received: 8 October 2022
Accepted: 7 November 2022
Published: 11 November 2022

1. Introduction

Chemotherapy is the most important treatment for patients with advanced colorectal cancer (CRC) [1]. The FOLFOX regimen is a classic first-line treatment regimen for CRC, mainly composed of oxaliplatin (OXA), calcium folate, and fluorouracil [2,3]. OXA-based chemotherapy is one of the most commonly used therapeutic strategies after surgery [4]. OXA-resistance is a key contributor to treatment failure and tumor progression [5]. Tumor-related molecular mechanisms of OXA-resistance reported mainly include [6,7]: (1) overexpression of ATP binding box (ABC) transporter; (2) DNA damage repair; (3) block cells G_2 phase arrest; (4) enhance the anti-apoptosis ability of cells. Therefore, finding the underlying mechanism and the means to reverse/sensitize OXA resistance are urgently needed for the treatment of CRC patients.

Various active ingredients from Chinese medicine can inhibit chemotherapy-induced drug resistance in CRC [8]. Studies have shown that curcumin can reverse OXA-resistance in OXA-resistant cell line HCT116/OXA [9]. Spica Prunellae extract enhanced fluorouracil (FU) sensitivity in 5-FU-resistant human CRC HCT-8/5-FU cells [10]. Resveratrol increased the sensitivity of HCT116 and CT26 cells to cetuximab [11]. Dihydroisotanshinone I (DT) was also reported to induce apoptosis in CRC cell lines HCT116 and HT-29, and significantly inhibited tumor growth in a HCT116 xenograft nude mouse model [12]. Dihydrotanshinone I (DHTS) inhibits the formation of osteosarcoma by decreasing both the transcriptional activity and the total protein expression of β-catenin [13]. However, whether DHTS can inhibit OXA-resistant CRC and the underlying molecular mechanism is unknown.