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Cryptotanshinone attenuates the stemness of non-small cell lung cancer cells via promoting TAZ translocation from nuclear to cytoplasm

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Abstract

Background: Cancer stem cells (CSCs) are regarded as the root of tumor progression, thus representing an anti-cancer therapy through targeting this cell sub-population.

Methods: Non-small cell lung cancer (NSCLC) CSCs were enriched by non-adherent spheroid formation analysis. Lentivirus infection was used to stably change gene expression. Cell cycle, EdU incorporation, cell apoptosis, cell viability, ALDH1 activity, spheroid formation and in vivo tumor initiation assays were performed to detect the effects of Cryptotanshinone (CT), a traditional Chinese herb medicine, on the stemness of NSCLC cells. RNA-sequencing combined qRT-PCR and western blot analysis were constructed to explore the underlying mechanism contributing to CT-mediated effects.

Results: CT could attenuate the stemness of NSCLC CSCs, as evident by the reduced spheroid formation ability, stemness marker expression and ALDH1 activity. Additionally, CT provoked NSCLC CSCs entry into the cell cycle. RNA-sequencing analysis showed that Hippo signaling pathway was highly enriched in NSCLC CSCs with CT treatment. Further experiments disclosed that CT decreased TAZ (a regulatory master of Hippo pathway) expression via promoting its nuclear-cytoplasm translocation in NSCLC CSCs. Also, overexpression of TAZ partially saved the attenuation of CT on the stemness of NSCLC CSCs. Notably, CT enhanced the sensitivity of tyrosine kinase inhibitor (TKI) and chemotherapy in NSCLC CSCs.

Conclusions: This work reveals that CT attenuates NSCLC CSC stemness, implying the possibility of CT as an adjuvant therapy for NSCLC.

Keywords: Cryptotanshinone, Stemness, Non-small cell lung cancer, TAZ, Hippo

Background

Lung cancer is common malignant tumor in clinic with a high morbidity and mortality and ranks the first in tumors, among which non-small cell lung cancer (NSCLC) accounts for 80% [1]. Because NSCLC has no obvious symptoms in the early stage, most of the patients are diagnosed with advanced stage. At present,

radiotherapy, chemotherapy and targeted drug therapy are the main treatment in clinic, however, many patients, such as KRAS-mutant NSCLC, are not response or resistant to chemotherapy and targeted drug therapy [2]. Therefore, it is important to find novel ways to treat NSCLC.

Tumor initiating cells, also known as cancer stem cells (CSCs), have been regarded as the root of tumorigenesis [3]. It was found that targeting CSCs or attenuating the stemness could suppress tumor development, progression and decrease drug resistance. For example, salinomycin kills breast CSCs by sequestering iron in

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