Cryptotanshinone suppresses cell proliferation and induces apoptosis in renal cell carcinoma as an STAT3 inhibitor

Zhiguo Chen¹, Wei Zhai²

¹Department of Urology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, Shanghai, 200072, China
²Department of Urology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 200127, China

Correspondence: Wei Zhai
E-mail: jacky_zw2002@hotmail.com
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Cryptotanshinone (CPT) is a lipid-soluble constituent isolated from the root of Salvia Miltiorrhiza Bunge. Except the widely known antimicrobial, cardioprotection and antiinflammation effect, recent studies emphasize the potent anticaner activity of CPT in a wide variety of human cancers. Our previous study paid attention to the function of CPT against RCC. Results demonstrated that CPT could significantly suppress RCC formation in vitro and in vivo as a specific STAT3 inhibitor, indicating the potential therapeutic value of CPT against RCC.

Keywords: cryptotanshinone; renal cell carcinoma; cell proliferation; apoptosis; STAT3

Renal cell carcinoma (RCC) is one of the ten most frequently occurred human cancers [1, 2]. About 65% of the patients are localized RCC at initial diagnosis, which can be cured by surgery, such as total or partial nephrectomy [3]. The left is relapsed RCC or metastatic RCC (mRCC) in which metastatic lesions are detected. Due to the low response rate of RCC to conventional cytotoxic chemotherapy, only a small percentage of the patients benefit from cytokine therapies [4]. With the emergence of targeted drugs, the treatment for mRCC patients has been improved dramatically over the past decade [5, 6]. Unfortunately, drug resistance comes into being in some patients after a period of targeted therapy, which results in poor prognosis of the patients [7]. Consequently, novel potent agents or therapeutic strategies are still urgently needed.

Tanshinone I, tanshinone IIA and cryptotanshinone (CPT) are the major lipid-soluble constituents isolated from the root of Salvia Miltiorrhiza Bunge, a traditional Chinese medicine. They exhibit diverse biological activities, such as antimicrobial [8], cardioprotection [9], antiinflammation [10] and anticancer [11]. Recently, numerous studies highlight the anticancer properties of CPT in a wide variety of human cancers. However, little is known about the effect of CPT in RCC due to the lack of relevant research. Our recently published study demonstrated the specific function and underlying molecular mechanisms of CPT against RCC.

In the study, CPT inhibited the phosphorylation of STAT3 (Tyr705) and attenuated the nuclear translocation of STAT3, which account for the suppression of STAT3 activation. RCC cells were arrested at G0/G1 phase and cell growth was
restricted with the down-regulation of several crucial proteins, such as p-AKT, HGF, CyclinD1, C-MYC and MEKK2. Moreover, CPT induced RCC cell apoptosis, following the increase of Cleaved-Caspase-3 while down-regulation of anti-apoptotic proteins (Bcl-2 and Survivin). Furthermore, RCC xenograft mouse model demonstrated the anti-tumor effect of CPT in vivo. Tumor formation was significantly suppressed in mice. Collectively, CPT could suppress the development of RCC as an STAT3 inhibitor. 

Not just be characterized by suppressing cell survival, CPT exerted diverse pharmacological effects, such as suppressing cell migration and invasion of ovarian cancer and melanoma cancer, reducing angiogenesis in human umbilical vein endothelial cells, inducing cell autophagy of colon cancer. In addition, the combination of CPT with some chemotherapeutic agents also achieved remarkable results. For instance, CPT synergized with Arsenic trioxide to induce apoptosis of liver cancer and breast cancer cells; synergized with imatinib to suppress the survival of K562 cells; enhanced the sensibility of ovarian cancer cells to cisplatin; potentiated the therapeutic effect of doxorubicin to gastric carcinoma. Moreover, CPT was effective to drug resistant lung cancer and colon cancer cells. All of these demonstrate the potent anticancer effect of CPT and the promisingly extensive application of CPT in human cancer therapy.

Accumulating evidence has confirmed the essential effect of STAT3 on tumorigenesis. Hyperactive STAT3 was detected in numerous human tumors, including RCC. Furthermore, STAT3 blocking with small molecule inhibitors suppressed the formation of RCC. Apart from the intimate relativity of STAT3 with tumorigenesis, feedback activation of STAT3 was proved to be implicated in the development of drug-resistance. In addition, increased p-STAT3 was observed in sunitinib-resistant RCC xenograft mouse model. According to all of these, we can combine CPT with clinical approved multikinase inhibitors, such as sorafenib and sunitinib, to potentiate the efficacy or even reverse drug-resistance of these agents.

Despite the great medicinal value, there are still many obstacles, such as the low oral bioavailability, to overcome before CPT could be applied to clinical practice for cancer therapy. More investigations should be conducted to bring us more comprehensive understanding on the anticancer effect of CPT. In general, the study provides insights into the therapeutic value of CPT for RCC. It has the potential to be developed as a therapeutic agent or adjuvant against RCC in the future.

Conflicting interests

The authors have declared that no competing interests exist.

References