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LETTER TO EDITOR

The research prospect on ferroptosis induced by auraptene in hepatocellular carcinoma cells

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Dear Editor,

In this letter, we attempted to summarize the specific mechanism by which auraptene, a natural product, regulates hepatocellular carcinoma (HCC) cell growth through the ferroptosis pathway.

HCC is one of the most common malignancies worldwide. Although significant advancements have been made in the treatment of HCC in recent years, drug-induced side effects and drug resistance still exist and seriously hinder the efficacy of treatment for patients with HCC.[1-4] Hence, it is urgent to identify new targets and candidate compounds, especially natural compounds that exert anti-tumor effects for the diagnosis and treatment of HCC. Ferroptosis, a new type of programmed cell death that is different from apoptosis, necrosis, and pyroptosis, is characterized by iron- and reactive oxygen specifies (ROS)-dependent lipid peroxidation and destruction of the cell membrane.[5] Ferroptosis is tightly regulated by a series of proteins and metabolites in cells. The cystine/glutamate antiporter subunit solute carrier family 7 member 11 (SLC7A11) and selenium-containing enzyme glutathione peroxidase 4 (GPX4) are the main ferroptosis defense proteins.[6] SLC7A11 mediates extracellular cystine uptake for intracellular production of glutathione (GSH), which is a cofactor of GPX4 that catalyzes the reduction of toxic phospholipid peroxides to non-toxic lipid alcohols, leading to ferroptosis evasion.[7-9] Importantly, it was reported that metastatic or chemotherapy-resistant tumor cells are prone to ferroptosis. Thus, the discovery of compounds targeting tumor cell ferroptosis may be an attractive strategy for cancer treatment.

Auraptene, a coumarin derived from *Citrus* plants and fruits,[10] has low toxicity and good biocompatibility. It has been reported that auraptene exerts anti-tumor, anti-inflammatory, antigenotoxic, and neuroprotective activities.[11] In mouse colorectal cancer cells, auraptene was able to reduce the content of glutathione S-transferase, thereby inhibiting tumor growth and incidence.[12] Intriguingly, auraptene can exert cytotoxic effects through the induction of ROS in acute myeloid leukemia cell lines.[13]

We recently revealed that auraptene exerts anti-tumor effects in HCC cells through ferroptosis induction.[14] Auraptene induces excess intracellular ROS production and the addition of ROS scavengers – N-acetyl-L-cysteine and GSH – can impede the inhibition of HCC cell proliferation and viability induced by auraptene. Intracellular total ROS elevation is the prerequisite for ferroptosis, to determine whether the ferroptosis pathway is involved in auraptene-induced cell death in HCC cells, we assayed the lipid ROS level and found that auraptene can significantly increase lipid ROS level in HCC cells. Of note, ferroptosis inhibitors ferrostatin-1 and deferoxamine mesylate can inhibit auraptene-induced HCC cell death, demonstrating auraptene promotes HCC cell death

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mainly through the ferroptosis pathway. Mechanistically, auraptene treatment induces SLC7A11 ubiquitin-proteasome degradation, leading to the downregulation of intracellular GSH production and upregulation of ROS and lipid ROS levels, thereby leading to ferroptotic cell death. Importantly, low doses of auraptene increase the sensitivity of HCC cells to ferroptosis induced by RSL3 or cystine deprivation, implying that the use of auraptene alone or in combination with other ferroptosis inducers may be an attractive strategy for patients with HCC.

Different from previous studies on auraptene's regulation of ROS in normal cells, we focused on the anti-tumor activity of auraptene in HCC cells through metabolic regulation and explored the molecular mechanism by which auraptene regulates ferroptosis. Our study has identified positive regulation of ROS in HCC cells by auraptene and established that auraptene can cause ferroptosis in HCC cells by degrading SLC7A11, a key protein of ferroptosis.[14] This study provides a research model for anti-tumor research with a natural product and provides the potential of auraptene for HCC treatment.

Auraptene has shown anti-cancer effects by targeting different cell signaling pathways such as cytokines, growth factors, transcription factors, and apoptosis factors.[15] Maleki *et al.*[16] reported that prenylation at position six of the coumarin ring significantly improved the anticancer activity of auraptene. They examined eight coumarins and found that auraptene showed the best anti-cancer activity with the minimal cytotoxicity to normal cells. Vakili *et al.*[17] conducted a study on the side effects of auraptene and found that different concentrations (125 – 2000 mg/kg body weight) had no effect on mortality in rats. Moreover, a series of detection indexes such as alanine transaminase, aspartate transaminase, and hemoglobin were all within the normal reference range. The histopathological examination of the liver, kidney, lung, and other organs also showed that auraptene had no toxic effect. The anticancer activity of auraptene has been demonstrated in many *in vivo* and *in vitro* studies. Pharmacokinetic studies have found that oral administration of auraptene in rats is effective and safe in the concentration range of 0.5 – 200 ng/mL, with oral bioavailability of about 8.5%.[18]

In summary, our work reported that the natural product auraptene is a potential anti-cancer drug through inducing HCC cell ferroptosis, and the detailed mechanism and pharmacology of auraptene will contribute to its application in clinic in the future.

Conflict of interest

The authors declare that they have no competing interests.

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