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DHA exhibits synergistic therapeutic efficacy with cisplatin to induce ferroptosis in pancreatic ductal adenocarcinoma via modulation of iron metabolism

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Pancreatic ductal adenocarcinoma (PDAC) is an extremely lethal cancer with limited treatment options. Cisplatin (DDP) is used as a mainstay of chemotherapeutic agents in combination with other drugs or radiotherapy for PDAC therapy. However, DDP exhibits severe side-effects that can lead to discontinuation of therapy, and the acquired drug resistance of tumor cells presents serious clinical obstacles. Therefore, it is imperative to develop a more effective and less toxic therapeutic strategy. We and others have previously discovered that dihydroartemisinin (DHA) represents a safe and promising therapeutic agent to preferentially induce cancer cell ferroptosis. In the present study, we find that DHA could intensively strengthen the cytotoxicity of DDP and significantly reduce its effective concentrations both in vitro and in vivo. Combination of DHA and DDP synergistically inhibits the proliferation and induces DNA damage of PDAC cells. Mechanically, the combinative treatment impairs mitochondrial homeostasis, characterized by destroyed mitochondrial morphology, decreased respiratory capacity, reduced ATP production, and accumulated mitochondria-derived ROS. Further studies show that ferroptosis contributes to the cytotoxic effects in PDAC cells under the challenge of DHA and DDP, together with catastrophic accumulation of free iron and unrestricted lipid peroxidation. Moreover, pharmacologic depleting of the free iron reservoir or reconstituted expression of FTH contributes to the tolerance of DHA/DDP-induced ferroptosis, while iron addition accelerates the ferroptotic cell death. In summary, these results provide experimental evidence that DHA acts synergistically with DDP and renders PDAC cells vulnerable to ferroptosis, which may act as a promising therapeutic strategy.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer which is an extremely lethal cancer with poor prognosis and high recurrence rate. PDAC often harbors the universal mutations in the proto-oncogene *K-RAS* (>90% prevalence in pancreatic cancer), which persistently accelerates and activates various oncogenic events (e.g., uncontrolled proliferation, sustained angiogenesis, metastasis, or invasion), thus leading to metabolic reprogramming and resistance to cell death [1, 2]. Most patients with pancreatic cancer were diagnosed at a late stage even with distant metastasis and died within several months. Although the diagnosis and treatment of pancreatic cancer have achieved great progress, the outcomes of patients are still not satisfactory, especially in those patients with *K-Ras* oncogenic mutant [3]. The survival benefits of standard chemotherapies are still limited with a median survival of fewer than 6 months [4], the 5-year survival rate for pancreatic cancer patients remains less than 10% [5]. Therefore, it is imperative to develop more effective and less toxic therapies that sensitize cancer cells to chemotherapy agents. Ferroptosis, a new mode of regulated cell death (RCD), is more prone to occur in *Ras* mutant cancer cells, which might open up a new strategy to solve this problem [6].

Cisplatin (DDP), an effective platinum-based chemotherapeutic agent, has been used to treat various types of solid tumors, including lung, breast, esophageal, ovarian, and pancreatic cancers [7, 8]. The inhibition of proliferation through DNA damage in rapidly dividing cells is the main anticancer mechanism of DDP. Other mechanisms of DDP-induced cytotoxicity are involved in impairing glycolysis, mitochondrial dysfunction, and accumulation of reactive oxygen species (ROS) [9]. However, DDP exhibits severe side-effects that can lead to discontinuation of therapy and acquired drug resistance, which may contribute to the treatment

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