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Synergistic antitumor effect of combined paclitaxel with FEN1 inhibitor in cervical cancer cells

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ABSTRACT

Studies on cervical cancer are urgently required to improve clinical outcomes. As a major anticancer drug for cervical cancer, paclitaxel has been used for many years in clinical therapy but its therapeutic efficacy is limited by common obstacle from cancer cells. The enhanced DNA repair pathways of cancer cells have been proved to survive DNA damage induced by chemotherapeutic drug. Inhibitors of specific DNA repair pathway can sensitize cancer cells to the treatment of chemotherapeutic drugs. In this paper we found that the effect of paclitaxel can be significantly improved when used in combination with FEN1 inhibitor SC13, suggesting a synergistic mechanism between the two compounds. Our studies suggest that FEN1 inhibition could be a novel strategy of tumor-targeting therapy for cervical cancer. Our work also revealed that paclitaxel demonstrates stronger synergistic effect with SC13 than other common used chemical drugs such as doxorubicin, carboplatin or camptothecin on cervical cancer cells.

1. Introduction

Globally, cervical cancer is both the fourth-most common cause of cancer and death among affected women [1]. The outcome of patients with metastatic cervical cancer is very poor once occurring with metastasis and their 1-year survival is less than 20%. In 2012 alone, 8% of total cases and death were reported with an estimated 528,000 cases and 266,000 deaths [2,3]. To date, chemotherapy (cisplatin, paclitaxel) and surgery are still valuable and promising treatments for resistant or recurrent metastatic cervical cancer [3–5]. Although chemotherapy is considered as the standard treatment for patients with advanced or recurrent cervical cancer, the resistance to chemotherapeutic drug may develop, thus greatly compromising the efficacy to treat advanced or recurrent cervical cancer [6].

Originally separated from natural plants, paclitaxel is a microtubule-stabilizer that selectively arrests cells in the G2/M phase of the cell cycle. As a member of the taxane class of anticancer drugs, paclitaxel has been used as one of the most common chemotherapeutic agents [7]. As a promising antitumor agent, paclitaxel acquired wide application in clinical uses for its remarkable anti-tumor activity on many forms of cancer including ovarian [8], pancreatic [9], breast [10], and other solid tumors [11]. However, there still are some limitations towards its wide clinical application. Paclitaxel is faced with various challenges including low solubility in water and the relative selectivity for target cells. Furthermore, drug resistance remains a major obstacle to cancer chemotherapy. Hence, efforts to obtain smarter targeting paclitaxel have never stopped [12]. Furthermore, how to overcome chemotherapy tolerance and drug resistance have been studied during the last decades [7,13].

In order to improve the therapeutic effect of paclitaxel on cervical cancer, several pre-clinical and clinical studies have been conducted. Cisplatin has been reported to enhance the anti-cancer activity of paclitaxel among cases of cervical cancer [14–17]. Cisplatin binds to nuclear DNA, leads to disruption in transcription and replication, and subsequently induces DNA damages. If cisplatin-induced DNA damages are not efficiently processed by DNA repair machinery, the apoptosis will eventually be triggered by the cytotoxic processes and accumulated DNA damage [4,18]. Growing studies indicated that DNA repair pathways can enable cancer cells to survive DNA damage induced by chemotherapeutic drugs [19]. Thus, inhibitors of specific DNA repair pathways might prove efficiency when used in combination with DNA-damaging chemotherapeutic drugs [19].

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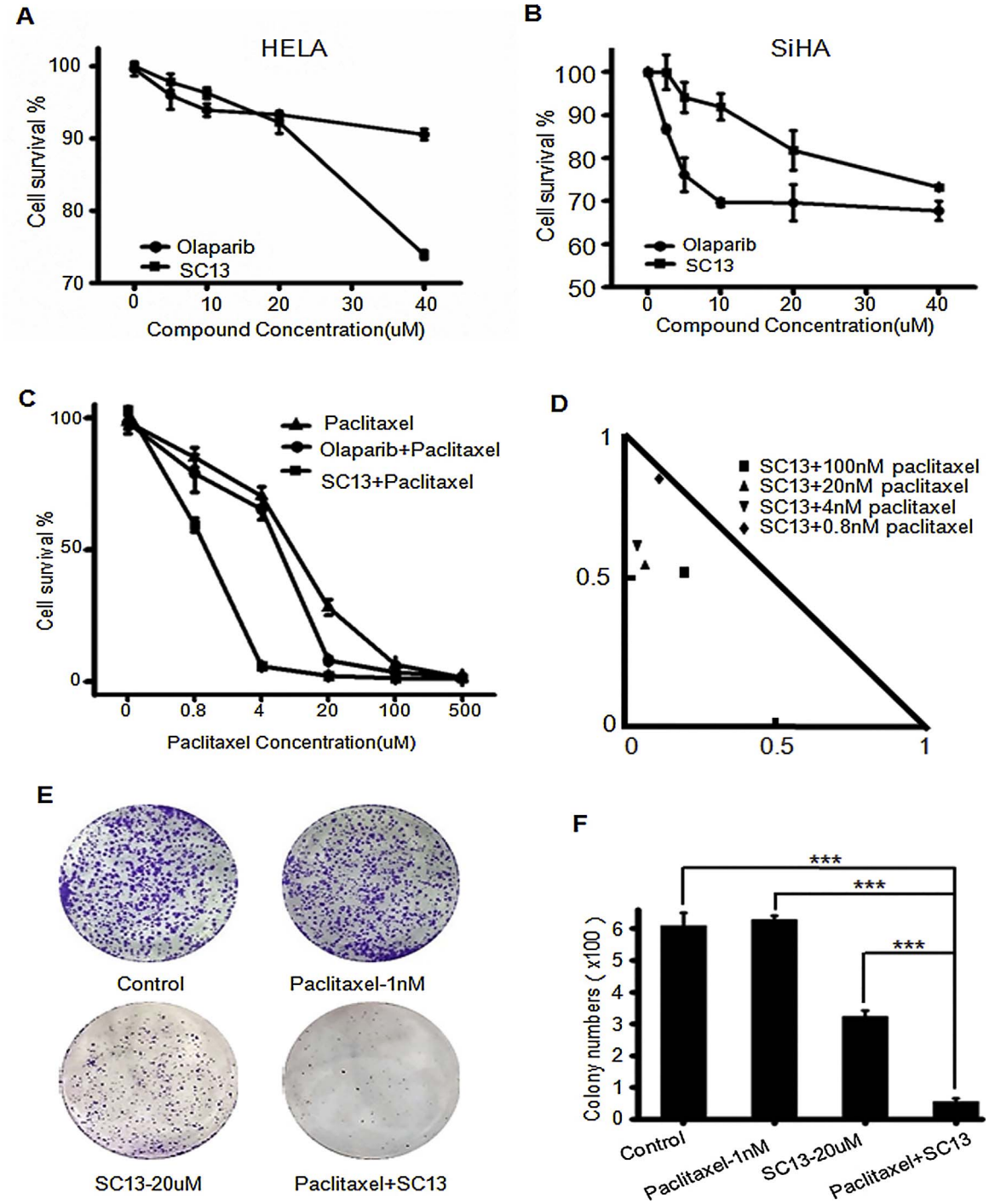

Fig. 1. Anti-proliferative effects of paclitaxel or SC13 alone and in combination on cervical cancer cells. Shown are the effects of SC13 or Olaparib alone on (A) HeLa or (B) SiHA cell proliferation, 48 h treatment. (C) Drug sensitivity assay of HeLa cells following 48 h treatment with paclitaxel or SC13 and in combination on HeLa cells. (D) Anti-proliferative effects of paclitaxel and SC13 on HeLa cells, 48 h treatment. The interactions between paclitaxel and SC13 were analyzed with isobologram method. If combination data points fall to the left of the line, on the line, or to the right of the line, the compounds show a synergistic, non-interactive, or antagonistic interaction respectively. (E) Colony formation of HeLa cells after treatment with compound alone or in combination. (F) A statistical quantification of panel E. ***, $P < 0.001$.

DNA flap endonuclease 1 (FEN1) is now recognized as a central component of cellular DNA metabolism, for its multiple important roles in maintaining genome stability and integrity by participating in both DNA replication and repair [20,21]. FEN1 has been reported to be over-expressed in many forms of cancer [22–24]. The co-treatment with FEN1 inhibitor could increase the sensitivity of cancers to DNA-damaging chemotherapeutic drugs. Further, reports of paclitaxel-induced DNA damage [25–28] lead us to consider the combination of paclitaxel and FEN1 inhibitor-SC13 for the treatment of cervical cancer [29,30].

In this paper we proved that the combinative treatment of SC13 and paclitaxel drastically suppressed CDK2/4 and cyclin expression, thus significantly induced cell cycle arrest in cervical cancer cells. SC13 co-treatment sensitized cancer cells to low concentration paclitaxel treatment, which means that the side effect of paclitaxel could be avoided. Our study suggests that targeting FEN1 could be a novel strategy as a tumor-targeting therapy for cervical cancer. The combination of Sc13 and paclitaxel would be beneficial to the efficient and economical therapy of cervical cancer and other caner type.