Cordycepin inhibits pancreatic cancer cell growth in vitro and in vivo via targeting FGFR2 and blocking ERK signaling

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[ABSTRACT] Cordycepin (3′-deoxyadenosine) from Cordyceps militaris has been reported to have anti-tumor effects. However, the molecular target and mechanism underlying cordycepin impeding pancreatic cancer cell growth in vitro and in vivo remain vague. In this study, we reported functional target molecule of cordycepin which inhibited pancreatic cancer cells growth in vitro and in vivo. Cordycepin was confirmed to induce apoptosis by activating caspase-3, caspase-9 and cytochrome c. Further studies suggested that MAPK pathway was blocked by cordycepin via inhibiting the expression of Ras and the phosphorylation of Erk. Moreover, cordycepin caused S-phase arrest and DNA damage associated with activating Chk2 (checkpoint kinase 2) pathway and downregulating cyclin A2 and CDK2 phosphorylation. Very interestingly, we showed that cordycepin could bind to FGFR2 (KD = 7.77 × 10−9) very potently to inhibit pancreatic cancer cells growth by blocking Ras/ErK pathway. These results suggest that cordycepin could potentially be a leading compound which targeted FGFR2 to inhibit pancreatic cells growth by inducing cell apoptosis and causing cell cycle arrest via blocking FGF/Ras/ERK signaling for anti-pancreatic cancer new drug development.

[KEY WORDS] Cordycepin; FGFR2; Apoptosis; Pancreatic cancer; Ras/Erk

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal cancers, owing to its poor clinical diagnosis and chemoresistance [1]. Moreover, the tumor is often inoperable at diagnosis due to its severe metastasis and invasiveness [2]. Gemcitabine has been recommended as the standard first-line treatment for pancreatic cancer since 1997 [1], whereas offering weak efficacies but strong resistance [4]. Therefore, novel therapeutic treatments are urgently needed.

Fibroblast growth factors (FGFs) consist of 22 different growth factors that regulate embryonal development, wound healing, cell proliferation and survival by binding to fibroblast growth factor receptors (FGFR) and activating downstream pathways [14]. Aberrant FGF signaling has a unique and critical role in the development of malignant tumor. It is reported that FGF signaling pathway shows the highest enrichment containing non-synonymous mutations for different kinase genes [9]. Clinical histopathology studies have shown that the increasing production of bFGF secreted by pancreatic cancer cells induces further hyperplastic lesions of the pancreas [10]. Moreover, FGFR2, the subtype 2 receptor for FGF, is overexpressed in pancreatic tumor. Hence, targeting FGFR2 and regulating its downstream pathways might be a therapeutic strategy in PDAC. FGF-stimulation on FGFR results in activation of the Ras/Mitogen-activated protein kinase (MAPK) signaling cascade [13]. There is evidence that over-activated ERK MAPK signaling pathway is responsible for human oncogenesis and is involved in aberrant development in cancers [12]. In addition, the ERK MAPK signaling plays an important role in regulating cell growth, apoptosis, cell cycle arrest and so on [13].
Cordycepin (3’-deoxyadenosine), a naturally nucleoside analog, is the major bioactive component isolated from *Cordyceps militaris*. More evidences have shown that cordycepin may inhibit tumor cells growth \(^{[16-19]}\). Recently, Zhang et al. reported that cordycepin might induce human pancreatic cancer cells apoptosis and suppress the tumor growth in vivo \(^{[17]}\). However, its functional molecular target and the related mechanism of action remain unclear. In this study, we show evidence that cordycepin inhibits pancreatic cancer cells growth in vitro and in vivo by targeting FGFR2 and blocking ERK/MAPK signaling.

**Material and Method**

**Reagents**

Cordycepin was prepared in Institute of Edible Fungi, Shanghai Academy of Agricultural Sciences and extracted from *Cordyceps militaris* by macroporous resin \(^{[19]}\). 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) was from sigma-Aldrich, USA. Dimethyl Sulfoxide (DMSO) was purchased from E. Merck, Germany. aFGF and FGFR2 were purchased from Sino Biological (Beijing, China). aFGF (Sino Biological, Cat #: 10013-HNAE; Sources from Human, A DNA sequence encoding the mature form of human FGF acidic (AA97245.1) (Phe 16-Asp 155) was expressed, with an additional Met at the N-terminus. E. Coli expressed, activity measured in a cell proliferation assay using BALB/c 3T3 mouse fibroblasts. The ED50 for this effect is typically 50–200 pg mL\(^{-1}\). FGFR2 (Sino Biological, Cat #: 10824-H08H; Sources from Human, A DNA sequence encoding the human FGFR2 (NP_000132.3) extracellular domain (Met 1-Glu 377) was expressed, fused with a polyhistidine tag at the C-terminus. HEK293 Cells expressed, Measured by its ability to inhibit FGF acidic dependent proliferation of Balb/c3T3 mouse embryonic fibroblasts. The ED50 for this effect is typically 200–400 ng mL\(^{-1}\). Other reagents were obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

**Cells culture**

All cells were obtained from the Cell Bank in the Type Culture Collection Center of the Chinese Academy of Sciences, Shanghai, China. The pancreatic cancer cell line BxPC-3 and AsPC-1, and the normal pancreatic cell line HPDE6-C7 were maintained in RPMI-1640 medium containing 10% FBS and antibiotics (100 U mL\(^{-1}\) penicillin, 100 μg mL\(^{-1}\) streptomycin, Invitrogen). The pancreatic cancer cell line PAN1 was cultured in DMEM medium supplemented with 10% FBS and antibiotics (100 U mL\(^{-1}\) penicillin, 100 μg mL\(^{-1}\) streptomycin, Invitrogen). These cell lines were all cultured at 37 °C in a 5% CO\(_2\) incubator.

**MTT assay**

BxPC-3 (3 × 10\(^3\) cells/well) cells were seeded into 96-well plate and incubated under normal culture condition overnight. Then cells were cultured with or without cordycepin for 72 h, and incubated with 5 mg mL\(^{-1}\) of MTT (3-[4, 5-dimethyl thiazol-2-yl]-2,5-diphenyl tetrazolium bromide) for another 4 h. The formazan crystals produced from MTT in the living cells were dissolved in dimethyl sulfoxide (DMSO). The color absorbance was detected at 490 nm by a spectrophotometer (Thermo Scientific, West Palm Beach, FL). The effect of cordycepin on cell viability was calculated as (sample/control) × 100%.

**Western blotting**

Total protein was extracted by lysing cells with an equal volume of the RIPA buffer (Beyotime, China). The cytoplasmic protein was isolated using Nuclear and Cytoplasmic Protein Extraction Kit (Sangon Biotech, China). The protein samples were separated by SDS–polyacrylamide gel electrophoresis and transferred onto a polyvinyl difluoride (PVDF) membrane (Life Science). After blocking with 5% nonfat milk for 2 h, the membrane was incubated with primary antibodies overnight at 4 °C, followed by incubation with secondary antibodies for 2 h, the blots were visualized with enhanced chemilumine-scene reagent (Pierce). Antibodies used were listed in Supplementary Table S1.

** Colony formation**

BxPC-3 cells (1 × 10\(^3\) cells/well) were seeded and incubated in a 6-well plate overnight and then treated with different concentrations of cordycepin. The medium containing cordycepin was replaced every 3 days. After 2 weeks, the colonies were clearly visible and stained with Giemsa for counting.

**RNA extraction, RT–PCR and quantitative real-time PCR**

After cordycepin treatment, total RNA was extracted from cultured cells using Trizol reagent (Invitrogen, USA). Complementary DNA (cDNA) was synthesized from 2 μg total RNAs using M-MLV reverse transcriptase (Takara Biotechnology, Dalian, China). Then PCR amplification was performed with rTaq (Takara Biotechnology, China) following the manufacturer’s instructions. PCR primers were shown in Supplementary Table S1.

**Surface plasmon resonance (SPR) analysis**

SPR measurements for binding affinity analysis were conducted on a BIACORE T200 (GE Healthcare, Stockholm, Sweden). The human recombinant proteins were immobilized to a CM5 sensor chip by a standard amine coupling method. Different concentrations of cordycepin or aFGF dissolved in HBS-EP buffer (150 mol L\(^{-1}\) NaCl, 3 mmol L\(^{-1}\) EDTA, 10 mol L\(^{-1}\) HEPES and 0.05% surfactant P20, pH 7.4) were injected onto the sensor chips. In competitive inhibition assays, certain concentration of aFGF (29.67 nmol L\(^{-1}\)) was incubated with increasing concentrations of cordycepin and then injected to the chip. Kinetic parameters were evaluated by BIACORE T200 Evaluation Software Version 1.0.

**Transwell assay**

Transwell assay was used to evaluate migration ability. BxPC-3 cells (1 × 10\(^3\) cells/well) in 100 μL of serum-free medium were seeded in the upper chamber. And the lower chamber was filled with medium containing 10% FBS and different concentrations of cordycepin. After 8 h incubation, the migrated cells were stained by 0.1% crystal violet and then photographed by a microscope (Olympus BX51).
Apoptosis and cell cycle analysis by flow cytometry

Cells (3 × 10⁴ cells/well) were seeded in a 6-well plate and incubated overnight. After treatment, cells were harvested using 0.25% Trypsin and washed with cold PBS. Cells were fixed in ice-cold 75% ethanol at 4 °C overnight. After washing, the cells were incubated with PBS containing RNase A (100 μg mL⁻¹) in 37 °C water bath for 1 h and incubated on the ice with 50 μg mL⁻¹ PI (Invitrogen, USA) for 15 mins, the DNA content was measured by flow cytometry with ModFit LT 3.0 software (Becton Dickinson, Franklin Lakes, NJ). Apoptotic or necrotic cells were stained with Al- exa(Flour 488 Annexin V and PI, afterwards the samples were analyzed on FACSCalibur (Becton Dickinson).

Xenograft model

All animal studies were carried out according to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. BxPC-3 cells (3 × 10⁴ cells/mouse) were subcutaneously injected into the flank of female BALB/cA nu/nu mice (6–8 weeks old). Xenografted animals were treated daily with cordycepin (10 mg kg⁻¹) in saline via oral administration, and animals from control group were treated with equivalent volumes of normal saline when tumor was palpable. The tumor volume (V) was calculated as followed: V = (length × width)². On the 32nd day, mice were euthanized and tumor tissues were excised.

Immunohistochemistry

Tumors were excised and fixed in 4% paraformaldehyde, then embedded in paraffin and sectioned for immunohistochemical analysis. Cell proliferation was evaluated by staining the sections with Ki67 antibody (CST). The expression of ERK phosphorylation was shown by staining p-Erk antibody (CST). Semiquantitative image analysis was used by Image Pro Plus software.

Statistical analysis

All data were presented as mean values ± SEM. P-value of the difference between groups were analyzed with Student's t-test, a single factor analysis of variance and unpaired using the PRISM software (GraphPad Software). Values of P less than 0.05 were considered statistically significant. (P < 0.05, **P < 0.01, ***P < 0.001).

Results

Cordycepin (3′-deoxyadenosine) inhibited PDAC cells in vitro and in vivo

MTT assay was used to test the effect of cordycepin on pancreatic cancer cell viability. As shown in Fig. 1A, cordycepin inhibited the cell viabilities of pancreatic cancer cells BxPC-3, CFPAC-1, AsPC-1, PANC-1 and SW1990 in a dose-dependent manner. IC₅₀ of cordycepin on these five cell lines were 38.85, 72.99, 150.1, 213.1, 349.3 μmol·L⁻¹, respectively. Obviously, BxPC-3 cells were more sensitive to cordycepin treatment. The inhibition rate of this compound on BxPC-3 cells at the concentration of 100 μmol·L⁻¹ was around 90%. However, cordycepin nearly had no toxicity on normal pancreatic cell line HPDE6-C7 at its effective concentra-

tion (Fig. 1B). These results indicated that cordycepin might have negligible toxic effects on normal pancreatic tissues at least under the effective dose.

Furthermore, we detected the effects of cordycepin on the colony formation and migration of BxPC-3 cells. As shown in Fig. 1C and Fig. 1D, cordycepin significantly reduced the size of BxPC-3 colonies and inhibited migration of BxPC-3 cells at the concentration of 50 or 100 μmol L⁻¹.

To determine whether cordycepin could inhibit tumor growth in vivo, tumor xenograft model was employed in this study. Tumor volume was calculated every 3 or 4 days for 32-day treatment. The results showed that cordycepin significantly reduced BxPC-3 xenograft tumor growth and tumor weights (Figs. 1E–1G). Moreover, the body weights of mice showed no significant changes comparing to the control group (Fig. 1H). The above results suggest that cordycepin could inhibit the tumor growth without significant side effects.

Cordycepin induced apoptosis in BxPC-3 cells

Inducing apoptosis of tumor cells is general strategy of anti-tumor agents. After treated with 50 and 100 μmol L⁻¹ cordycepin for 48 h, the percentage of apoptotic cells of control, 50 and 100 μmol L⁻¹ groups was 3.68%, 29.48%, and 43.79%, respectively (P < 0.001, Fig. 2A). To understand the underlying mechanism, the activation of caspase-3 and caspase-9, which played significant roles in cell apoptosis were analyzed [20]. Western blotting results indicated that the expressions of cleaved caspase-3 and caspase-9 were significantly upregulated by cordycepin treatment (Fig. 2B). Caspase 9 could be triggered by the release of cytochrome c [21]. Therefore, we detected cytochrome c as well. Indeed, the release of cytochrome c into the cytosol was increased after cordycepin treatment (Fig. 2C). Bax, one of the members of BCL-2 family, is known to trigger apoptosis [22]. As expected, Bax and FasL were dramatically upregulated in cordycepin treated group (Fig. 2D). These data demonstrated that caspasesthat pathway might be critical for cordycepin-induced BxPC-3 cells apoptosis.

Cordycepin induced BxPC-3 cells cycle arrest

To further explore the cell growth inhibition of cordycepin, BxPC-3 cells treated with 100 μg L⁻¹ cordycepin were analyzed by flow cytometry after propidium iodide (PI) staining. The percentage of cells in S phase was increased dose-dependently, indicating that cordycepin arrested BxPC-3 cells in S phase (Figs. 3A, 3B). Cyclin A2-CDK2 complex played an important role in regulating cell progression from G1 to S phase [23]. Cyclin A2 and CDK2 phosphorylation were dramatically downregulated in the treatment group (Figs. 3C, 3E). Cyclin A2-CDK2 complex could be negatively regulated by the phosphorylation of ATM, ATR and chk2 was significantly reduced (Figs. 3D). In addition, the results showed that the phosphorylation of ATM, ATR and CHK1 was upregulated (Fig. 3F), suggesting that cordycepin induced DNA damage. These results clearly illustrated that cordycepin induced S phase arrest via effecting the expres-
Fig. 1  Cordycepin (3′-deoxyadenosine) inhibited PDAC cells BxPC-3 in vitro and in vivo. (A) The cells were cultured with cordycepin (0, 6.25, 12.5, 25, 50, 100, 200, 400 μmol·L\(^{-1}\)) for 72 h. Cell viability was assessed by MTT assay. (B) The IC\(_{50}\) of cordycepin on BxPC-3 cells is 82.01 μmol·L\(^{-1}\) according to MTT assay. (C) Representative images of BxPC-3 colonies were shown after cordecepin treatment. BxPC-3 cells were incubated with cordycepin (0, 50, 100 μmol·L\(^{-1}\)) for 2 weeks. The colony size and the colony numbers were quantified for statistical analysis. (D) BxPC-3 cells were treated with cordycepin (0, 50, 100 μmol·L\(^{-1}\)) for 8 h. The migration abilities were evaluated by Transwell assay and the migration cells were photographed. (E) The curves of tumor volumes (mean ± SEM) indicate the tumor growth of cordycepin treatment group and control group. (F) The BxPc-3 xenograft tumors were photographed. (G) Excised tumor weights were measured. (H) The body weights of the nude mice were measured during the study. The experiments were repeated thrice. Data were represented as mean ± SEM; **P < 0.01, ***P < 0.001
Cordycepin bound to FGFR2 and impaired aFGF-induced BxPC-3 cells growth

Fibroblast growth factors (FGFs) and Fibroblast growth factor receptor (FGFR) were implicated in tumor angiogenesis and their expression is high in clinical pancreatic tumor specimens [10]. We therefore sought to investigate whether cordycepin could disrupt FGF-induced cell growth. BxPC-3 cells were treated with aFGF (20 ng·mL⁻¹) or bFGF (20 ng·mL⁻¹), respectively. As expected, aFGF and bFGF significantly stimulated cell growth. Nevertheless, the effects were abrogated in the presence of cordycepin (100 μmol·L⁻¹)

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**Fig. 2** Cordycepin induced apoptosis in BxPC-3 cells. (A) BxPC-3 cells were incubated with cordycepin (0, 50, 100 μmol·L⁻¹) for 48 h and stained with Annexin V and PI. Annexin V was analyzed by flow cytometry. (B and C) BxPC-3 cells were incubated with 100 μM cordycepin for indicated time. The protein levels of cleaved caspase-3, cleaved caspase-9 and Cytochrome c were measured by Western blotting. β-tubuln was used as a control for protein loading. (D) BxPC-3 cells were treated with 100 μmol·L⁻¹ for indicated time. RT-PCR was employed to analyze mRNA level of Bax and FasL. Integrated optical densities of bands normalized by 18s were shown below. The experiments were repeated thrice. Data were represented mean ± SEM; **P < 0.01; ***P < 0.001
and the inhibition was more significant in aFGF treatment group. Results above showed that cordycepin could significantly inhibit aFGF induced cell growth, thus the role of aFGF involved was further investigated in this study.

The extracellular domain of FGFR consists of the acidic box, which was essential for interacting with heparin sulfate proteoglycan (HSPG) [25]. Cordycepin also contains free alkaline amino groups. Therefore we wonder whether cordycepin could interact with FGFR or/and aFGF as well. Firstly, Surface Plasmon Resonance (SPR) was employed to evaluate the affinity of aFGF to FGFR2, and the $K_D$ value for aFGF-FGFR2 was $6.44 \times 10^{-9}$ (Fig. 4C). Then we analyze the interaction of aFGF or FGFR2 in the presence of cordycepin (Fig. 4D). The results showed that there is almost no combination between aFGF and cordycepin (Fig. S2), whereas, the $K_D$ value for FGFR2-cordycepin was $7.77 \times 10^{-9}$, suggesting similar affinity of ligand (aFGF) with receptor (FGFR2). We supposed whether the interaction of cordycepin with FGFR2 led to the inhibition of FGFR2 phosphorylation. The result showed that cordycepin suppressed the phosphorylation of FGFR2 (Fig. 4E). In addition, we also found that FGFR2 inhibitor AZD4574 could impede the cell viability of BxPC-3 cells (Figs. 4F, 4G). The observation above supports the hypothesis that aFGF plays a key role in cordycepin-driven cell growth inhibitory effects.

Cordycepin caused cell death via inhibiting ERK pathway

To confirm the molecular mechanism of cordycepin-induced cell death, we examined the effect on ERK signaling pathway, one of the downstream pathways of FGFR2. Treatment of BxPC-3 cells with 100 $\mu$mol·L$^{-1}$ cordycepin for 12 or 24 h significantly decreased the phosphorylation of ERK and the expression of Ras ($P < 0.05$; Fig. 5A). In addition, the transcription factors (c-Fos, c-myc, stat1) implicated in ERK signaling were downregulated after cordycepin treated (Fig. 5B). When FGFR2 was inhibited by its inhibitor, AZD4547, the ERK phosphorylation was decreased (Fig. 5C). We used the MEK inhibitor PD98059 which can inhibit ERK phosphorylation to treat BxPC-3 cells (Fig. 5D). After PD98059 (50 or 100 $\mu$mol·L$^{-1}$) treatment, the growth and mi-
The expression of ERK signaling involved transcription factors were decreased in response to PD98059 as cordycepin did (Fig. 5G). Importantly, the cell cyclin-dependent kinase inhibitor p21 was activated and cyclin A2 was inhibited after the treatment of PD98059 (Fig. 5H). These results suggest that anti-tumor effects of cordycepin depend on FGFR-ERK signaling.

Based on the above results and the fact that cordycepin impeded the growth of BxPC-3 xenografts (Fig. 1E), we hypothesized that the downregulation of FGFR/Ras/ERK signaling by cordycepin may attribute to the inhibition of tumor growth in vivo via interrupting FGFR /Ras /ERK signaling pathway.
growth in vivo. In order to address this question, immunohis-
tochemistry and Western blotting were employed to examine
the related proteins in tumor tissue. The staining of cell pro-
liferation marker Ki67 was lower in cordycepin treatment
group compared to the control group (Fig. 6A). In addition,
the phosphorylation of ERK in xenografted tumor tissues was
downregulated after cordycepin treatment (Fig. 6B). Com-
pared to the control group, the expression level of Ras and

ERK phosphorylation was downregulated in cordycepin-trea-
ted xenografted tumors (Fig. 6C), which was consistent with
in vitro results in response to cordycepin. These data sug-
Sected that cordycepin exerted anti-tumor effect in vivo might be through blocking FGFR/Ras/ERK signaling pathway.

Discussion

Pancreatic ductal adenocarcinoma is notorious for lack-
In this study, we showed that cordycepin inhibited the migration of pancreatic cancer cell BxPC-3 in vitro. Also, cordycepin impeded BxPC-3 cells growth in vitro and in vivo by targeting FGFR2 and multiple signaling pathways.

We found that cordycepin treated-BxPC-3 cells released larger amount of cytochrome c from mitochondria to cytosol. Previous studies have shown that the release of cytochrome c could stimulate caspase-9 and caspase-3 and then trigger cell apoptosis [27-30], as we have seen in our study. The mRNA levels of FasL and Bax were upregulated after cordycepin treatment. It was reported that ERK Mitogen-activated protein kinase (MAPK) cascades were related to cell survival, proliferation, and differentiation [31]. In this study, ERK phosphorylation and Ras was inhibited by cordycepin in BxPC-3 cells. These results suggested that cordycepin triggered apoptosis via activating caspase signaling and affecting MAPK cascades in BxPC-3 cells.

Once DNA damage was triggered, ATM, ATR and Check point kinase2 (Chk2) was activated to regulated many cellular processes. We demonstrated that phosphorylation of ATM, ATR and Checkpoint2 (Chk2) was significantly upregulated by cordycepin (Fig. 3F). Afterwards, the activated Chk2 leaded to downregulation of CDK2 and Cyclin A2. Accordingly, these data suggested that cordycepin was ATM/ATR dependent to induce cell cycle arrest.

Aberrant FGFR signaling is a common phenotype in a variety of solid tumors and here is evidence that targeting FGFR could be therapeutically beneficial across PDAC [36]. In our study, cordycepin could strongly bind to FGFR2, the affinity of cordycepin to FGFR2 is similar to that of aFGF to FGFR2 (Figs. 4C, 4D). FGFRs activated various signaling pathways.
pathways, including ERK and PI-3 kinase signaling cascades \(^{[37, 38]}\). FGFR2 inactivation by cordycepin only led to disruption of ERK signaling pathway. Meanwhile, the ERK phosphorylation was also inhibited by FGFR2 inhibitor (AZD4547) in BxPC-3 cells (Fig. 5C). Furthermore, cell cycle was arrested by MEK inhibitor (PD98059) via activating p21 and inhibiting cyclin A2 (Fig. 5H). FGFR activation had been reported to recruit PI-3 kinase \(^{[39]}\). However, in our study, cordycepin treatment had no influence on PI-3 kinase signaling pathway (Fig. S1). The experimental results indicated that cordycepin targeted FGFR2 to impede Erk MAPK signaling pathway which was a novel regulatory mechanism inhibited BxPC-3 cells growth. Importantly, to our knowledge, in vivo model was firstly studied to evaluate anti-tumor efficacy of cordycepin on pancreatic cancer.

Conclusions

Taken together, Cordycepin could be a potential candidate for the treatment of pancreatic ductal adenocarcinoma.

References


