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Fenofibrate inhibits the growth of prostate cancer through regulating autophagy and endoplasmic reticulum stress

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ABSTRACT

Fenofibrate is a fibric acid derivative which exhibits a role of peroxisome proliferator-activated receptor-alpha agonist. It is widely utilized in therapy of hyperlipidemia and hypercholesterolemia. Its anticancer function is discovered in recent years. However, the role of fenofibrate in prostate cancer (PCa) is poorly understood. In this study, we investigated the function and mechanism of fenofibrate in PCa cells. Firstly, fenofibrate treated PCa cells showed more apoptosis compared with the control group. Further, we found that fenofibrate induced autophagy but finally blocked its complete flux in PCa cells through regulating AMPK-mTOR pathway. The intermediate metabolite from uncompleted autophagy induced endoplasmic reticulum stress (ER stress) via PERK and IRE1 signalings. In vivo mice model confirmed that fenofibrate inhibited the growth of PCa. This study suggests that fenofibrate is an effective inhibitor of PCa by regulating autophagy and ER stress.

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1. Introduction

Prostate cancer (PCa) is the most common cancer of genital system. In developed country, it is the second cause of cancer related death of males [1]. Research on molecular mechanisms of prostate cancer will help us understand the development and progression of prostate cancer.

Fenofibrate is a fibric acid derivative. Due to its regulational function of glucose and lipid metabolism, it was used in therapy of hyperlipidemia and hypercholesterolemia [2]. This agent exhibits a role of peroxisome proliferator-activated receptor-alpha agonist, and it has been implicated in the inhibition of cancer cells. Fenofibrate could inhibit the growth of cancer cells [3], inhibit the movement and metastases of cancer cells [4], inhibit the tumor angiogenesis [5]. In the prostate cancer cell line, fenofibrate was reported to reduce the expressions of androgen receptor (AR) and AR target genes [6], which indicated the anticancer role of fenofibrate in prostate cancer. However, how fenofibrate exerts antiproliferativeeffects in prostate cancer remains unclear. By activating autophagy related molecular signaling, fenofibrate could induce autophagy in normal cells [7,8]. In prostate cancer cells, here we report that it induced autophagy but finally blocked its complete flux.

Endoplasmic reticulum (ER) is a cell organelle where synthesize and fold proteins. A variety of physiological and pathological changes can be collectively called "ER stress". When ER stress perturbs ER homeostasis, the ER will mount the unfolded protein response (UPR) as an adaptive and protective response [9,10]. PKR-like eukaryotic initiation factor 2α kinase (PERK), inositol-requiring enzyme-1 (IRE1) and activating transcription factor-6 (ATF6) are the three crucial proteins during the UPR. When PERK are activated, it phosphorylates the eIF2α (eukaryotic translation initiation factor 2α) and inhibits protein translation [9]. IRE1α is one of isoforms of IRE1 which expressed more ubiquitously, and its active form is phosphorylated IRE1α (p-IRE1α) [10]. Active IRE1 recruits signaling molecules which engaged in survival and inflammatory process. Processed ATF6 acts as an active transcription factor in the UPR [11]. These three branches of the UPR help cells to resolve ER stress. However, if the ER function is severely impaired, it will elicit apoptotic signals. C/EBP homologous protein (CHOP), also known as

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growth arrest and DNA damage-inducible gene 153 (GADD153), is a crucial component of the ER stress-mediated apoptosis pathway. CHOP is regulated by ER stress through not only inducing expression of CHOP, but also undergoing stress-induced phosphorylation of the CHOP protein. Phosphorylated CHOP has enhanced transcriptional activation in the apoptotic event [12].

Here, we show that fenofibrate inhibited the complete autophagy and induced ER stress-mediated cell apoptotic death with CHOP signaling. These results suggest the relationship between apoptosis and ER stress signals in prostate cells under fenofibrate treatment.

2. Materials and methods

2.1. Cell culture and treatment

The human PCa cell lines PC-3 were purchased from KeyGene Biotech (Nanjing, China). Cells were cultured in RPMI-1640 supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μg/ml streptomycin at 37 °C in a humidified atmosphere with 5% CO2.

2.2. Reagents and antibodies

Fenofibrate were purchased from Sigma Chemicals. Antibodies (p-eIF2a, p-IRE1a, CHOP, LC3, p62, p-AMPK and p-mTOR) were purchased from Cell Signaling Technology. Goat anti-rabbit and rabbit anti-goat IgGhorseradish peroxidase (HRP)-conjugated secondary antibodies were purchased from Beyotime Biotechnology. Apoptosis detection kit was purchasedfrom BD.

2.3. Western blot analysis

Samples were homogenized in a lysis buffer containing a

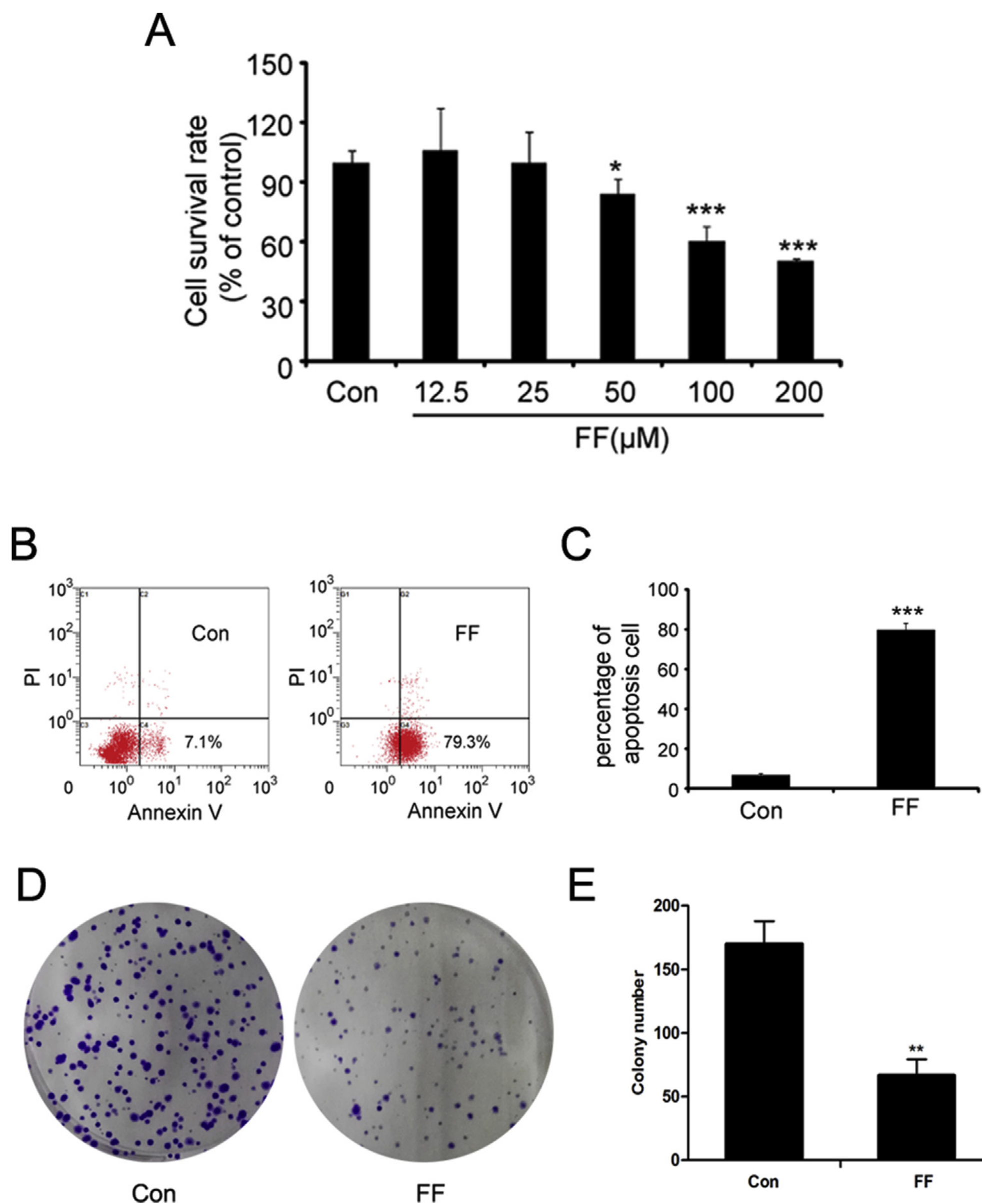

Fig. 1. Fenofibrate induced apoptosis in prostate cancer cells. 1a. Growth of prostate cancer cells PC-3 was inhibited following treatment with different concentrations of fenofibrate. 1b and c. After be cultured with fenofibrate, apoptosis of prostate cancer cells measured by flow cytometry analysis using Annexin-FITCand PI staining. 1d and e. Colony formation revealed that the number of prostate cancer cells are reduced by fenofibrate treatment. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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