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Review Article

Fatty Acid Synthase Inhibitor Cerulenin Suppresses Colorectal Cancer in Combination with Oxaliplatin

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Abstract

Fatty acid synthase (FASN) is highly expressed in many kinds of human cancers, and the potential use of FASN inhibitors were reported. Colorectal cancer (CRC) is one of the most common cancers with over one million new cases per year. The main cause of death by CRC is distant metastasis, especially liver metastasis. The effective chemotherapy for CRC is required worldwide. Expression of FASN was evaluated in both murine and human CRC cell lines. Cerulenin, a natural inhibitor of FASN, induces apoptosis in these cell lines. The ability of cerulenin to prevent the development of liver metastases of CRC cell lines was investigated. The number and size of metastatic CRC in the liver are significantly reduced by treatment with cerulenin. Oxaliplatin is one of the best chemotherapeutic agents of CRC. Cerulenin has a synergistic effect with oxaliplatin in vitro and in vivo. Cerulenin treatment is associated with reduced levels of phosphorylated Akt in CRC cell lines, suggesting that inhibition of this signal transduction pathway might be involved in the chemopreventive activity of cerulenin. Based on this study, inhibiting FASN would be an effective strategy in treating liver metastases and unresectable CRC, especially in combination with oxaliplatin.

Keywords: Fatty Acid; Inhibitor; Colorectal Cancer; Cerulenin

Introduction

Colorectal cancer (CRC) is one of the most common cancers in the world. Around 90% of CRC deaths are caused by metastasis, not by primary solid tumors [1,2].The liver is the most frequent site of distant metastasis in CRC. Approximately 20% of patients have liver metastases when the primary tumor is diagnosed [3], and half of the patients ultimately develop liver metastases during the course of CRC [4]. In the treatment of liver metastases, hepatic resection is the only curative treatment. Unfortunately, only 10% to 25% of patients with liver metastases are candidates for liver resection because of tumor number, size or location [5,6]. Also, when curative resection of the metastatic CRC is performed, 30% to 50% of patients have a recurrence in the liver [7,8]. Systemic chemotherapy is the last hope for patients with unresectable liver metastases of CRC. Nowadays, combination regimens of infusion 5-FU with either oxaliplatin (e.g., Folinic acid, 5-Fluorouracil and Oxaliplatin (FOLFOX)) or irinotecan (e.g., Folinic acid, 5-Fluorouracil and Irinotecan (FOLFIRI)) are the popular regimens for metastatic CRC [9]. Recently, three biological agents were indicated for the treatment of colorectal cancer, such as bevacizumab [10], cetuximab [11], and panitumumab [12]. Though recent systemic chemotherapy advances prolong survival in patients with unresectable disease [13], long-term survivors treated with only chemotherapy are rare [14].

The cancer cell is different from normal cells in many points. In contrast to normal cells, the majority of fatty acids in malignant cells are derived from de novo lipogenesis that emphasizes the importance of upregulation of endogenous lipid biosynthesis in malignant transformation [15].

Fatty acid synthase (FASN)

Fatty acid synthase (FASN), the key enzyme of de novo lipogenesis, is significantly upregulated in many cancers including CRC [15]. In normal adults, FASN is mainly expressed in cells with lipid metabolisms, such as liver and adipose tissues [16].Under usual diet, the *de novo* fatty acid synthesis in the normal cell is rarely needed and the FASN protein level is low [17].FASN is a 270-kDa cytosolic enzyme containing seven catalytic domains [18].FASN synthesizes palmitate from one acetyl-CoA, seven malonyl-CoA and seven NADPH [16,17]. The expression of FASN has been found to be up-regulated in various human cancer cells including CRC [19-21]. FASN is elevated in aberrant crypt foci (ACF) compared with normal colonic mucosa [22]. Lipogenesis by cancer cells gives proliferative and survival advantages and drug resistance against chemotherapeutic drugs [23]. An increased expression of lipogenic enzymes is associated with a more aggressive metastatic phenotype in CRC [24]. Inhibition of lipogenesis targeting FASN induces apoptosis selectively in human cancer cells both *in vitro* and *in vivo* [25-27]. The differential expression of FASN, together with the different responses to FASN inhibition between cancer cells and normal cells, makes FASN a suitable target for cancer treatment. The pharmacological FASN inhibitors are cerulenin, C75, orlistat, luteolin and epigallocatechin-3-gallate (EGCG).

Various kinds of FASN inhibitors

Cerulenin is the first known FASN inhibitor, which is isolated from the culture filtrate of the fungus Cephalosporum caerulens [28-31]. It was originally used as an antifungal antibiotic and is a potent non-competitive irreversible inhibitor of FASN by binding to the active site of the KS domain [32-34]. Cerulenin treatment significantly

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decreases fatty acid synthesis and induces selective cytotoxicity in various types of cancer cells [35-37].

C75 is a chemically synthesized analogue of cerulenin [38]. C75 has significant anti-tumor effects against many types of cancer cells, including the human breast [38], prostate [36], and ovary [39], as well as renal carcinoma in xenograft animal models [40].

Orlistat is an anti-obesity drug approved by the U.S. Food and Drug Administration. Orlistat is also reported to inhibit FASN [41]. Several studies have shown that orlistat exhibits anti-tumor effects in many cancer cells *in vitro* and *in vivo* by inhibiting FASN activity [41-44]. Orlistathas a very poor solubility and oral bioavailability, and clinical application for cancer treatment is very difficult [45].

Luteolin, 3',4',5,7-tetrahydroxyflavone, is found in a variety of vegetables, fruits, and medicinal herbs. Luteolin has been shown to function as an anti-oxidant, anti-inflammatory, and anti-cancer agent [46]. Additionally, luteolin induces cell cycle arrest and apoptosis in the liver and lung cancercell lines [47,48]. Lim do Y et al. indicated that Luteolin inhibited HT-29 cell proliferation by inducing cell cycle arrest and apoptosis [49].

EGCG, which is green tea polyphenol, inhibits the activity of FASN [50,51]. EGCG induces apoptosis in human breast and prostate cancer cells [52-54]. EGCG suppresses FASN expression and downstream phosphatidylinositol-3-kinase (PI3K)/Akt pathway [55]. Recently, Maruyama T et al. revealed that EGCG strongly reduces liver metastasis of human CRC in SCID mice [56].

In this review, the effect of cerulenin on cell proliferation and apoptosis in murine CRC cell lines Colon 26 and CMT 93, and in human CRC cell lines HCT116 and RKO is discussed. The effect of cerulenin on the prevention of growth of liver metastatic lesions in mice and the synergistic effect of cerulenin and oxaliplatin are also discussed.

Dose-dependent inhibition of proliferation of CRC cell lines by cerulenin

Murata et al. [57] determined whether cerulenin treatment led to the inhibition of CRC cell proliferation. CRC cells were treated with various doses of cerulenin for 24 h, and cell viability was assayed using WST-8 assay and BrdU assay. Murine CRC cell lines Colon 26 and CMT93 were selected. As the dose of cerulenin increased from 100 to 200 μM, cell growth inhibition increased in a dose-dependent fashion in CRC cell lines. Shiragami et al. [58] evaluated human CRC cell lines HCT116 and RKO. Cerulenin-induced growth inhibition was found to be statistically significant in 12.5-100 μM of cerulenin.

Induction of apoptosis via activation of caspase-dependent pathway by cerulenin

The overexpression of FASN has been seen to cooperate with survival pathways, including the phosphatidylinositol-3-kinase (PI3K) / Akt pathway. CRC cell lines expressed FASN and phosphorylated Akt constitutively, and treatment of CRC cells with cerulenin suppressed FASN expression, dephosphorylated constitutive activated Akt, and increased cleaved caspase-3 in murine CRC cell lines Colon 26 and CMT 93, and in human CRC cell line HCT116 cells [57,58]. Inhibiting FASN decreases phosphorylation of Akt in ovarian cancer cells and suppresses human epidermal growth factor receptor 2 (HER2) in breast cancer cells [39,59]. The mechanism by which FASN inhibitor decreases Akt activation is still unclear, but one mechanism that is advocated is that fatty acids synthesized by FASN are incorporated into membrane phospholipids, which are known modulators of Akt activation [60,61]. FASN has a major role in the synthesis of phospholipids including phosphatidylinositol trisphosphate (PIP3) [62]. PIP3 binds to Akt and activates kinase phosphoinositidedependent protein kinase-1(PDK-1) with high affinity, and the phosphorylation of Akt is dependent on PIP3 [62].

Reduction of liver metastasis of CRC by cerulenin

Murata et al. [57] evaluated the potential effectiveness of cerulenin for metastatic liver tumors of the CRC cell line. By treatment with 30 mg/kg of cerulenin every 3 days, significant reduction of liver metastasis was observed. Tumor growth was significantly reduced by cerulenin administration. In the cerulenin group, apoptotic tumor cells were observed in the metastatic liver tumor.

Many efforts to treat xenograft cancers with cerulenin or its derivative of C75 were reported in ovary [63], prostate [36], mesothelioma [64], lung cancer [65], CRC [66,67], and murine CRC liver metastasis using cerulenin [57]. To investigate the physiological consequences of in vivo inhibition of FASN, Murata et al. [57] administered cerulenin (30 mg/kg body weight every 3 days) to mice by i.p. injection. In this amount there was no significant weight loss in the cerulenin treatment group. In the prior studies, the use of cerulenin or C75 was hampered by transient but severe anorexia and weight loss. Therefore, this compound could also limit use in the clinical setting [68,69]. Loftus et al. [68] reported that cerulenin treatment of 60 mg/kg daily for 7 days caused severe weight loss. Pizer et al. [63] reported that cerulenin treatment of 80 mg/kg per daily for 7 days caused severe weight loss. These reports suggest that 30 mg/kg every 3 days is acceptable for reducing side effects. At this amount,

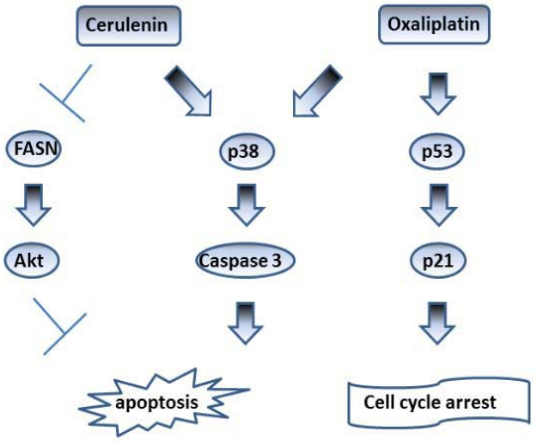

Figure 1: The scheme of the combination therapy consists of cerulenin and oxaliplatin. Cerulenin inhibits FASN and deactivates Akt. Cerulenin also activates p38. These reactions finally activate caspase-3 and induce apoptosis.Oxaliplatin induces the p53-p21 pathway which causes cell cycle arrest. In combination with cerulenin and oxaliplatin, p53-p21 pathway and p38 are activated, which causes cell cycle arrest and apoptosis. This figure was modified from [58].

serum triglyceride was significantly decreased in the cerulenin group. That means that FASN was actually inhibited in our animal model. Newly developed FASN inhibitor C93, which inhibits FASN but has no significant effect on fatty acid oxidation, is effective for treatment of human lung cancer xenografts. As a result, C93 does not cause anorexia or weight loss [70,71]. Although there is no report discussing CRC, C93 might be an effective agent for CRC treatment with minimal side effects.

Induction of apoptosis via activation of caspase-dependent pathway by cerulenin combined with oxaliplatin

Shiragami et al. [58] determined whether oxaliplatin treatment led to the inhibition of human CRC cell proliferation. CRC cells were treated with various doses of oxaliplatin for 24 h and as the dose of oxaliplatin increased from 0.5 to 2.5 μM, cell growth inhibition increased in a dose-dependent manner in CRC cell lines HCT116 and RKO.They also revealed that cerulenin and oxaliplatin have synergic antitumor effects. In a xenotransplant mouse model, the combination therapy, which consists of 2.5 mg/kg of oxaliplatin and 15 mg/kg of cerulenin, had the same tumor shrinkage effect compared to the oxaliplatin 5 mg/kg group; which means that by adding cerulenin, oxaliplatin dose could be reduced.

Shiragami et al. [58] determined the mechanism of the observed synergistic effect of cerulenin and oxaliplatin. Dephosphorylated constitutive activated Akt, activation of p38 and increased cleaved caspase-3 were observed in CRC cells with cerulenin treatment. Oxaliplatin induced p53-p21 pathway and p38, but did not increase cleaved caspase-3. In combination with cerulenin and oxaliplatin, p53-p21 pathway and p38 activation occurred and induced caspase-3 cleavage, finally causing apoptosis. Figure 1 shows the scheme of the combination therapy consisting of cerulenin and oxaliplatin.

p38 MAP kinase is a member of the MAP kinase family and is activated by a variety of cellular stresses, including osmotic shock, inflammatory cytokines, UV light and growth factors [72-76]. Activated p38 MAP kinase appears to have multiple targets in the apoptotic pathway. p38 MAP kinase activates caspase and induces apoptosis [77]. Oxaliplatin activates p38 MAP kinase phosphorylation in human CRC [78]. The p53 protein plays a pivotal role in the maintenance of genomic stability [79,80]. Activation of p53 can lead to either cell cycle arrest and DNA repair or apoptosis [81]. DNA damage induces p53 activation and activated p53 up-regulates p21 transcription [82].

Oxaliplatin is a most promising chemotherapeutic agent, which consists of FOLFOX for unresectable CRC [9,83]. Neurotoxicity is a severe and treatment-limiting side-effect of several chemotherapeutic agents [84]. Sensory neurotoxicity is a potentially limiting factor in many patients who might otherwise achieve good results with oxaliplatin therapy [85]. In patients with severe neurotoxicity, reduction or discontinuation of oxaliplatin is often required. This study revealed that cerulenin can potentiate oxaliplatin in *in vitro* and *in vivo*. Cerulenin is one of the better combinations with oxaliplatin, which achieves reduction of oxaliplatin and long-term tolerated chemotherapy for unresectable CRC.

Conclusion

In conclusion, cerulenin has a cytotoxic effect on murine and human CRC cell lines. Moreover, cerulenin potentiated cytotoxicity of oxaliplatin. Cerulenin would be effective in treatment of unresectable CRC, especially liver metastasis. Also, cerulenin is synergistically effective in combination with oxaliplatin, which reduces the dose of oxaliplatin and would make it possible for the patient to endure the chemotherapy over a longer period.

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