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Mini-review

Biological effects of conjugated linoleic acid on obesity-related cancers

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ABSTRACT

Considerable evidence suggests that obesity and overweight play an important role in cancers i.e., breast, colon, endometrial, kidney, pancreatic, and liver. In fact, overweight and obesity are now established risk factors for cancer and cancer-related mortality. Conjugated linoleic acid (CLA) consists of a group of positional and geometric fatty acid (FA) isomers that are derived from linoleic acid (LA) [18:2(*n*-6)], which occurs naturally in food with a high concentration in products from ruminant animals. Studies in both *in vitro* cell and *in vivo* animal models have shown that CLA, specifically cis 9-trans 11 and trans 10-cis 12 CLA isomer, inhibits the initiation and promotion stages of carcinogenesis, suggesting that CLA has received considerable attention as a chemopreventive agent. In this review, the biological activities and multiple mechanisms of CLA in obesity-related cancers including cell lines, animal models and clinical observations are explained.

Contents

1. Introduction

During the past several decades, the percentage of overweight and obese adults and children has increased markedly [1]. Obesity is associated with increased risks of cancers of the breast, colon, endometrial, kidney, pancreatic, and liver cancer [2–7]. One study, using NCI Surveillance, Epidemiology, and End Results (SEER) data, estimated that, in 2007 in the United States, about 34,000 new cases of cancer in men (4 percent) and 50,500 in women (7 percent) were due to obesity [8]. The percentage of cases attributed

Abbreviations: AEH, atypical endometrial hyperplasia; CLA, conjugated linoleic acid; ERα, estrogen receptor alpha; GRAS, Generally Regarded as Safe; LA, linoleic acid; LXR, Liver X Receptor; PE, polyethyleneimine; ROS, reactive oxygen species; RCC, renal cell carcinoma; SCD, stearoyl-CoA desaturase; SEER, Surveillance, Epidemiology, and End Results; UCC, urothelial cell carcinoma.

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to obesity varied widely for different cancer types but was as high as 40 percent for some cancers, particularly endometrial cancer and esophageal adenocarcinoma [9]. Also, several studies have explored why being overweight or obese may increase cancer risk and growth, suggesting that people who are obese have more fat tissue that can produce hormones, such as insulin or estrogen, which may cause cancer cells to grow [10–12].

Conjugated linoleic acid (CLA) is a family of at least 28 isomers of linoleic acid found especially in the meat and dairy products derived from ruminants [13]. As the name implies, the double bonds of CLA are conjugated [13,14]. CLA was discovered accidentally by researchers looking for mutagens in beef [15]. In 1979, researchers from the University of Wisconsin applied a beef extract to mice skin [16]. The mice were then exposed to a strong carcinogen and when the researchers counted the number of tumors developed by the mice 16 weeks later, they found that the mice exposed to the beef extract had 20% fewer tumors [16]. The identity of this anti-carcinogen was not discovered till almost a decade later in 1987 [16]. Micheal Pariza, the scientist who discovered CLA, later remarked that "few anti-carcinogens, and certainly no other known fatty acids, are as effective as CLA in inhibiting carcinogenesis in these models" [17,18]. Although CLA is best known for its anti-cancer properties, researchers have also found that the cis-9, trans-11 form of CLA can reduce the risk for cardiovascular disease and help fight inflammation [19,20]. CLA is also known for its body weight management properties, which include reducing body fat and increasing lean muscle mass [21]. Over 30 clinical studies have been published investigating the effect of CLA on weight management [22]. The trials have quite variable designs, which lead to inconsistency [22]. However a meta-analysis conducted in 2007 clearly shows that CLA does indeed have a small impact on fat mass [23]. In July 2008, CLA received a no objection letter from the FDA on it Generally Regarded as Safe (GRAS) status for certain food categories including fluid milk, yogurt, meal replacement shakes, nutritional bars, fruit juices and soy milk [24]. With GRAS status, food companies are now able to add CLA to products in these food categories [24].

This review primarily focuses on current CLA publications along with a number of beneficial effects of CLA on obesity-related cancers (Fig. 1). Although scientific studies mainly investigated the effects of individual CLA isomers on cancer prevention *in vitro*, this review summarizes the effects of both individual and mixture of CLA isomers on the development and progression of cancer in animal *in vitro* and *in vivo*. Also, this review provides the biological activities and multiple mechanisms of CLA in clinical observations.

2. CLA and breast cancer

Breast cancer is the malignancy most frequently diagnosed and is the second most common cause of cancer deaths among women in worldwide [25]. Also, approximately 230,000 women are predicted to be diagnosed in the USA with invasive breast cancer in 2012 and 39,500 deaths are expected, suggesting a need for new therapeutic approaches [25,26]. CLA has been shown to down-regulate cell proliferation in breast cancer. Specifically, it has been shown that trans 9-trans 11 CLA isomer suppresses cell proliferation and induces apoptosis via Liver X Receptor (LXR) in MCF-7 breast cancer cell lines [27]. Trans 10-cis 12 CLA isomer has also been shown to inhibit cell growth and invasion through PI3K/Akt signaling pathway in MCF-7 breast cancer cell lines [28]. Moreover, it has been demonstrated that treatment of the cells with trans 9-trans 11 and trans 10-cis 12 CLA isomer significantly decrease stearoyl-CoA desaturase (SCD) protein levels in both

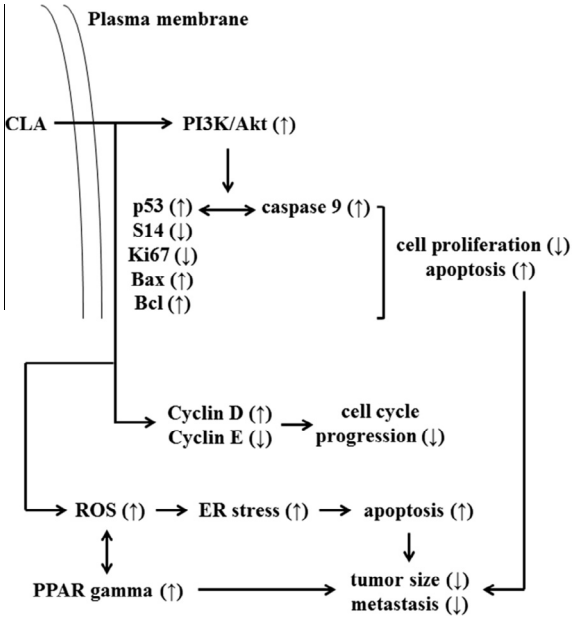

Fig. 1. Proposed mechanism of CLA on obesity-related cancers animal *in vitro*, animal *in vivo* and human *in vivo*. CLA activates PI3K/Akt signaling and stimulates tumor suppressor gene, p53, which up-regulates caspapse 9 in animal *in vitro*. Also, CLA down-regulates S14 and Ki67 in human *in vivo* but up-regulates Bax and Bcl in animal *in vivo*. These pathways decrease cancer cell proliferation, increase cancer cell apoptosis, and inhibit tumor growth. CLA also participates in cell cycle progression by modulating cyclin D and E expression in animal *in vitro*. CLA generates ROS and ER stress in animal *in vitro* and this pathways increases cancer cell apoptosis. Also, CLA increases expression level of PPAR gamma in animal *in vitro*, animal *in vivo* and human *in vivo*, suggesting that CLA decreases tumor size and metastasis. This figure was modified according to the signaling pathways previously described by other groups.

MDA-MB-231 and MCF-7 breast cancer cell lines [18]. Previously, I have also demonstrated that CLA mixture stimulates apoptosis via p53-mediated signaling pathway in MCF-7 breast cancer cell lines [29]. Recently, the anti-cancer activity of CLA was investigated on nude mice xenografted human breast MCF-7 tumors, following intravenous injections of CLA, showing that CLA displays a significantly enhanced tumor growth inhibition effect, which is consistent with the observations in *in vitro* cytotoxicity tests [30]. Also, this report observed that coupling of gemcitabine (GEM), a nucleoside analog agent, with CLA has a longer plasma half-life, a higher bioavailability and a stronger anti-tumor activity compared to that of unmodified-GEM and/or -CLA in MCF-7 cells-injected female BALB/c nude mice [30]. These results suggest that the novel CLA–GEM coupling prepared would be a promising pro-drug of CLA for future clinical use of breast cancer treatment. The major finding in a proof of principle study is that preoperative administration of at least a 10 day course of treatment with of 7.5 g/day CLA significantly reduced expression of S14 and reduced the proliferation marker Ki-67 in primary invasive breast cancer tissue [31]. This report demonstrated, clinical study (Women with Stage I-III- breast cancer) that breast cancer tissue expression of S14, but not fatty acid synthase and lipoprotein lipase, was decreased after a short course of treatment with 7.5 g/day CLA [31]. This metabolic dependency should be explored as it opens up the possibility of a future line of novel investigate drugs for breast cancer management. The limitations of these two studies above are relatively small sample size and short duration of CLA treatment, suggesting that further exploitation of this suppression *in vivo* may require an escalating dosing/timing/sampling study design. Despite these limitations, CLA consumption has been shown to be safe and well-tolerated, 7.5 g/day for up to 20 days