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A Potential Anticarcinogenic Agent: Conjugated Linoleic Acid (CLA)

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Despite the immense expenditure worldwide on cancer research during the past 30 yr, and the notable advances made in this area, the death rate for patients with invasive and metastatic carcinoma of the colon, breast, lung, pancreas, prostate, and bladder have not decreased very much (Sporn, 1996). Most cancers have a multifactorial etiology with both genetic and environmental factors contributing to risk. A review of epidemiologic studies suggests that about 35% of cancer deaths are attributable to diet with a range of 20 to 60% for the various sites (Doll, 1992). The food we eat contains components that may either help cause or help prevent cancer (Doll, 1996).

CLA (Conjugated Linoleic Acid): The acronym CLA refers to various positional and geometric isomers of linoleic acid (*cis*-9, *cis*-12-octadecadienoic acid) for which the two double bonds have a conjugated arrangement instead of methylene interruption (Parodi, 1999). CLA consists of eight possible geometric isomers, however, two (c-9, t-11 and t-10, c-12) tended to be the predominant isomers naturally found in animal tissues. The natural origin of CLA was shown to be microbial isomerization of dietary linoleic acid by rumen microorganisms. Hence, ruminant species and their products were found to be the richest sources of CLA (Cook and Pariza, 1998). Dairy products are recognized as major dietary sources of CLA, of which c-9, t-11-18:2 is the major isomer, representing 80-90% of total CLA in bovine milk (Chin *et al*., 1992). CLA has attracted considerable attention because of its potential beneficial effect as anticarcinogenic agent.

Anticarcinogenic Properties of CLA: Interest in CLA as an anticarcinogen grew from the observation by Pariza and his colleagues that both raw and grilled ground beef contained a component that could inhibit mutagenesis. This inhibitor was later shown to possess anticarcinogenic properties (Pariza, 1997). The anticarcinogen was purified and identified as four isomers of linoleic acid with conjugated diene unsaturation (Ha *et al*., 1987). These isomers of CLA were synthesized by base-catalyzed isomerization of linoleic acid and used subsequently in a number of studies. The results of them showed that the isomers suppressed tumor development in a range of animal models and inhibited growth in many cancer cell lines (Parodi, 1997).

In rat mammary tumor models, CLA has proved a potent anticarcinogen and feeding with CLA resulted in a significant reduction in tumor incidence (Ip *et al*., 1991; 1994). These two experiments demonstrated that CLA acted in a dose-dependent manner at up to 1 g/100 g of diet after which there was no further benefit. Inhibition of mammary tumors by CLA was not influenced by the amount or type of fat in the diet (Ip *et al*., 1996). It is important to underline from these experiments that feeding CLA only during the postweaning and peripubertal period and before carcinogen administration affords protection against subsequent mammary tumor development. On the other hand, when rats with mature mammary glands do not receive CLA supplementation until the time of tumor induction, the feeding for life is required to gain protection.

In cell culture studies, physiologic concentrations of CLA inhibited the proliferation of human malignant melanoma, color ectal and breast cancer cells (Shultz *et al*., 1992) and three lung adenocarcinoma cell lines (Schonberg and Krokan, 1995).

Mechanisms for CLA action, although often studied, are still largely unresolved. Various studies have suggested that CLA may act by antioxidant mechanisms, prooxidant cytotoxicity, inhibition of nucleotide and protein synthesis, reduction of cell proliferative activity and inhibition of both DNA-adduct formation and carcinogen activation (Parodi, 1999). Holman *et al*. (1991) claim that unusual isomers of polyunsaturated fatty acids can inhibit the metabolism of normal polyunsaturated acids, such as linoleic acid, at many steps in the normal metabolic cascade. They can also be precursors of unusual eicosanoids or inhibit synthesis of normal eicosanoids. The most important eicosanoid precursor is arachidonic acid, which is synthesized from linoleic acid (a promoter of mammary tumors) by elongation and desaturation. Eicosanoids derived from the arachidonic acid cascade have been implicated in mammary tumor development, possibly by interaction with growth factors and oncogenies. Mammary tumors can be inhibited by agents that interfere with the arachidonic acid cascade (Rose, 1997). The anticarcinogenic action of CLA may, in part, be explained by its ability to inhibit arachidonic acid-derived eicosanoids.

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