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Short Communication

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Correlates of Breast Cancer and Indole-3-Carbinol: Medicinal Development and Strategies of Natural Products

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Abstract

Estrogen-responsive breast cancer cells, such as MCF7 and T47D cells, express both estrogen receptor ER and ERß. Indole-3-carbinol (I3C) strongly down-regulated ER protein and transcript levels, without altering the level of ERß protein, in both cell lines. In cells transfected with the ER promoter linked to a luciferase gene reporter, I3C ablated ER promoter activity1-5. Dietary indole-3-carbinol prevents the development of estrogen-enhanced cancers including breast. Whereas estrogen increases the growth and survival of tumors, indole-3-carbinol causes growth arrest and increased apoptosis and ameliorates the effects of estrogen. In these findings best use indole-3-carbinol together with other nutrients (genistein) to achieve maximum benefits for cancer prevention. Investigator evaluated whether genistein, which is the major isoflavonoid in soy, would alter the ability of indole-3-carbinol/DIM to cause apoptosis and decrease expression driven by the estrogen receptor (ER)-alpha.

Synergistic effect of indole-3-carbinol and genistein for induction of GADD expression, thus increasing apoptosis, and for decrease of expression driven by ER-alpha. Because of the synergistic effect of indole-3-carbinol and genistein, the potential exists for prophylactic or therapeutic efficacy of lower concentrations of each phytochemical when used in combination. I3C inhibits the enzyme elastase. High levels of elastase in breast cancer cells are suggestive of a poor prognosis because elastase shortens cyclin E, a cellular chemical involved in controlling the cell cycle, and the shortened version of cyclin E speeds up the cell cycle, therefore making cancer cells proliferate faster.I3C prevents the elastase shortening of cyclin E, thus halting the growth of breast cancer cells.

Introduction

Indole-3-carbinol, a compound that occurs naturally in vegetables such as cabbage, induces the expression of cytochrome P-450 1A1, which shifts the estrogen metabolic pathway in favor of C-2 hydroxylation and away from the formation of 16 hydroxyestrone, a suspected endogenous carcinogen. Increased 16-hydroxylation of estrogen is associated with greater risk of breast cancer. The production of 4-hydroxyestrone is also inhibited by I3C. I3C can also induce a G1 cell-cycle arrest of human MCF-7 breast cancer cells that is accompanied by the selective inhibition of cyclin-dependent kinase 6 expression and stimulation of p21 gene expression. In indole-treated cells, a fraction of I3C was converted into natural diindole product -3-3'- diindolylmethane, which accumulates in the nucleus; suggests that DIM may have a role in the transcriptional activities of I3C. Indole-3-carbinol from Brassica vegetables also contains micronutrients that provide additional DNA protection from reactive oxygen species the growth of breast cancer cells. Oxidative stress is believed to have a complex and multifunctional role in the development of most age related chronic diseases. In the context of carcinogenesis, increased oxidative stress may damage DNA beyond DNA repair capacity, leading to the clonal expansion of initiated cells.

Estrogens metabolic pathway

Estrogens are metabolized by a series of oxidizing enzymes in the cytochrome P450 family. These are the detoxification enzymes that break down all manner of drugs, hormones, and environmental toxins into generally less harmful metabolites. Scientists have discovered how the parent estrogen compounds are modified in the C-2, C-4, or C-16 pathways. Particular enzymes within this family, namely cytochrome P450 1A1 and 1A2, are activated or stimulated, then more parent estrogens are metabolized into C-2-hydroxylated compounds. However, if cytochrome P450 3A4 and 1B1 are activated, then more C-4 and C-16 are produced. The C-16-alpha version tends to damage DNA and cause abnormal cellular proliferation, while the C-2 metabolite has less estrogenic activity.2,3 If the proportion of C-16-alpha-hydroxyestrone can be decreased while the C-2-hydroxyestrone is increased-changing the ratio between the two-cancer risk could be reduced 7,10 . Estrogen increases the growth and survival of tumors, I3C causes growth arrest and increased apoptosis and ameliorates the effects of estrogen. Our goal is to best use I3C together with other nutrients to achieve maximum benefits for cancer prevention. This study has examined the possibility that induction of growth arrest in response to DNA damage (GADD) in genes by diindolylmethane (DIM), which is the acid-catalyzed condensation product of I3C, promotes metabolically

stressed cancer cells to undergo apoptosis. Investigator evaluated whether genistein, which is the major isoflavonoid in soy, would alter the ability of I3C/DIM to cause apoptosis and decrease expression driven by the estrogen receptor (ER)-alpha. So I3C is also known to support the liver's detoxification processes as well as normal cellular reproduction.

Conclusion

Indole-3-carbinol inhibits enzyme elastase which is responsible for the proliferation of cancer cells. I-3-C favours the C2-metabolic pathway and inhibits C4 and C16 metabolic pathways.I-3-C shows beneficial effect on oral administration. In contrast to Tamoxifen which is antiestrogenic drug, I-3-C shows no side effects like hot flashes, symptoms of menopause, blood clotting, stroke and uterine cancer. Along with the treatment of breast cancer,I- 3-C shows antioxidant and blood thinning property.I-3-C enhances the activity at low frequency doses with isoflavanoids [1-3].

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