A COMBINATION OF OMEGA-3 FATTY ACIDS AND A BUTYRATE-PRODUCING FIBER MITIGATES COLON CANCER DEVELOPMENT

J.R. Lupton[1], L.M. Sanders[1], J.C. Mann[1], N. Popovic[1], A.A. Glagolenko[3], L.A. Davidson[1], L.A. Braby[3], J.R. Ford[3], R.J. Carroll[2], N. Wang[2], R.S. Chapkin[1] and N.D. Turner[1]
[1]Faculty of Nutrition, [2]Statistics Dept., [3]Nuclear Engineering Dept., Texas A&M University, College Station, TX

INTRODUCTION

Galactic cosmic radiation-induced cancer risk is a major limitation to long-duration missions, with colon cancer development being a likely target since it is the second leading cause of death from cancer in the United States today and strikes men and women equally. In our unique combined model of a colon specific carcinogen (azoxymethane; AOM) with or without an oxidative DNA damaging insult (1 Gy, 1 GeV/nucleon Fe ions), the addition of radiation resulted in early termination of a significant portion (18.4%) of the irradiated rats compared to rats treated only with AOM. However, at each stage of the tumorigenic process (initiation, promotion, and final tumor development) a diet high in fish oil (omega 3 fatty acids) and pectin (a fiber fermented to butyrate) was able to protect against colon carcinogenesis.

MATERIALS AND METHODS

Rats (n = 560 male Sprague Dawley) were divided into two groups (+/- irradiation) and consumed one of four diets (fish oil or corn oil as the lipid source; pectin or cellulose as the fiber source). They were terminated at three different time points: initiation stage (0 – 24 h post AOM); promotion stage (6 wk post AOM); and tumor stage (31 wk post AOM). DNA damage was assessed at initiation, aberrant crypt formation at progression and tumors at the tumor stage. In addition, markers of colon cytokinetics were assessed (cell proliferation, apoptosis and differentiation) and mucosal and fecal samples were collected from the rats to measure changes in colon cell gene expression patterns over time using microarray technology.

RESULTS

The combined fish oil/pectin diet was protective at each stage of the colon tumorigenic process. At the initiation stage, fish oil resulted in lower levels of the oxidative DNA adduct 8-OHdG than did the corn oil diets ($P < 0.001$). At the promotion stage (aberrant crypt formation), the fish oil/pectin diet produced a lower number ($P< 0.05$) of high multiplicity aberrant crypt foci (the ones most likely to result in colon tumors). A decrease in colon cell apoptosis is known to accompany the development of colon cancer, and radiation reduced ($P = 0.034$) the proportion of colon cells undergoing apoptosis. In contrast, pectin upregulated apoptosis ($P = 0.020$). At the final tumor stage, the fish oil/pectin diet resulted in only 1/3 of the relative risk for tumor development as compared to the corn oil/cellulose or corn oil/pectin diets ($P = 0.066$). In comparing gene expression profiles from mucosa, the fish oil/pectin diet vs the corn oil/cellulose diet showed significant changes in the expression of genes involved in lipid metabolism, nutrient transport and xenobiotic metabolism. Modifications to existing fecal polyA isolation procedures improved the quality and quantity of cRNA generated (~100-fold). An average of 13,000 were expressed at robust levels, with 19,000 genes having low to negligible expression.

CONCLUSIONS

Diets containing fish oil and/or pectin were effective in decreasing colon cell DNA damage, aberrant crypt formation, and tumors and could be considered an effective countermeasure against radiation-enhanced colon carcinogenesis. Fecal polyA can be used as a non-invasive measure of colonocyte gene expression.

ADDITIONAL INFORMATION

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