Strain- and Sex-linked Effects of Dietary Polyunsaturated Fatty Acids on Tumor Growth and Immune Functions in Mice

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ABSTRACT

In the present paper, we studied the influence of different levels of dietary polyunsaturated fatty acids (PUFA) on the immune system and tumor growth in young mice. Female BALB/c mice fed a PUFA-rich diet display an enhanced body growth, proliferative response to mitogens in vitro, and rate of growth of a spontaneous transplantable adenocarcinoma as compared to PUFA-poor diet-fed females. Such effects are, however, limited by sex and strain background genes located outside the H-2 complex. The influence of dietary PUFA content is evident in female but not in male BALB/c mice. Moreover, in female DBA/2 mice with the same haplotype (H-2d) of the major histocompatibility complex as that of BALB/c mice, low dietary PUFA determines a reduced tumor growth only, but it does not affect body growth and proliferative response to mitogens in vitro.

INTRODUCTION

Changes in the levels of PUFA affect the mitotic rate and thus modulate several cell activities involving mitosis. Variations in the culture medium PUFA concentration modulate the lymphocyte response to lectins as well as the proliferative rate of several cell clones. In vivo, s.c. injection or p.o. administration of PUFA has been shown to affect the lymphocyte blastogenic response to mitogens and to depress the phagocytic function of the reticuloendothelial system. High levels of dietary PUFA enhance the incidence of chemically induced tumors (4, 10, 14, 20) and the growth rate of transplantable tumors (3, 13, 21, 22), whereas low levels seem to have little influence on both events.

In this paper, we have examined the influence of PUFA-rich and PUFA-poor diets on young mice. It is shown that variations in PUFA intake influence body growth, the proliferative response to mitogens, and the growth rate of a transplantable adenocarcinoma. These effects, however, are strongly modulated by the sex and strain background genes of the animal.

MATERIALS AND METHODS

Mice. Syngeneic BALB/c (H-2d) and DBA/2 (H-2d) mice were purchased from Charles River Laboratories, Calco, Italy. They were about 2 weeks old and weighed 10 ±1 g at the beginning of the experiments.

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Diet. The composition of the PUFA-rich and PUFA-poor diets is shown in Table 1. The PUFA-rich diet contained 3% corn oil (34.3% linoleic acid; 49.6% oleic acid), with an unsaturated/saturated fatty acid ratio of 5.85. The PUFA-poor diet contained 3% coconut oil (traces of linoleic acid; 7.5% oleic acid) with an unsaturated/saturated fatty acid ratio of 0.09. Both diets were manufactured by Piccioni (Brescia, Italy), and their caloric value was the same (4.011 calories/g). Male and female mice were randomly divided into groups of 20 mice each and fed with either PUFA-rich or PUFA-poor diets given ad libitum. The quantity consumed and the weight of the mice were measured twice weekly.

Cell Preparation. After 40 and 80 days on PUFA diets, the animals were sacrificed by decapitation. Sterile single-spleen-cell suspensions were prepared, and RBC were osmotically lysed. Unless otherwise specified, cells were cultured in Roswell Park Memorial Institute Medium 1640 supplemented with 5% fetal bovine serum, 2 µg/mL streptomycin, penicillin (100 units/ml), concanavalin A, (type III; Sigma Chemical Co., St. Louis, Mo.) 20 µg/mL final concentration; or lipopolysaccharide from Escherichia coli 0111:B4, 5 x 10⁻⁴ M 2-mercaptoethanol. All reagents were obtained from Grand Island Biological Co. (Grand Island, N. Y.).

Cell Separation. Removal of phagocytic cells by carbonyl iron and magnet treatment was performed as described by Landolf et al. (17). Nylon wool purification was done as described by Julius et al. (15). Splenic macrophages were obtained by plating 10⁶ spleen cells in 20 ml of Roswell Park Memorial Institute Medium 1640 containing 10% fetal bovine serum on 100 x 25-mm Falcon plastic culture dishes (Becton-Dickinson, Mountain View, Calif.) for 6 hr at 37°C. The nonadherent cells were vigorously washed away, and adherent populations were removed by scraping with a rubber policeman.

Mitogen Response. Four x 10⁶ cells from spleen cell preparations were distributed among the flat-bottomed wells of a Falcon No. 3040 microtiter plate. Triplicate microcultures were incubated with or without phytohemagglutinin (Grand Island Biological Co.), 1:100 final dilution; concanavalin A, (type III; Sigma Chemical Co., St. Louis, Mo.) 20 µg/mL final concentration; or lipopolysaccharide from Escherichia coli 0111:B4 (Difco Laboratories, Detroit, Mich.), 80 µg/mL final concentration; for 56 hr at 37°C in a humidified CO₂ atmosphere before pulsing with 1 µCi of [³H]Thd (specific activity, 2 Ci/mmol; Sorin, Saluggia, Italy) for 16 hr. Cultures were harvested on paper filters with a semiautomatic suction device and counted by liquid scintillation spectrometry. Mitogen-induced DNA synthesis was expressed as the difference in incorporation of [³H]Thd between control (unstimulated) and test lymphocytes (stimulated) measured in cpm. Each determination was repeated at least 4 times, and a representative experiment is reported in the tables. S.D. is not reported, since only experiments in which it did not exceed 7% were considered.

Tumor Challenge. After 40 days on the diet, mice were...
challenged with a BALB/c adenocarcinoma (ADK-11) that originated spontaneously in a BALB/c female from our colony (8). Its earlier transplant generations were preserved by slow freezing and storage at −80°C. The tumor preparations used had been transplanted in syngeneic recipients no more than 10 times. BALB/c mice were given injections s.c. in the inguinal region of 0.2 ml of a single-cell suspension of 2 x 10⁴ living ADK-11 cells per ml. Previous observations had shown that this dose induces about 70% tumor incidence in BALB/c mice of the same age fed on a standard, balanced mouse diet (8).

Determinations of tumor regressions were never observed in mice with tumors >5 mm in mean diameter. Mice bearing tumors >20 mm in mean diameter were killed immediately. It should also be pointed out that tumor regressions were never observed in mice with tumors >5 mm in mean diameter.

Statistical Analysis. Groups of mice from each experiment were tested for significant differences in latency and survival times by a nonparametric Gehan ranking test (2).

RESULTS

Diet Effect on Body Growth. Groups of 20 male and female BALB/c mice weighing 10 ± 1 g were fed with PUFA-rich or PUFA-poor diets given ad libitum. With both diets, the mean food uptake increased during the first 10 days and then stabilized at about 2.5 ± 0.2 g/animal/day. However, while the caloric uptake per mouse was about the same in all groups, marked differences were observed in somatic growth rate. The mean body weight of the male BALB/c mice fed with either diet increased for the first 2 weeks and thereafter stabilized at 16 ± 0.5 g. PUFA-rich diet-fed female BALB/c displayed a similar growth pattern and stabilization at 18 ± 0.7 g. By contrast, the mean body weight of PUFA-poor diet-fed female BALB/c decreased after the initial 2-week period and stabilized at approximately two-thirds of that of the other BALB/c groups (Chart 1). These differences were not observed in the female DBA/2 groups, in which the mean food uptake was about 2.5 ± 0.3 g/animal/day. DBA/2 mice of both groups increased in weight at the same rate and reached a mean body weight of 22 ± 0.3 g after 60 days. These strain- and sex-linked discrepancies in growth pattern were observed on each of the 2 occasions the experiment was repeated.

Diet Effects on Proliferative Response to Mitogens. After 40 days, the proliferative response to mitogens displayed by unfractionated spleen cells from PUFA-rich and PUFA-poor diet-fed male and PUFA-poor diet-fed female BALB/c mice were similar (Table 2), whereas those from PUFA-rich-fed female BALB/c mice consistently displayed a response towards both B- and T-cell mitogens that was twice as high. When the test was performed after 80 days on PUFA diet, these differences were still evident although less marked in the case of concanavalin A. The response of fractionated spleen cell populations was tested to characterize the leukocyte populations involved in the proliferation differences observed after 40 days (Table 3). After macrophage-like cell removal by carbonyl iron treatment, PUFA-poor diet-fed females still displayed the highest response of the BALB/c groups. Moreover, such removal did not affect the ratios between the proliferation patterns in BALB/c groups as compared to that of unfractonated spleen cells. Similar findings were obtained by using spleen cells enriched for T-lymphocytes by passage through nylon columns.

A similar, progressive, and parallel inhibition of B- and T-lymphocyte proliferative response to mitogens was observed on adding to the cultures increasing numbers of macrophage-like spleen cells from the various PUFA diet-fed BALB/c mice
Dietary PUFA and Immune Function

Table 2

Proliferative response to mitogens by unfractionated spleen cells from BALB/c and DBA/2 mice fed a PUFA-rich and PUFA-poor diet for 40 and 80 days

<table>
<thead>
<tr>
<th>Strain</th>
<th>Sex</th>
<th>Diet</th>
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<th>LPS</th>
<th>PHA</th>
<th>Con A</th>
<th>None</th>
<th>LPS</th>
<th>PHA</th>
<th>Con A</th>
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<tbody>
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<td>PUFA-rich</td>
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<td>33</td>
<td>100</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>100</td>
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<td>16</td>
<td>100</td>
<td>48</td>
<td>100</td>
<td>4</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>PUFA-poor</td>
<td>2</td>
<td>18</td>
<td>55</td>
<td>8</td>
<td>2</td>
<td>15</td>
<td>55</td>
<td>8</td>
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<td>PUFA-rich</td>
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<td>28</td>
<td>100</td>
<td>85</td>
<td>100</td>
<td>4</td>
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<td>37</td>
<td>37</td>
<td>3</td>
<td>37</td>
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</table>

a Mitogen added.
b LPS, lipopolysaccharide 011:K:PHA, phytohemagglutinin; Con A, concanavalin A.
c The [%]H][dThd uptake is expressed as mean cpm x 10^3 of triplicate cultures. S.D. never exceeded ±7% of the mean and is therefore not reported.
d Numbers in parentheses, percentages of PUFA-rich diet-fed female mice (arbitrarily taken as 100%).

Table 3

Proliferative response to mitogens by carbonyl iron and magnet or nylon wool column-fractionated spleen cell population from BALB/c and DBA/2 mice fed PUFA-rich and PUFA-poor diets for 40 days

<table>
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<th>Sex</th>
<th>Diet</th>
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<th>PHA</th>
<th>Con A</th>
<th>None</th>
<th>LPS</th>
<th>PHA</th>
<th>Con A</th>
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<td>PUFA-rich</td>
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<td>52</td>
<td>100</td>
<td>40</td>
<td>100</td>
<td>37</td>
<td>100</td>
<td>37</td>
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<td></td>
<td></td>
<td>24</td>
<td>60</td>
<td>21</td>
<td>57</td>
<td>0.5</td>
<td>60</td>
<td>66</td>
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<td>22</td>
<td>50</td>
<td>19</td>
<td>63</td>
<td>0.4</td>
<td>48</td>
<td>61</td>
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<td>60</td>
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<td>PUFA-poor</td>
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<td>0.3</td>
<td>81</td>
<td>94</td>
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<td>19</td>
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</tbody>
</table>

a Mitogen added.
b LPS, lipopolysaccharide 011:BPHA, phytohemagglutinin; Con A, concanavalin A.
c The [%]H][dThd uptake is expressed as mean cpm x 10^3 of triplicate cultures. S.D. never exceeded ±7% of the mean and is therefore not reported.
d Numbers in parentheses, percentages of PUFA-rich diet-fed female mice (arbitrarily taken as 100%).

(data not shown). As previously reported, this suppressor activity of macrophages is dependent neither on cell overcrowding nor on thymidine release or medium depletion (23).

While PUFA-rich diet consistently enhanced the response to mitogens in female BALB/c mice, in female DBA/2 mice it was without effect (Tables 2 and 3). The influence of high dietary contents of PUFA on B- and T-lymphocyte proliferative activity is thus sex and strain limited.

Diet Effects on Tumor Growth. Lastly, we tested the effects of differences in dietary PUFA intake on the takes and proliferative rate of an ADK-11 of BALB/c origin. This tumor was chosen because its takes and proliferation rate are strongly modulated by the spontaneous reactivity of syngeneic hosts (6, 8), even though it is poorly immunogenic in syngeneic mice as determined by immunization-protection tests (5).

BALB/c and DBA/2 mice were challenged with ADK-11 cells after 40 days on PUFA diets. As shown in Chart 2, the final tumor incidence in BALB/c was about the same in all groups. No significant differences in mean latency or survival time were observed in PUFA-rich diet-fed males and females and PUFA-poor diet-fed males (Table 4), whereas a significant delay in tumor onset and a lower proliferation rate were observed in PUFA-poor diet-fed females (Chart 2, Table 4). ADK-11 injected in DBA/2 mice is rapidly rejected on the basis of multiple differences at minor histocompatibility antigens (9). However, after removal of infiltrating la+ passenger leukocytes, the DBA/2 reaction becomes weaker, and tumor cells proliferate, although at a lower rate than in syngeneic BALB/c mice so that

Chart 2. Effect of PUFA diets on tumor incidence. A, BALB/c mice challenged with 2 x 10^6 ADK-11 cells; B, DBA/2 mice challenged with 5 x 10^6 ADK-11 cells treated twice with anti-la antibody. Male mice fed on a PUFA-rich (○) or PUFA-poor (●) diet.
death eventually occurs (7, 9).

When $1 \times 10^6$ ADK-1t cells treated twice with anti-la* antibody and complement were injected into female DBA/2 mice, tumor incidence was about 50% lower, the period of latency was longer, and the proliferation rate was lower in the PUFA-poor diet-fed animals as compared to PUFA-rich diet-fed groups.

This decrease in tumor proliferative capability in PUFA-poor diet-fed female BALB/c and DBA/2 mice was consistently observed on the other 2 occasions on which the experiment was repeated.

**DISCUSSION**

The results presented in this paper show that the effects of dietary PUFA content on the immune system and tumor proliferation are rather complex and markedly dependent on sex and non-H-2 strain background genes.

In the BALB/c strain, in fact, no discrepancies were observed between PUFA-rich and PUFA-poor diet-fed male mice, whereas significant differences were evident in the females. This sex-limited effect may possibly be related to differences in endocrine environment, as suggested by Hopkins and West (13). In BALB/c females fed on PUFA-rich diet, enhancements in body growth, response to mitogens, and tumor growth rate are evident, while no such effects were observed in PUFA-poor diet-fed females, in line with data showing a general amplification of various mitosis-dependent functions by PUFA and their metabolic products (11, 12, 16, 19).

The effect of the diet, however, appears to be more complex when the data are evaluated in the light of the sex-limited influence of PUFA diets in BALB/c mice. In this case, the only function enhanced in PUFA-rich diet-fed females is the B- and T-lymphocyte blastic response to mitogens.

Suppressor macrophage activity does not appear to be affected, since parallel dose-inhibition curves of the response to mitogens were observed on adding increasing numbers of adherent cells from both PUFA-rich and PUFA-poor diet-fed mice.

In PUFA-poor diet-fed females, reduced body growth was evident when compared with males and PUFA-rich diet-fed females, even though the calorie uptake per mouse was similar in all BALB/c groups. In these same mice, the growth rate of syngeneic ADK-1t cells was strongly reduced. This decrease of tumor growth in PUFA-poor diet-fed females fits in well with reports on marked influence of dietary PUFA on the proliferation of several kinds of neoplastic cells (3, 13, 22).

The adenocarcinoma ADK-1t was chosen for these experiments because previous studies had shown that its growth is strongly influenced by spontaneous immunoreactivity of the syngeneic host (6, 8). However, since no reduction in tumor growth was evident in PUFA-rich diet-fed BALB/c females, it can be assumed that spontaneous reactivity to ADK-1t is not markedly affected by dietary PUFA, because it is for the most part a mitosis-independent activity (8). The differences in tumor growth rate between PUFA-rich and PUFA-poor diet-fed female BALB/c mice thus appear to be mainly dependent on the influence of the diets on tumor mitotic activity. It is possible that the inhibitory effects of PUFA-poor diet may be amplified by the "normal" spontaneous host reactivity, which may prove more effective against a tumor with a depressed growth rate.

By contrast, in DBA/2 females, neither diet had any marked effect on body growth and proliferative response. Besides the hormonal influence, therefore, other genes must be involved. These genes appear to be strain background genes, located outside the major histocompatibility complex (H-2), since DBA/2 and BALB/c mice carry the same H-2d haplotype. However, while both male BALB/c and female DBA/2 mice appear to be equally insensitive to PUFA diets, in PUFA-poor diet-fed DBA/2 females, the growth and final takes of ADK-1t tumor are strongly reduced. Since, in general, tumor growth rate is highly sensitive to dietary PUFA (11, 12, 16, 19), it is possible that proliferation of the ADK-1t tumor is modulated by the interplay between PUFA and various host factors (sex hormones, background genes) to a much greater extent than other mitosis-dependent functions. It must be noted that even after la* cell removal the growth of ADK-1t in DBA/2 mice is slowed down by DBA/2 reaction towards minor histocompatibility antigens expressed on the ADK-1t cell surface (7, 9). It is therefore quite conceivable that tumor-proliferative capability already affected by PUFA deprivation is further hindered by DBA/2 immune reactivity, itself apparently unaffected by the PUFA-poor diet.

**REFERENCES**


Announcements

(Requests for announcements must be received at least 3 months before publication.)

CONFERENCE ON BREAST CANCER

The American College of Radiology is sponsoring its 19th National Conference on Breast Cancer, to be held from March 9 to 13, 1981, at the Hotel Del Coronado, San Diego, California. The program of the conference, which is cosponsored by the American Cancer Society, the College of American Pathologists, and the Society for the Study of Breast Disease, will feature panel discussions, workshops, a symposium on benign breast disease, and a women’s forum on breast cancer. The faculty will be drawn from various disciplines including diagnostic radiology, economic systems, epidemiology, family practice, internal medicine, medical oncology, obstetrics and gynecology, pathology, plastic and reconstructive surgery, preventive medicine, psychiatry, therapeutic radiology, and surgery. Registration is limited; the fee is $275. Write to: American College of Radiology, Breast Cancer Conference, 6900 Wisconsin Avenue, Chevy Chase, Maryland 20015.

SYMPOSIUM ON GASTROENTEROLOGY

The Second Yosemite Gastroenterology Symposium will be held from March 15 to 18, 1981, at the Ahwahnee Hotel in Yosemite National Park, California. The symposium, which is sponsored by the Division of Gastroenterology and Extended Programs in Medical Education, University of California School of Medicine, San Francisco, and the Central California Committee for Gastroenterology, is designed to provide the internist and family practitioner with an intensive review of gastrointestinal disorders, their diagnosis, and current therapy, with emphasis on management. The program will consist of case discussions, seminars, and half-day didactic sessions on diseases of the colon, liver, biliary tract, and esophagus, and peptic diseases. This program meets the criteria for 16 hr in Category I of the AMA Physician’s Recognition Award and the CMA Certification Program. It is also approved for 16 elective hr by the American Academy of Family Physicians. For further information, please contact: Fresno Division, Extended Programs in Medical Education, 5 Area Health Education Center, 5110 East Clinton Way, Suite 201, Fresno, California 93727.

SYMPOSIUM ON SURGICAL TREATMENT AND RECONSTRUCTION FOR BREAST CANCER

An International Symposium on Surgical Treatment and Reconstruction for Breast Cancer will be held in Madrid, Spain, on March 20 and 21, 1981. For information, write to: Dr. R. de la Plaza, Red Cross Centre for Burns and Plastic Surgery, Calle Lisboa, 6, Madrid-8, Spain.

SHORT COURSES AT THE MARINE BIOLOGICAL LABORATORY

The Marine Biological Laboratory, Woods Hole, Massachusetts, will conduct the following residential laboratory courses in Spring 1981: April 26–May 1—Freeze-etching in Electron Microscopy May 3–5—Electron Microscopy in the Biological Sciences May 10–16—Analytical and Quantitative Light Microscopy in Biology, Medicine, and Materials Sciences May 17–23—Mariculture: Culture of Marine Invertebrates for Research Purposes

For details, write to: Dr. Morton D. Maser, Assistant Director for Educational and Research Services, Marine Biological Laboratory, Woods Hole, Massachusetts 02543.

SYMPOSIUM ON ADVANCES IN CANCER TREATMENT RESEARCH

The Sixth Annual Symposium on Advances in Cancer Treatment Research will take place from March 12 to 14, 1981, at the Baltimore Convention Center, Baltimore, Maryland. For additional information, contact: Program of Continuing Education, University of Maryland School of Medicine, 10 South Pine Street, Baltimore, Maryland 21201.

SUBSPECIALTY EXAMINATION IN MEDICAL ONCOLOGY

The 1981 Subspecialty Examination in Medical Oncology will be given by the American Board of Internal Medicine on November 10, 1981. The registration period is from January 1, 1981, to April 1, 1981; the deadline for cancellation is October 1, 1981. For application forms, write to: American Board of Internal Medicine, 3624 Market Street, Philadelphia, Pennsylvania 19104.

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Erratum

In the October 1980 article by M. Giovarelli et al., entitled "Strain-and Sex-linked Effects of Dietary Polyunsaturated Fatty Acids on Tumor Growth and Immune Functions in Mice," the name of the third author of the article was listed incorrectly. The author’s name is Giancarlo Ugazio, not Gianfranco Ugazio.
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