Fish oil supplementation inhibits the expression of major histocompatibility complex class II molecules and adhesion molecules on human monocytes1–3

David A Hughes, Andrew C Pinder, Zoe Piper, Ian T Johnson, and Elizabeth K Lund

ABSTRACT To test the hypothesis that fish oil supplementation can inhibit the expression of functionally associated molecules on the surface of human blood monocytes, we randomly assigned 12 healthy adults to receive either an n–3 polyunsaturated fatty acid–rich fish oil supplement for 21 d or to receive no supplement. The percentage of monocytes expressing major histocompatibility complex (MHC) class II molecules (HLA-DR, -DP, and -DQ), intercellular adhesion molecule-1, and leukocyte-function-associated antigen-1, and the intensity of expression of each molecule were quantified before and after the study period. Monocytes were examined immediately after blood sampling and again after incubation in serum-free culture medium for 24 h in the presence of interferon-γ to up-regulate expression of MHC class II molecules by the monocytes. The intensity of expression of all the monocyte surface molecules examined was significantly reduced after fish oil supplementation (P < 0.025), although there was no change in the percentage of monocytes expressing each molecule. After incubation with interferon-γ, there was a similar inhibition of surface molecule expression (with the exception of HLA-DQ) by monocytes from the fish oil–supplemented group, and there was a reduction in the percentage of monocytes expressing both HLA-DR and -DP molecules (P < 0.025). No significant changes were observed in the reference group. Dietary supplementation with fish oil can inhibit the expression of surface molecules involved in the function of human antigen-presenting cells, a potential mechanism by which n–3 fatty acids may suppress cell-mediated immune responses. Am J Clin Nutr 1996;63: 267–72.

KEY WORDS Fish oil, n–3 fatty acids, humans, monocytes, MHC class II molecules, adhesion molecules

INTRODUCTION

Dietary fish oils, rich in n–3 polyunsaturated fatty acids (PUFAs), can alter the membrane composition of human white blood cells, increasing the membrane phospholipid concentrations of eicosapentaenoic acid (EPA; 20:5n–3) and docosahexaenoic acid (DHA; 22:6n–3) (1). Changes in membrane fatty acid composition can result in significant alterations in the activity of cells involved in the immune system (reviewed in reference 2). Populations that have high dietary intakes of fish, such as Greenland Eskimos, have a low incidence of inflammatory and autoimmune disorders (3), and the ability of n–3 PUFAs to modulate immune responses has led to a growing interest in the potential use of fish oil in the treatment of disorders involving overreactive immune responses, such as rheumatoid arthritis (4) and psoriasis (5).

Several in vitro and dietary supplementation studies have been performed to elucidate the mechanism of the immunosuppressive effect of n–3 PUFAs. Most studies were performed in rodents and concentrated on examining the effects of fatty acids on lymphocyte function (reviewed in reference 6). However, it is the mononuclear phagocytes (eg, monocytes, macrophages, and dendritic cells) that initiate cell-mediated immune responses by processing and subsequently expressing antigens on their surface membranes for recognition by appropriate T lymphocytes (7). Insufficient attention has been given to the influence of dietary fatty acids on the function of human mononuclear phagocytes.

A prerequisite for the antigen-presenting function of mononuclear phagocytes is the cell-surface expression of major histocompatibility complex (MHC) class II molecules (HLA-DR, HLA-DP, and HLA-DQ) (8). Because the degree of immune responsiveness of an individual has been shown to be proportional to both the percentage of MHC class II–positive monocytes and the density of these molecules on the cell surface (9), it is possible that n–3 PUFAs may suppress cell-mediated immune responses by inhibiting the cell surface expression of these molecules.

In addition to requiring the expression of MHC class II molecules, cell-cell adhesion appears to be critical for the initiation of a primary immune response, and it was shown recently that the ligand-receptor pair of intercellular adhesion molecule-1 (ICAM-1) and leukocyte-function-associated antigen-1 (LFA-1) is also capable of co-stimulating an immune response (10), enhancing T cell proliferation and lymphokine production.

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A diet rich in fish oil can suppress the expression of Ia molecules (the murine equivalent of human MHC class II molecules) on peritoneal cells from *Listeria*-infected mice (11), and we recently observed a reduced expression of MHC class II molecules and of ICAM-1 on human blood monocytes cultured in vitro in the presence of either EPA or DHA (12). However, to our knowledge, the present study is the first to quantify the effect of dietary fish oil supplementation on the cell surface expression of MHC class II molecules and adhesion molecules by human blood monocytes.

Because it has been reported that synovial fluid monocytes obtained from patients with rheumatoid arthritis express elevated concentrations of MHC class II molecules (13), we also examined the effect of dietary fish oil supplementation on ex vivo activated monocytes, cultured in the presence of interferon-γ, to up-regulate the expression of MHC class II molecules on the monocytes.

**SUBJECTS AND METHODS**

**Subjects and experimental design**

Three males and three females [age range 19–41 y, mean 28.2 y; body mass index (BMI, in kg/m²) range 18.7–24.3, mean 22.1] were randomly assigned to supplement their normal diet with 3 g/d of a fish oil supplement containing 930 mg EPA/d and 630 mg DHA/d as triacylglycerol (EPA Forte; Booker Health Products, Byfleet, United Kingdom) for 21 d. This dose was chosen because it is an amount that could readily be obtained from the consumption of fatty fish (eg, mackerel contains ~2.6 g n–3 fatty acids in an 85-g raw portion). One male and five female volunteers (age range 19–34 y, mean 24.8 y; BMI range 19.2–28.8, mean 24.0) who did not receive supplementation to their normal diet acted as a reference group. All participants were nonsmokers and none were receiving medication. Potential subjects were not selected if they used fish oil supplements or normally consumed more than one meal containing fish per week. All participants were requested not to eat fish known to contain high concentrations of n–3 fatty acids during the study period. In week 3 of the study all participants completed a 7-d dietary weighed intake record to assess compliance. Fasting (12 h) blood samples were taken at baseline and at 21 d of supplementation. The study was approved by the Institute of Food Research Ethical Committee.

**Monocyte isolation and purity assessment**

Monocytes were purified by density-gradient centrifugation with a method previously described in detail (14). This separation technique produces a higher purity of monocytes when compared with plastic-adherence methods, but requires that relatively large blood samples be taken to provide sufficient monocytes to study. Briefly, peripheral blood (typically 80 mL) from each volunteer was collected into tubes containing EDTA. Leukocyte-rich plasma was obtained by dextran 500 sedimentation and subjected to a period of hypersomolarity with the method of Recalde (15). The plasma was then layered onto NycoPrep 1.068 (Nycomed Ltd, Birmingham, United Kingdom) in 15-mL tubes (diameter 13 mm, Falcon 2097; Becton Dickinson, Oxford, United Kingdom), which were centrifuged for 15 min at 600 × g at 22 °C. The monocyte-containing fraction was aspirated and washed twice in 0.9% NaCl containing 0.13% EDTA and 1% albumin, by centrifugation at 600 × g for 7 min at 4 °C. The recovered cells were resuspended in minimal essential medium (MEM; Gibco BRL, Paisley, United Kingdom), counted, and adjusted to 5 × 10^7 cells/L for staining before flow cytometry.

The monocytes were >95% viable, as assessed by trypan blue dye exclusion, and >90% pure, as examined by immunostaining for CD14 expression (Serotec, Oxford, United Kingdom) as well as by analysis of cell size and granularity by flow cytometry. The contaminating lymphocytes were <8% T cells (expressing CD3; Serotec). Some platelets were usually present in the cell suspensions but no other leukocyte cell types were observed.

**Monocyte culture with interferon-γ**

A sample of eight million monocytes from each blood sample was resuspended to a total volume of 8 mL in HEPES-buffered RPMI containing 2 mmol L-glutamine/L, 100,000 U penicillin/L, and 100 mg streptomycin/L (Gibco BRL). The cells were cultured in 15-mL polystyrene tubes (Falcon 2097) in the presence of interferon-γ (Genzyme, West Malling, United Kingdom) to up-regulate surface molecule expression. An optimal concentration of 400 mg/L (previously determined) was used. After a 24-h incubation at 37 °C, the cells were placed on ice for 40 min to loosen any adherent monocytes. The cells were washed twice in MEM, counted using trypan blue dye exclusion to assess viability (which was always >90% after culture), and adjusted to a concentration of 5 × 10^7 cells/L in MEM for staining before flow cytometry.

**Monoclonal antibodies**

The following monoclonal antibodies were used to investigate monocyte surface antigen expression: antibodies to HLA-DR, HLA-DP, and HLA-DQ (Becton Dickinson); antibody to CD54 (ICAM-1); and antibody to CD11a (LFA-1; Serotec). FITC-labeled rabbit anti-mouse immunoglobulin F(ab')² fragment (Dako, High Wycombe, United Kingdom) was used as a second-layer antibody to detect monoclonal antibody binding. This FITC-labeled antibody was also used alone to control for nonspecific binding. Antibody to CD45 (common to all leukocytes; Serotec) was used as a positive control.

**Immunofluorescence**

Cells were stained with the various monoclonal antibodies by the technique described by Parker and Haslam (16). Briefly, 5 × 10⁶ cells in 100 μL MEM were incubated with an optimal concentration of each monoclonal antibody for 30 min at 4 °C. The cells were washed in MEM containing 10% Haemoccel (Hochst, Hownslow, United Kingdom) to reduce cell clumping, followed by the addition of the FITC rabbit anti-mouse immunoglobulin for 30 min at 4 °C. After a further washing, the cells were fixed in MEM containing 5% Haemoccel and 50% methanol and washed in phosphate-buffered saline. The cell nuclei were then stained with propidium iodide (0.025 g/L in the presence of ribonuclease (0.25 g/L) for 20 min at 37 °C immediately before flow cytometric analysis.

**Analysis of surface-marker expression by flow cytometry**

A 488-nm laser line was used to simultaneously excite FITC and propidium iodide. The instrument was calibrated daily.
using fluorescent, 1-μm latex beads (Fluoresbrite, Polysciences, Warrington, PA). Log FITC fluorescence was detected via a 530-nm band-pass filter and linear propidium iodide fluorescence emission via a 610-nm band-pass filter. Forward angle and 90° light-scatter characteristics were also recorded for each cell to give an indication of size and granularity, respectively, to aid in distinguishing the different populations. The percentages of FITC-positive cells in the monocyte populations (gated according to 90° and forward light-scatter characteristics) were determined by comparison with the FITC-only controls without monoclonal antibodies.

The intensity of expression of the cell surface markers on monocytes was determined with a previously reported method (17). The green (530 nm) fluorescence emission was converted back to a linear scale to calculate the linear median intensity value for the monocytes stained with monoclonal antibody and for the controls without monoclonal antibody. The intensity of FITC fluorescence relating to bound monoclonal antibody was obtained by subtracting the linear median intensity value for the control monocytes. The results were thus expressed as "relative median intensity" values.

## Statistical analysis

Differences between baseline and endpoint samples were analyzed with the Wilcoxon matched-pairs signed-ranks test for nonparametric data (18).

## RESULTS

### Compliance

All 12 participants completed the study. Those in the group supplemented with fish oil were given a known excess of capsules at the beginning of the study and the number of capsules returned at the end gave an indication of compliance; all participants returned the expected number of excess capsules. The 7-d weighed intake records indicated that no participants in the reference group consumed fish known to contain high concentrations of n-3 fatty acids, but one participant in the group supplemented with fish oil consumed one meal containing smoked herring (118 g; ie. ~3 g n-3 fatty acids).

### Effect of fish oil supplementation on surface molecule expression by monocytes

Table 1 shows the percentages of monocytes expressing the various surface molecules before and after 21 d of supplementation without (reference group) or with fish oil. Comparing baseline with endpoint samples, no significant changes in the percentages of any of the MHC class II molecules or adhesion molecules studied were observed in either the fish oil–supplemented or reference groups.

Table 2 shows the relative amount (median fluorescence intensity) of each surface molecule expressed on the monocytes. After 3 wk of fish oil supplementation there was a significant reduction in the intensity of expression of all the MHC class II molecules and of the adhesion molecules ICAM-1 and LFA-1 (P < 0.025; Wilcoxon matched-pairs signed-ranks test). No significant changes were observed in the reference group.

### Effect of fish oil supplementation on surface molecule expression by monocytes stimulated ex vivo with interferon-γ

Table 3 shows the percentages of monocytes expressing each surface molecule after a 24-h incubation with interferon-γ. There was a significant reduction in the percentage expression of both HLA-DR and HLA-DP molecules on monocytes obtained from the fish oil–supplemented group (P < 0.025). No significant changes were observed in the reference group.

Table 4 shows the relative amount (median fluorescence intensity) of each surface molecule expressed on the monocytes after a 24-h incubation with interferon-γ. There was a significant reduction in the surface expression of HLA-DR, HLA-DP, and LFA-1 (P < 0.025) and of ICAM-1 (P < 0.05) on monocytes stimulated with interferon-γ obtained after fish oil supplementation. Again, no significant changes were observed in the reference group.

## DISCUSSION

The findings in this study show that dietary fish oil supplementation, in amounts that are easily obtainable via the consumption of fatty fish, can inhibit the expression of MHC class II molecules and the adhesion molecules ICAM-1 and LFA-1 on the surface of human peripheral blood monocytes. The expression of these molecules is a prerequisite for antigen presentation, the initiating process of cell-mediated immune responses, and it has been shown that variability in the expression of MHC class II molecules alters the degree of immune responsiveness of an individual to antigenic stimulation (9, 19). Therefore, it is possible that one of the mechanisms whereby n-3 PUFA-rich diets may suppress cell-mediated immune responses involving the expression of MHC class II molecules is inhibition of the expression and/or intensity of expression of the various surface molecules.
TABLE 2
Relative median fluorescence intensity of surface molecule expression on blood monocytes before and after fish oil supplementation

<table>
<thead>
<tr>
<th></th>
<th>HLA-DR</th>
<th>HLA-DP</th>
<th>HLA-DQ</th>
<th>ICAM-1</th>
<th>LFA-1</th>
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<tbody>
<tr>
<td>Reference group</td>
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<tr>
<td>(n = 6)</td>
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<tr>
<td>Before</td>
<td>65.3 (45.6–69.1)</td>
<td>25.4 (19.1–32.5)</td>
<td>15.9 (5.2–22.6)</td>
<td>20.1 (9.4–24.6)</td>
<td>56.3 (35.8–60.6)</td>
</tr>
<tr>
<td>After</td>
<td>55.8 (44.4–71.6)</td>
<td>28.8 (16.0–32.9)</td>
<td>18.7 (4.4–19.5)</td>
<td>18.9 (8.9–26.9)</td>
<td>51.0 (37.9–59.9)</td>
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<tr>
<td>Fish oil group</td>
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<td>(n = 6)</td>
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<tr>
<td>Before</td>
<td>58.3 (46.0–78.5)</td>
<td>33.2 (14.8–40.7)</td>
<td>18.3 (5.6–27.9)</td>
<td>21.7 (17.4–27.3)</td>
<td>56.1 (52.8–58.9)</td>
</tr>
<tr>
<td>After</td>
<td>45.1 (36.0–56.7)</td>
<td>19.5 (5.3–37.0)</td>
<td>12.8 (0.4–37.0)</td>
<td>13.5 (0.2–20.4)</td>
<td>46.0 (20.8–53.5)</td>
</tr>
</tbody>
</table>

1 Median; range in parentheses. HLA-DR, HLA-DP, and HLA-DQ, major histocompatibility complex class II molecules; ICAM-1, intercellular adhesion molecule-1; LFA-1, leukocyte-function-associated antigen-1.
2 Significantly different from before supplementation, P < 0.025 (Wilcoxon matched-pairs signed-ranks test).

Responses is by inhibiting the function of antigen-presenting cells.

We recently showed that both EPA and DHA can inhibit the expression of MHC class II molecules and ICAM-1 molecules on the surface of human monocytes in vitro, in a dose-dependent manner (12), at concentrations of these fatty acids that are achievable in blood plasma with amounts of fish oil supplementation (3 g/d) (1) similar to that used in the current study. Because it was shown that the amount of EPA incorporated into human blood monocytes increases significantly within 2 wk of fish oil supplementation (20), it is possible that the changes in surface molecule expression observed in the present study resulted from a change in the fatty acid composition of the monocyte cell membrane. The observation that a beneficial effect of fish oil supplementation in patients with rheumatoid arthritis was only observed after a longer period of supplementation (≥12 wk) (21), suggests that a longer period of time is required for the incorporation of n-3 PUFAs into the membranes of monocytes present within the synovia of inflamed joints.

Several animal studies have shown that n-3 PUFAs can inhibit the expression of Ia molecules (the murine equivalent of human MHC class II molecules). Kelley et al (22) reported that dietary supplementation with fish oil suppresses autoimmune lupus in MRL-lpr mice and prevents an increase in macrophage surface Ia expression. Mosquera et al (23) showed that administration of fish oil to mice and rats by esophageal gavage reduced the percentage of peritoneal macrophages that expressed Ia compared with saline-gavaged controls, and Huang et al (11) showed that fish oil–fed mice infected with Listeria monocytogenes had a reduced expression of Ia on the surface of peritoneal macrophages compared with mice fed other fat sources. In addition, it has been shown that EPA can inhibit the antigen-presenting function of mouse splenocytes (24). Dietary enrichment with EPA inhibited the ability of spleen cells to present antigens to murine helper T cell clones and pretreatment of splenocytes in vitro with EPA also resulted in inhibition of antigen-presenting cell function. Seyland et al (25) reported that DHA can suppress human antigen-presenting cell function. Epidermal cells (as antigen-presenting cells) or T cells were preincubated separately with DHA for 24 h, washed, and cocultured with antigen. Preincubation of the epidermal cells with DHA promoted an inhibitory effect on proliferation, whereas preincubation of T cells did not influence the proliferation compared with controls. Taken together, the results of these studies and those of the current study support the hypothesis that n-3 PUFAs suppress cell-mediated immune responses, at least in part, by inhibiting antigen-presenting cell function.

The significant decrease in the percentage of monocytes expressing HLA-DR and HLA-DP after interferon-γ stimulation, together with a decrease in the number of ICAM-1 and LFA-1 molecules expressed on the cells, supports the possibility that fish oil supplementation may be beneficial in the treatment of rheumatoid arthritis, a disorder in which elevated numbers of MHC class II molecules (13, 26) and ICAM-1 molecules (27) have been observed on monocytes present in chronically inflamed joints. A reduction in the expression of these molecules could reduce helper T cell activation and thus decrease the production of inflammatory cytokines and the production of antibodies by B cells at these localized sites of disease. However, most studies reporting a beneficial effect of fish oil supplementation in patients with rheumatoid arthritis used higher doses of fish oils (>5 g/d; recently reviewed in

TABLE 3
Percentage of ex vivo interferon-γ-stimulated monocytes expressing each surface molecule before and after fish oil supplementation

<table>
<thead>
<tr>
<th></th>
<th>HLA-DR</th>
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<th>HLA-DQ</th>
<th>ICAM-1</th>
<th>LFA-1</th>
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<tr>
<td>Reference group</td>
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<td>(n = 6)</td>
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<tr>
<td>Before</td>
<td>93.6 (91.2–96.4)</td>
<td>82.3 (63.0–92.4)</td>
<td>52.3 (7.4–84.2)</td>
<td>86.2 (69.7–92.0)</td>
<td>97.6 (86.0–98.6)</td>
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<tr>
<td>After</td>
<td>94.0 (90.4–96.0)</td>
<td>82.8 (65.0–91.9)</td>
<td>64.0 (21.6–89.7)</td>
<td>87.2 (70.9–96.1)</td>
<td>95.8 (80.4–96.6)</td>
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<tr>
<td>Fish oil group</td>
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<tr>
<td>Before</td>
<td>95.3 (90.1–97.1)</td>
<td>89.2 (51.7–92.1)</td>
<td>53.6 (14.7–73.8)</td>
<td>86.3 (70.1–88.6)</td>
<td>88.6 (74.8–94.0)</td>
</tr>
<tr>
<td>After</td>
<td>86.7 (70.6–95.4)</td>
<td>75.3 (45.9–88.2)</td>
<td>34.5 (28.8–80.1)</td>
<td>77.9 (49.6–86.4)</td>
<td>90.8 (78.5–96.0)</td>
</tr>
</tbody>
</table>

1 Median; range in parentheses. HLA-DR, HLA-DP, and HLA-DQ, major histocompatibility complex class II molecules; ICAM-1, intercellular adhesion molecule-1; LFA-1, leukocyte-function-associated antigen-1.
2 Significantly different from before supplementation, P < 0.025 (Wilcoxon matched-pairs signed-ranks test).
TABLE 4
Relative median fluorescence intensity of surface molecule expression on ex vivo interferon-γ-stimulated blood monocytes before and after fish oil supplementation

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<th>ICAM-1</th>
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<tr>
<td>Reference group (n = 6)</td>
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<tr>
<td>Before</td>
<td>97.4 (75.0–107.3)</td>
<td>56.5 (48.5–99.9)</td>
<td>34.6 (15.9–51.0)</td>
<td>54.2 (41.5–61.5)</td>
<td>54.4 (40.6–62.6)</td>
</tr>
<tr>
<td>After</td>
<td>95.1 (88.0–105.9)</td>
<td>56.4 (33.0–71.5)</td>
<td>32.1 (4.6–50.3)</td>
<td>55.1 (43.3–67.0)</td>
<td>58.6 (46.9–61.2)</td>
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<tr>
<td>Fish oil group (n = 6)</td>
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<tr>
<td>Before</td>
<td>97.2 (85.3–100.9)</td>
<td>67.6 (33.6–72.9)</td>
<td>32.6 (11.8–37.8)</td>
<td>54.6 (45.1–66.8)</td>
<td>56.8 (52.0–62.1)</td>
</tr>
<tr>
<td>After</td>
<td>79.6 (69.8–89.8)</td>
<td>51.6 (31.7–66.3)</td>
<td>26.5 (19.1–37.0)</td>
<td>45.7 (33.1–58.1)</td>
<td>51.2 (43.1–57.0)</td>
</tr>
</tbody>
</table>

1 Median; range in parentheses. HLA-DR, HLA-DP, and HLA-DQ, major histocompatibility complex class II molecules; ICAM-1, intercellular adhesion molecule-1; LFA-1, leukocyte-function-associated antigen-1.
2,3 Significantly different from before supplementation (Wilcoxon matched-pairs signed-ranks test): 2 P < 0.025, 3 P < 0.05.

reference 21). One study found that patients receiving 90 mg EPA and DHA · d⁻¹ · kg body wt⁻¹ achieved a higher score of clinical measures of benefit than did patients given one-half of that dose (28). This raises the probability that greater supplementation is required to increase the concentration of n-3 PUFAs in the synovial fluid to a concentration that will inhibit the expression of functionally associated surface molecules on cells present at the sites of inflammation.

The results of the present study might also be of relevance to the suggested inverse relation between long-term fish oil intake and atherogenesis (29). There is increasing evidence of a chronic immune and inflammatory involvement in the formation of atherosclerotic lesions (30); the presence of chronically stimulated T cells within lesions and the expression of MHC class II molecules on lesional monocytes-macrophages indicates that these cells are actively participating in the local immune response occurring during atherogenesis. Human dietary fish oil supplementation studies have shown that EPA and DHA are incorporated into the lipids of advanced atherosclerotic plaques (31); it is possible that a reduced expression of MHC class II molecules might inhibit the antigen-presenting function of the local macrophages, thereby prolonging, if not preventing, lesion development.

Several mechanisms might be involved in the modulatory effect of n-3 PUFAs on the expression of monocyte surface molecules. The incorporation of these fatty acids into the cell membrane can increase its fluidity and thus influence the expression of membrane proteins (32). Increasing the cholesterol content of human monocyte cell membranes, which causes a decrease in membrane fluidity, leads to an increase in MHC class II molecule expression (14). Therefore, it is possible that an increase in membrane fluidity would have an opposite effect on MHC class II expression and may also influence the expression of adhesion molecules. The effect of these n-3 PUFAs on the fluidity of human monocyte membranes and the possible relation between fluidity and the expression of these cell surface molecules is currently being examined.

A large body of evidence supports the hypothesis that many of the effects of n-3 PUFAs on the immune system are mediated via changes in the production of eicosanoids, which can influence various stages of an immune response (reviewed in reference 33). An increased availability of n-3 PUFAs in membrane phospholipids results in a decreased cellular production of prostaglandin E₂ and an increased production of prostaglandin E₃ (34). A change in eicosanoid production can influence the expression of cell membrane molecules. However, because prostaglandin E₂ can inhibit the expression of Ia molecules on stimulated macrophages (35), it is unlikely that this mechanism is a major contributor to the changes in surface molecules observed in this study. In addition, it has been reported that the reduction in Ia expression by peritoneal macrophages seen in mice and rats fed fish oil (23) was not related to prostaglandin E₂ production by the peritoneal cells. Nevertheless, because the production of several cytokines is under negative control by prostaglandin E₂, several studies investigated the effect of n-3 PUFAs on cytokine production. Both in vitro and in vivo studies showed that n-3 PUFAs can inhibit the synthesis of proinflammatory cytokines such as interleukin 1 and tumor necrosis factor-α by human mononuclear cells (reviewed in reference 36), suggesting that suppression of cytokine production is another mechanism contributing to the beneficial effect of fish oils in the treatment of inflammatory disorders.

There is also growing evidence that n-3 PUFAs can directly or indirectly influence the induction of messenger RNA encoding cell surface molecules. For instance, it has recently been shown that DHA can inhibit the cell surface expression of vascular cell-adhesion-molecule-1 (VCAM-1) on human endothelial cells (37), in parallel with a decrease in VCAM-1 messenger RNA. DHA may influence cytokine-induced nuclear translocation of specific transcription factors such as nuclear factor-κB (38).

In conclusion, we showed that low-dose fish oil supplementation can inhibit the expression of surface molecules on human peripheral blood monocytes that are involved in the adherence and antigen-presenting function of the surface molecules. Although caution should be exercised in interpreting the results of this study, which involved a low number of participants, the findings do support the possibility that fish oil may be beneficial in the treatment of autoimmune disorders, which are associated with the abnormally elevated expression of both MHC class II molecules and adhesion molecules at the active sites of disease. Whether fish oil supplementation can influence the expression of these surface molecules on mononuclear phagocytes within these sites remains to be established.

REFERENCES
1. Marangoni F, Angeli MT, Colli S, et al. Changes of n-3 and n-6 fatty acids in plasma and circulating cells of normal subjects, after pro-


