Abbreviations used: Con A, concanavalin A; DAG, diacylglycerol; GvH, graft versus host; HETE, hydroxyeicosatetraenoic acid; HvG, host versus graft; IL, interleukin; LT, leukotriene; LX, lipoxin; NK cells, natural killer cells; PBL, peripheral blood lymphocyte; PC, phosphatidylcholine; PG, prostaglandin; PI_P, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PS, phosphatidylserine; PUFA, polyunsaturated fatty acid; TAG, triacylglycerol; TNF, tumour necrosis factor; TX, thromboxane.

Can \( n - 3 \) polyunsaturated fatty acids be used as immunomodulatory agents?

P. C. Calder

Department of Biochemistry, University of Oxford, South Parks Road, Oxford OXI 3QU, U.K.

Biosynthesis of unsaturated fatty acids

All mammals can synthesize fatty acids \( \textit{de novo} \) from acetyl coenzyme A. The end product of the fatty acid synthetase enzyme is palmitic acid (16:0), which in turn can be elongated to stearic acid (18:0). There is little need for the synthesis of saturated fatty acids in Western man, because the diet normally supplies adequate amounts. However, cell membranes require unsaturated fatty acids to be provided to maintain their structure, fluidity and function. Therefore a mechanism for the introduction of double bonds (i.e. desaturation) exists. The introduction of one double bond between carbon atoms 9 and 10 is catalysed by the enzyme \( \Delta^9 \)-desaturase, which is universally present in both plants and animals. This enzyme results in the conversion of stearic acid to oleic acid (18:1\( \text{n}-9 \)). Plants, unlike animals, can insert additional double bonds into oleic acid between the existing double bond at the 9-position and the methyl terminus of the carbon chain; a \( \Delta^12 \)-desaturase converts oleic acid into linoleic acid (18:2\( \text{n}-6 \)), whereas a \( \Delta^5 \)-desaturase converts linoleic acid into \( \text{\( \omega \)}-6 \) fatty acids (18:3\( \text{n}-3 \)). Many marine plants, especially the unicellular algae in the phytoplankton, also perform chain elongation and further desaturation of \( \text{\( \omega \)}-6 \) fatty acids to yield \( n - 3 \) polyunsaturated fatty acids (PUFAs) with 20 and 22 carbon
atoms and 5 or 6 double bonds (Figure 1). It is the formation of these long-chain \(n-3\) PUFAs by marine algae and their transfer through the food chain to fish that accounts for the abundance of eicosapentaenoic and docosahexaenoic acids (20:5\(-\)3 and 22:6\(-\)3, respectively) in some marine fish oils. Animal cells can also convert \(\alpha\)-linolenic acid to eicosapentaenoic and docosahexaenoic acids; by a similar series of reactions linoleic acid is converted via \(\gamma\)-linolenic (18:3\(-\)6) and dihomo-\(\gamma\)-linolenic (20:3\(-\)6) acids to arachidonic acid (20:4\(-\)6) (Figure 1). The \(n-9, n-6\) and \(n-3\) families of PUFAs are not metabolically interconvertible in mammals.

**Fatty acids as eicosanoid precursors**

**The precursors and pathways of eicosanoid synthesis**

Eicosanoids are a family of oxygenated derivatives of dihomo-\(\gamma\)-linolenic, arachidonic and eicosapentaenoic acids. Eicosanoids include prostaglandins (PGs) and thromboxanes (TXs), which together are termed prostanoids, and leukotrienes (LTs), lipoxins (LXs), hydroperoxy-eicosatetraenoic acids (HPETEs) and hydroxy-eicosatetraenoic acids (HETEs). In most conditions the principal precursor for these compounds is arachidonic acid, and the eicosanoids produced from arachidonic acid seem to have more potent biological functions than those released from dihomo-\(\gamma\)-linolenic or eicosapentaenoic acids. The precursor PUFA is released from membrane phosphatidylcholine (PC) by the action of phospholipase \(A_2\) or from membrane phosphatidylinositol 4,5-bisphosphate (PIP\(_2\)) by the actions of phospholipase C and diacylglycerol (DAG) lipase.

The pathways of eicosanoid synthesis begin with cyclo-oxygenase, which yields the PGs and TXs, or with the 5-, 12- or 15-lipoxygenases, which yield the LTs, HPETEs, HETEs and LXs (Figure 1). A third pathway, which operates
through the microsomal cytochrome P-450, results in formation of epoxides, which are converted to HETEs. The amounts and types of eicosanoid synthesized are determined by the availability of arachidonic acid, by the activities of phospholipase A₂ and phospholipase C and by the activities of cyclo-oxygenase and the lipoxygenases.

The major biologically active products of the cyclo-oxygenase pathway are PGₐ₂, PGE₂, PGI₂ (prostacyclin), PGF₂ₐ, and TXA₂, although these are produced in a cell-specific manner. These compounds usually have a short half-life and act locally to the cell from which they are produced. Their production is initiated by particular stimuli (e.g. cytokines, growth factors, endotoxin, zymosan, oxygen free radicals, antigen–antibody complexes, bradykinin, collagen or thrombin) and, once produced, they themselves are able to modify the response to the stimulus. Different prostanoids have different, sometimes opposite, effects; for example, TXA₂ increases platelet aggregation whereas PGI₂ inhibits platelet aggregation. PGs are associated with the inflammatory response, and cyclo-oxygenase products (PGs, prostacyclin) are aspirin and related non-steroidal anti-inflammatory drugs. It seems that each of the lipoxygenase enzymes has a particular cellular distribution: 5-lipoxygenase is found in mast cells, monocytes, macrophages and granulocytes; 12-lipoxygenase is found in platelets and some epithelial cells; and 15-lipoxygenase is found in young myeloid cells and some epithelial cells.

The n–3 PUFAs, eicosapentaenoic and docosahexaenoic, competitively inhibit the oxygenation of arachidonic acid by cyclo-oxygenase. In addition, eicosapentaenoic acid (but not docosahexaenoic acid) is able to act as a substrate for both cyclo-oxygenase and 5-lipoxygenase. Ingestion of fish oils that contain n–3 PUFAs will result in a decrease in membrane arachidonic acid levels and a concomitant decrease in the capacity to synthesize eicosanoids from arachidonic acid (see below); eicosapentaenoic acid gives rise to the 3-series PGs and TXs and the 5-series LTs (Figure 1). The eicosanoids produced from eicosapentaenoic acid do not always have the same biological properties as the analogues produced from arachidonic acid. For example, TXA₂ is less active than TXA₁ in aggregating platelets and constricting blood vessels, and LTB₄ is less active than LTB₁, with regard to chemotactic and aggregatory properties in human neutrophils. In contrast, PGI₂ is as active as PGI₁ in inhibiting platelet aggregation and promoting vasodilation.

The synthesis of eicosanoids by cells of the immune system

Macrophages synthesize a range of cyclo-oxygenase and lipoxygenase products (reviewed in [1,2]); the exact profile of eicosanoids formed depends on the species and anatomical site of origin of the macrophages and the nature of the stimulus. Studies concerning eicosanoid synthesis by lymphocytes have proved controversial (see [3]). Many studies indicate that lymphocytes do not synthesize cyclo-oxygenase or lipoxygenase products (see [3,4] for references). Nevertheless, lymphocytes contain similar amounts of arachidonic acid in their membrane phospholipids to macrophages, and mitogen-stimulated lymphocytes release arachidonic acid extracellularly. There is evidence that macrophages use this released arachidonic acid for eicosanoid synthesis. Indeed, in the presence of lymphocytes, macrophages produce increased amounts of PGE₂ in vitro. Thus it seems that among immunocompetent cells, macrophages are the principal, and perhaps the only, source of eicosanoids, but that an interaction between lymphocytes and macrophages exists.

Effects of eicosanoids on cells of the immune system

Not only are immune cells a source of eicosanoids, but they are also subject to their regulatory effects; the most well documented effects are those of PGE₂. In vitro, PGs are involved in modulating the intensity and duration of inflammatory and immune responses; PGE₂ has a number of pro-inflammatory effects including fever, erythema, increased vascular permeability, vasodilation and enhancement of pain and oedema caused by other agents such as bradykinin and histamine. In chronic inflammatory conditions, increased activity of suppressor T cells and increased rates of PGE₂ production are observed, and elevated PGE₂ production has been observed in patients suffering from infections, whose T cells show depressed functional responses. It is generally accepted that PGE₂ is a regulator of immune cell functions; the age and type of target cell and the concentration of PGE₂ determine the nature of the response.

PGs seem to play a role in regulating the differentiation of both T and B lymphocytes; for example PGE₂ induces immature thymocytes to
differentiate into mature T cells. In addition, the functions of T cells, B cells, natural killer (NK) cells and macrophages are modulated by eicosanoids; these effects are reviewed elsewhere [2,3,5]. T lymphocytes have receptors for PGE, and PGE\textsubscript{2} and these compounds suppress T-lymphocyte proliferation, T-cell-mediated cytotoxicity, interleukin (IL)-2 production and NK cell activity \textit{in vitro} (see [2,3,5] for references). B cells have receptors for the E-series PGs, and PGE\textsubscript{2} can influence antibody production. PGs inhibit production of IL-1 and tumour necrosis factor (TNF) by macrophages [6]. Some macrophage enzyme activities are also modulated by PGs, as is expression of major histocompatibility class II receptors. There are conflicting reports about the effects of LTs on lymphocyte proliferation (see [4] for references), but NK cell activity is enhanced by LTB\textsubscript{4} [7]. LTB\textsubscript{4} and LTC\textsubscript{4} enhance IL-1 production by macrophages [6] and LTB\textsubscript{4} enhances interferon (IFN)-\gamma production by lymphocytes [7]. Figure 2 summarizes the effects of arachidonic acid-derived eicosanoids on lymphocyte functions. Because they influence eicosanoid production (see below), it is clear that \textit{n}-3 PUFAs can modulate immune-cell functions by eicosanoid-mediated effects.

**Modulation of eicosanoid synthesis by $n-3$ PUFAs**

Culture of macrophages or lymphocytes with \textit{n}-3 PUFAs results in replacement of arachidonic acid in phospholipids by the \textit{n}-3 PUFA provided [8-12]. As a result of this modification, smaller amounts of arachidonic acid-derived eicosanoids are produced by these cells. Dietary lipid modulation also results in significant modification of the fatty acid composition of macrophages isolated from the peritoneal cavity of mice [13-15] or rats [8,16-18], of lymphocytes isolated from rat lymphoid tissues [16,19] and of monocytes isolated from human peripheral blood [20,21]. It is widely reported that feeding laboratory animals with \textit{n}-3 PUFA-containing oils such as linseed or fish oil results in decreased production of arachidonic acid-derived eicosanoids [8,13,15,16,22,23]. Fish oil supplementation of the human diet results in similar changes [20,21]. The suppression of the amount of arachidonic acid-derived eicosanoids is mirrored by an elevation in the level of eicosapentaenoic acid-derived eicosanoids. As indicated earlier, these latter compounds are often less biologically potent than the analogues synthesized from arachidonic acid. Thus significant effects upon processes such as platelet aggregation, vasoconstriction, neutrophil function, inflammation and immunity result.

**PUFAs and signal transduction**

Apart from influencing the pattern of eicosanoids produced (see above), it is possible that \textit{n}-3 PUFAs influence signalling within cells of the immune system in other ways. Many lipids are involved directly in intracellular signalling pathways; for example, hydrolysis of membrane phospholipids such as PIP\textsubscript{2} and PC by phospholipases generates second messengers such as DAG. Other phospholipids have roles in activating or stabilizing enzymes involved in intracellular signalling; for example, phosphatidylserine (PS) is required for protein kinase C (PKC) activation. Because PIP\textsubscript{2}, PC, PS and DAG all contain fatty acyl chains attached to the 1 and 2 positions of the glycerol moiety, it is conceivable that changing the type of fatty acid present may alter the precise properties of these compounds with regard to their functions in signal transduction. Indeed, PKC is more active in the presence of dioleoylglycerol or diarachidonylglycerol than the presence of diacylglycerols containing two saturated fatty acids or one saturated and one unsaturated fatty acid [24]. Bell and Sargent [25] showed that the activity of rat spleen PKC differed in the presence of various combinations of PS and DAG each with differing fatty acid compositions, although the ‘observed effects were complex.’ They found that PKC was less active in the
presence of an \( n-3 \) PUFA-rich PS compared with a PUFA-poor PS irrespective of the fatty acid composition of the DAG [25]. Recently, Fowler et al. [26] reported that feeding mice for 10 days on a diet containing 1% purified ethyl ester of either eicosapentaenoic or docosahexaenoic acid resulted in enrichment of spleen lymphocyte DAG species with the fatty acid administered; the total mass of DAG was elevated in the docosahexaenoic acid-fed mice.

In addition to the effects of fatty acids on intracellular signalling mechanisms due to changes in the fatty acid composition of the phospholipids involved, it has been proposed that unsaturated fatty acids themselves may have a direct effect (see [27] for references). This direct modulatory effect of fatty acids has been most extensively documented in relation to PKC activity, which was shown to be enhanced by docosahexaenoic acid [28]. In contrast, although Speizer et al. [29] reported that eicosapentaenoic and docosahexaenoic acids increased PKC activity in the absence of PS and DAG, they found that in the presence of both PS and DAG each of these fatty acids caused up to 60% inhibition of PKC activity. Another study has shown that eicosapentaenoic and docosahexaenoic acids inhibit rat lymphocyte PKC activity in the presence of calcium, PS and DAG [30].

\( n-3 \) PUFAs and lymphocyte functions in vitro

Several studies have shown that \( \alpha \)-linolenic, eicosapentaenoic and docosahexaenoic acids inhibit antigen-, mitogen- or cytokine-stimulated proliferation of lymphocytes isolated from rodent lymphoid tissues (lymph nodes, spleen, thymus) and from human peripheral blood [31-41]; these studies have been reviewed in detail elsewhere [4,42,43]. The inhibitory effects of \( n-3 \) PUFAs on lymphocyte proliferation are not mediated by eicosanoids [34,36,39-41], nor do they occur as a result of lipid peroxidation [40,44]. The evidence for these conclusions is discussed in detail elsewhere [43]. Not only do \( n-3 \) PUFAs affect the response of lymphocytes to antigen, they may also affect the ability of antigen-presenting cells to present antigen; Fujikawa et al. [45] found that a triacylglycerol (TAG) containing eicosapentaenoic acid inhibited the ability of murine spleen cells to present antigen (keyhole limpet haemocyanin) to helper T-cell lines.

The proliferation of lymphocytes depends upon the production of IL-2. Culture of concanavalin A (Con A)-stimulated rat lymph-node lymphocytes with \( \alpha \)-linolenic, eicosapentaenoic or docosahexaenoic acids resulted in a 40–50% lower concentration of IL-2 in the culture medium than if the cells were cultured in the absence of fatty acids [37]. Similarly, culture of human peripheral blood lymphocytes (PBLs) with \( n-3 \) PUFAs resulted in 70–90% lower IL-2 concentrations in the culture medium [38]. These findings suggest that \( n-3 \) PUFAs may affect IL-2 production by mitogen-stimulated lymphocytes.

Yamashita et al. [46] showed that TAGs containing either eicosapentaenoic or docosahexaenoic acid cause concentration-dependent inhibition of human peripheral blood NK cell activity.

**Dietary \( n-3 \) PUFAs and lymphocyte and macrophage functions**

**Lymphocyte proliferation**

Studies involving the feeding of diets rich in \( n-6 \) PUFAs, such as corn, soybean, safflower or sunflower oils, to laboratory animals have recently been reviewed [4,43]. In recent years there has been increased interest in the effects of \( n-3 \) PUFA-containing oils (canola, linseed, fish) on lymphocyte proliferation. Several studies have reported that feeding such oils to laboratory animals (rats, mice, rabbits, chickens) suppresses the response of spleen lymphocytes to mitogenic stimuli including Con A, pokeweed mitogen and phytohaemagglutinin (PHA) [47-52].

Recently, we reported that feeding rats for 10 weeks on a diet containing 20% fish oil results in markedly suppressed Con A- and PHA-stimulated spleen, thymus, lymph node and PBL proliferation *ex vivo* [53-55]. Feeding with the fish oil diet decreased the level of expression of adhesion molecules (CD2, ICAM-1, LFA-1) on resting and/or mitogen-stimulated spleen lymphocytes [55]. Spleen lymphocytes from animals fed with this diet also showed a lower level of expression of the IL-2 receptor after mitogenic stimulation [55]. Thus, we proposed that the immunomodulatory effects of fish oil could be due to the decreased level of expression of key surface molecules.

Meydani et al. [56] reported the results of supplementing the diets of healthy young (22–33 years of age) or older (51–68 years of age) women with encapsulated \( n-3 \) PUFAs (approximately 2.4 g per day); the mitogenic response of
PBLs to PHA was lowered after 12 weeks of supplementation in the older women. Recently, Meydani et al. [57] reported a decreased response of PBLs to Con A or PHA after supplementation of the diet of volunteers on a low-fat, low-cholesterol diet with encapsulated n-3 PUFAs, whereas Endres et al. [58] found that 18 g of fish oil per day for 6 weeks resulted in lowered PHA-stimulated proliferation of PBLs 10 weeks after supplementation had ended (but not at the end of the supplementation period).

**Lymphocyte-mediated cytolyis**

Cytotoxic T-lymphocyte activity has been reported to be significantly diminished after feeding fish oil to mice or chickens [59-61]. Meydani et al. [62] found that feeding young mice with a diet containing 10% fish oil for 6 weeks caused a decrease in spleen NK cell activity compared with feeding with chow or corn oil; there were no differences in NK cell activity when these diets were fed to older mice. Feeding mice with a diet containing 10% fish oil suppressed spleen NK cell activity compared with a 10% linseed oil diet [60]. In the study of Berger et al. [52], female mice were fed for 5 months on diets containing 10% olive, safflower, linseed or fish oil, and the spleen NK cell activity of the pups was determined before they were weaned; the activity was lower in the fish-oil group than in the safflower- or olive-oil groups. Recently, Yaqoob et al. [63] showed that feeding 20% fish oil to weanling rats for 10 weeks significantly decreased spleen NK cell activity compared with feeding a low-fat diet or high-fat diets containing coconut, safflower or evening primrose oils. No studies have investigated the effect of dietary lipids on human NK cell activity, although intravenous injection of a TAG containing eicosapentaenoic acid into healthy volunteers resulted in suppression of peripheral blood NK cell activity 24 h later [46].

**Lymphocyte-derived cytokine production**

In contrast with the large number of studies of the effects of fish-oil feeding on the production of macrophage-derived cytokines ex vivo (see below), there have been only three studies on lymphocyte-derived cytokines. Two studies have reported that supplementation of the diet of healthy human volunteers with fish oil capsules significantly lowers IL-2 production by PBLs ex vivo [56,58]. The only animal study that has been reported so far showed no effect of feeding 20% fish oil to weanling mice on production of IL-2 by Con A-stimulated spleen lymphocytes [51]. However, mitogen-stimulated spleen lymphocytes from mice fed with fish oil produced less IL-4 and IL-10 than those from mice fed with a low-fat diet [51].

**Macrophage-derived cytokine production**

Because cytokine production by macrophages is regulated by eicosanoids, and because dietary lipids affect eicosanoid production (see above), it might be expected that dietary lipids, especially those containing n-3 PUFAs, affect cytokine production. A number of studies have reported that feeding rodents with n-3 PUFA-containing oils results in enhanced production of TNF ex vivo [15,17,22,64-66], although there are reports of decreased production [23,67] or no effect [68] after fish-oil feeding. A recent study showed that dietary fish oil increased IL-6 production by rat peritoneal macrophages [68], and an earlier study reported increased IL-1 production [64]. Again, however, there are contradictory reports [23,67]. The most likely reason for the variations in experimental observations are the differing protocols used (see [4]). In agreement with some of these animal experiments (but in contrast with others), Endres et al. [21,58] and Meydani et al. [56] found that dietary fish-oil supplementation in humans diminished the ability of peripheral blood monocytes to produce TNF, IL-1α and IL-1β ex vivo, and Meydani et al. [56] also reported decreased IL-6 production. These studies are supported by the observations in vitro that fish oil and eicosapentaenoic acid inhibit IL-1 production by a macrophage-like cell line and by human monocytes [69,70].

**Production of reactive oxygen species and nitric oxide**

The enzymes that result in synthesis of superoxide, hydrogen peroxide and nitric oxide are regulated by eicosanoids, cytokines and PKC. Therefore dietary n-3 PUFAs might affect the production of reactive oxygen species and nitric oxide by macrophages and so regulate the cytotoxic activities of these cells. Indeed, peritoneal macrophages from mice fed with 20% fish oil for 8 weeks produced more superoxide and hydrogen peroxide in response to stimulation by a phorbol ester than macrophages from mice fed with a low-fat diet [23]. Furthermore, macrophages from the fish-oil-fed mice produced more nitric oxide in response to stimulation with lipopoly-
saccharide than those from mice fed with the low-fat diet [23]. Because superoxide and hydrogen peroxide are important macrophage-derived cytotoxic agents these observations suggest that dietary fish oil could affect the killing of microbial or tumour cells by macrophages. Nitric oxide seems to regulate lymphocyte functions and so fish-oil-induced modulation of its generation from macrophages could affect lymphocyte activity.

**Dietary \( n-3 \) PUFAs and inflammatory diseases**

The low incidence of cardiovascular disorders among populations consuming large quantities of oily fish has been well documented (see, for example, [71]), but the intense interest in fish oils and coronary heart disease has overshadowed the unusual pattern of the incidence of some other diseases in native Greenland Eskimos. Kromann and Green [71] described a very low incidence of autoimmune and inflammatory disorders, such as psoriasis, asthma and type I diabetes and the complete absence of multiple sclerosis, in a population of Greenland Eskimos compared with sex- and age-matched groups living in Denmark. Thus the \( n-3 \) PUFAs-containing fish oils in the Eskimo diet could have a role in protection of these types of disease. Most of these diseases are characterized by inappropriate activation of T cells resulting in attack on, and ultimately destruction of, host tissues. There have been a number of clinical trials assessing the benefits of dietary supplementation with fish oils or encapsulated \( n-3 \) PUFAs in several inflammatory and autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, psoriasis, atopic dermatitis, bronchial asthma and systemic lupus erythematosus. These studies are summarized in detail elsewhere [72]; some showed modest beneficial effects of \( n-3 \) PUFAs.

**Dietary \( n-3 \) PUFAs and transplantation**

Graft rejection in transplantation surgery is caused by an immune reaction to the foreign material introduced to the body; T cells have been implicated in accelerated graft rejection, but antibodies with specificity for the graft donor have also been observed after rejection, implying that both cell-mediated and humoral immunity play a part in the rejection process.

The eicosanoids have been classed into an anti-rejection group, which includes PG_E_2, PGE_2, PGJ_2, PGD_2 and 6-keto PGF_1α, and a pro-rejection group, which includes TXs, LTs and possibly some HETEs and HPETEs (see [73,74] for reviews). Because of their effect on the amount and types of eicosanoid made, \( n-3 \) PUFAs would be expected to influence graft survival.

The so-called popliteal lymph node assay provides a useful experimental model in rodents for measuring graft versus host (GvH) and host versus graft (HvG) responses elicited by injection of allogeneic cells into the footpad of the host. Using this assay, Mertin et al. [75] reported that both the GvH and HvG responses were suppressed after administration of a fish-oil concentrate (750 mg/kg body weight) by oesophageal catheter to mice before, or immediately after, the inoculation with allogeneic cells. Hinds and Sanders [76] showed that there is a suppressed HvG response in mice fed with a 16% fish-oil diet compared with those fed with a standard chow diet. Sanderson et al. [77] found significantly diminished GvH and HvG responses in rats fed with 20% fish oil compared with those fed with a low-fat diet or diets containing 20% by weight of coconut, olive, safflower or evening primrose oils. The immunosuppressive effect of fish oil has also been evaluated, usually favourably, in studies of organ (heart, kidney) transplantation in both laboratory animals [78–82] and humans [83]. In a typical result from the animal studies, it was reported that intravenous fat emulsions rich in \( n-3 \) PUFAs prolonged the survival of rat cardiac transplants by up to 60% [82]. Homan van der Heide et al. [83] reported that renal transplant patients that received fish oil (6 g/day for the first post-operative year) in combination with cyclosporin A had better kidney function and fewer rejections over one year compared with patients that received coconut oil and cyclosporin A. This finding is supported by the observations that fish oil potentiates the immunosuppressive effect of sub-optimal concentrations of cyclosporin A after renal or cardiac allografts in rats [78,79].

**Concluding remarks**

The amount and type of eicosanoids made can be affected by the type of fat consumed in the diet. It is now apparent that both eicosanoids and \( n-3 \) PUFAs are potent modulators of lymphocyte and macrophage functions *in vitro*. Although some of the effects of \( n-3 \) PUFAs could be brought about by modulation of the amounts and types of eicosanoid made, it is clear that these...
fatty acids can also elicit their effects by eicosanoid-independent mechanisms (Figure 3). Inclusion in the diet of high levels of certain lipids containing \( n-3 \) PUFAs markedly affects the functions of cells of the immune system subsequently tested \textit{in vitro}. Cellular components of both natural and acquired immunity are affected. Tests \textit{in vivo} are perhaps the most appropriate approach for determining the effect of different dietary \( n-3 \) PUFAs on immune function. Several studies indicate that diets rich in \( n-3 \) PUFAs are immunosuppressive \textit{in vivo}, although there have been a few studies in humans. Such \( n-3 \) PUFAs-induced immunosuppression may be of use as a therapy for disorders that involve an inappropriately activated immune response, and in the enhancement of graft survival.

Membrane molecules and macrophage endocytosis: scavenger receptor and macro-sialin as markers of plasma-membrane and vacuolar functions

R. P. da Silva, N. Platt, W. J. S. de Villiers and S. Gordon

Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford OX1 3RE, U.K.

Introduction

Macrophages are able to interact with a wide range of soluble and particulate ligands, through the use of specific plasma-membrane receptors that mediate endocytosis and phagocytosis, in the absence or presence of plasma-, matrix- or cell-derived opsonins [1]. Control of engulfment by macrophages depends on the particle and ligands involved, the receptors themselves and their interactions with signal-transducing and cytoskeletal molecules. Non-phagocytic interactions underlie trophic interactions of macrophages with developing haematopoietic cells in bone marrow and foetal liver, for example [2], whereas recognition and destruction of senescent or apoptotic host cells, as well as invading microorganisms, contribute to tissue homeostasis and host defence. Once a foreign agent resides within the endosomal/phagosomal compartment its fate depends on interactions with the contents and membrane of the vacuole, which undergo dynamic changes as molecules are added by membrane biogenesis, further endocytosis and fusion, or removed by retrieval and degradation. Figure 1 shows, schematically, some of the components known to be involved in macrophage vacuolar maturation and function. This pathway plays an important role in processing foreign antigens, particularly protein-derived peptides that associate with polymorphic major histocompatibility complex (MHC) type II molecules and can thus be recognized by T-lymphocyte receptors during induction of cellular immunity. However, much remains unclear about the role of macrophages versus specialized antigen-presenting cells, lymphoid dendritic cells, and the complex generation and fate of peptide antigens in infected macrophages, as opposed to the lymphoid cell lines often employed in experimental analysis of immune recognition.

Surprisingly little attention has been paid to characterizing membrane molecules of macrophages, which may contribute to selective interactions with extracellular as well as intravacuolar ligands and can be used as experimental probes to monitor changes within this compartment. Our laboratory has studied a range of macrophage membrane glycoproteins that can be used to investigate cell differentiation and immune activation [3]. In this article we illustrate how...