Dietary n-6 and n-3 fatty acids in immunity and autoimmune disease

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Lipid biology plays a significant role in the normal and pathological functioning of cells of the immune system (Hopkins et al. 1981; Dvorak et al. 1983; Schlager et al. 1983; Shipman et al. 1988; Roper et al. 1990; Goetzl et al. 1995; Pushkareva et al. 1995; Hennig et al. 1996). In addition to the physiological requirements of cells of the immune system for essential fatty acids, dietary fatty acid modulation of the membrane composition and functions of immune cells can affect both normal and pathological processes (Calder, 1996; Harbige, 1996; Hennig et al. 1996). Among the first immunologists to recognize the importance of dietary fatty acids in immunity and autoimmune disease were Peter Medawar and Jürgen Mertin (Medawar et al. 1979) in the UK and Gabriel Fernandes and Robert Good (Fernandes et al. 1972) in the USA. The importance of dietary fatty acids in the prevention or control of autoimmune disease in animal models is now well documented (Mertin, 1981; Levy et al. 1982; Kelley et al. 1985; Morrow et al. 1985; Robinson et al. 1986; Alexander et al. 1987; Harbige et al. 1995; Lin et al. 1996). However, the biochemical and immunological mechanisms by which dietary fatty acids affect the immune system and autoimmunity have remained largely obscure. In recent years new concepts in immunoregulation have emerged which are likely to be of significance to effects of fatty acid nutrition on immunity. Mosman & Coffman (1989) have characterized two different patterns of cytokine secretion by T-cells which lead to different functional responses. T helper, (Th1) cells produce interleukin (IL)-2, interferon-γ and tumour necrosis factor-α which are not synthesized by Th2 cells. In contrast, Th2 cells (but not Th1) produce IL-4, IL-5 and IL-10. Th1 cells enhance cell-mediated inflammatory activity, whereas Th2 cells synthesize cytokines that help B-cells develop into antibody-producing cells. There are also T-cells able to produce both Th1 and Th2 cytokines, referred to as Th0 cells (Male et al. 1996). Weiner (1997) has further characterized a Th3 T-cell subset that primarily produces transforming growth factor-β (TGFβ), provides help for immunoglobulin (Ig) A production, and has suppressive properties. Importantly, the overall balance of cytokine production by Th1, Th2, and Th3 cells affects the type of immune response generated, e.g. Th2 cytokines can down-regulate production of Th1 cytokines and vice versa (Male et al. 1996). Eicosanoids are known to affect these immunoregulatory mechanisms (Phipps et al. 1991), which may, in part, explain the complex relationship between the immune system, eicosanoids and the eicosanoid precursor polyunsaturated fatty acids derived from the diet. The balance of membrane fatty acids and eicosanoids is also known to influence inflammatory reactions (Terano et al. 1984; Lefkowith, 1988; Tate et al. 1989; Ross, 1993; Calder, 1996; Hennig et al. 1996).

Essential fatty acid-deficient diets and high- and low-fat diets in autoimmune disease

Diets deficient in essential fatty acids and diets low in fat markedly increase the survival and reduce spontaneous autoimmune disease in NZB × NZW F1 mice (primarily autoantibody mediated), a model of the human disease systemic lupus erythematosus (Hurd et al. 1981; Levy et al. 1982). Essential fatty acid-deficient diets also protect against autoimmune diabetes in the BB rat and in a low-dose-streptozotocin-treated mouse model of autoimmune diabetes (Lefkowith et al. 1990). High-fat (both lard and maize oil) diets increase the levels of natural thymocytotoxic and anti-DNA antibodies along with increased immune complex deposition, decrease T-cell mitogenic responses to concanavalin A (Con A), and accelerate the disease course in NZB × NZW F1 mice (Levy et al. 1982; Yumura et al. 1985). In addition, the same group (Morrow et al. 1985) reported that high-saturated-fat (lard) diets have deleterious effects on both macrophage phagocytosis and natural killer cell activity, the latter correlating with in vitro interferon production. In the NZB × NZW F1 autoimmune model a high-fat diet consisting of equal amounts of lard and soya bean oil (rich in linoleic acid) causes animals to develop more severe disease and have a shortened lifespan associated with increased IgG anti-cardiolipin antibodies (Lin et al. 1996, 1997). In contrast to some of the previously described findings, in rats clinical manifestations of a T-cell-mediated disease experimental autoimmune encephalomyelitis (EAE), an animal model for the human disease multiple sclerosis, appear potentiated by fat deficiency (Clausen & Möller, 1967; Selivonchick & Johnston, 1975). However, there does appear to be disparity in the effects of fat deficiency on EAE (Levine & Sowinski, 1980), and the effects of high-fat diets have not been investigated.

Abbreviations: Con A, concanavalin A; EAE, experimental autoimmune encephalomyelitis; Ig, immunoglobulin; IL, interleukin; LT, leukotriene; ova, ovalbumin; PG, prostaglandin; PHA, phytohaemagglutinin; Th, T helper; TGFβ, transforming growth factor-β.

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Autoimmunity, immune functions and n-3 fatty acids

Animal and human studies

The effects of dietary n-3 fatty acids on ex vivo lymphocyte functions, as judged by mitogen stimulation, have been consistent in both human and animal studies showing suppressed responses (Calder, 1996). Kelley et al. (1988) found that an n-3 fatty acid-rich diet (76 g fish oil/kg) decreased rabbit peripheral-blood lymphocyte mitogenic responses to Con A, phytohemagglutinin (PHA) and pokeweed (Phytolacca americana) mitogen ex vivo. Similarly, in rats fed on a high-fish-oil diet Yaqoob et al. (1994) reported decreased proliferative responses to Con A for spleen and lymph node lymphocytes. In mice fed on a high-fish-oil diet spleen lymphocytes showed decreased responses to Con A (Yaqoob & Calder, 1995). In both fish oil-fed and fish oil plus high- or low-dose oral ovalbumin (ova) tolerance induction, ova immunized mice exhibited markedly reduced spleen lymphocyte responses to ova ex vivo and, in ova-fed animals only, reduced ova-specific levels of serum IgG1, IgG2a and IgG2b (LS Harbige and BAC Fisher, unpublished results). In contrast, Morrissey et al. (1990) observed increased Con A-induced proliferation with a low-fish-oil diet (50 g/kg) plus additional vitamin E (150 mg/kg). This suggests that low-dose-fish-oil feeding may have different effects on proliferative responses, or that vitamin E may have an effect on mitogen-induced lymphoproliferation independent of fish oil n-3 fatty acids. Interestingly, Kelley et al. (1988) observed enhanced lymphocyte responses in rabbits fed on α-linolenic acid-rich linseed oil. However, this response may reflect evolutionary adaptation of rabbits to an α-linolenic acid-rich herbivorous diet, and highlights the importance of species differences. All the previously described ex vivo findings may not reflect fully those in vivo. For example, there appear to be site-specific differences in lymphocyte responses to dietary fatty acids (Yaqoob et al. 1994), which appear to be dependent on the local adipose-tissue lipid composition (Pond, 1996). It is interesting to note that adipose tissue around lymph nodes preferentially incorporates or selectively retains polyunsaturated fatty acids (Pond, 1996). This suggests that lymphoid cells inside lymph nodes can be locally supplied with the appropriate fatty acids for membrane and eicosanoid synthesis.

Several investigators have found reduced major histocompatibility complex class II molecule expression in rodents fed on fish oil (Huang et al. 1992; Sherrington et al. 1995), indicating a decreased ability of antigen-presenting cells to present antigen to T lymphocytes. Consistent with the previous findings, Fujikawa et al. (1992) found splenocytes acting as antigen-presenting cells from mice fed on the n-3 fatty acid eicosapentaenoic acid had a reduced ability to present antigen to T-cell clones. Experimental data on the effects of feeding n-3 fatty acids on macrophage phagocytic functions and the production of H2O2, superoxide and NO have been inconsistent (Calder, 1996). There are also inconsistent reports of the effects of feeding fish oil to rodents on tumour necrosis factor and IL-1 production by peritoneal macrophages (Calder, 1996). In rats fed on fish oil (Leitch et al. 1984) or pure ethyl ester of eicosapentaenoic acid (Terano et al. 1984), ex vivo peritoneal leucocytes produced less pro-inflammatory leukotriene (LT) B4 and more of the less-potent LTBB.

Hughes et al. (1995) found that fish oil supplementation in human subjects reduced expression of major histocompatibility complex class II DR molecules on peripheral-blood monocytes which suggests antigen presentation may be affected. Fish oil supplementation for 24 weeks reduced the relative percentage of peripheral blood CD4+ and increased the percentage of CD8+ cells in man (Meydani et al. 1993). In non-human primates fed on diets containing 1.3-3.3% energy as eicosapentaenoic acid and docosahexaenoic acid for 14 weeks increased peripheral-blood lymphocyte responses to Con A and PHA have been reported (Wu et al. 1996). These investigators also found that the plasma vitamin E level was maintained, and suggested that in the presence of adequate vitamin E concentrations lymphocyte mitogenic proliferative responses are enhanced. Again this indicates vitamin E may have independent effects on immune function and that the balance of n-3 fatty acids and vitamin E is important. The effects of fish oil supplementation have been extensively studied on human peripheral-blood mononuclear cell cytokine production ex vivo, particularly IL-1β, IL-6, IL-8, IL-2, IL-6, and tumour necrosis factor-α, showing decreased production of these cytokines (Calder, 1996). Administration of 12-O-tetradecanoylphorbol-13-acetate induces tumour necrosis factor-α gene expression in human HL-60 cells through arachidonic acid metabolites acting as regulating messengers (Horiguchi et al. 1989). It is well known that on feeding fish oil the n-3 fatty acid, eicosapentaenoic acid, displaces arachidonic acid in membrane phospholipids. It is possible, therefore, that the effects of n-3 fatty acids on some pro-inflammatory cytokines may be indirect, and may indicate the direct importance of arachidonic acid metabolism in their regulation. The delayed-type hypersensitivity response, which is an in vivo measure of cell-mediated immunity, was reported by Meydani et al. (1993) to be reduced in response to several recall antigens, including tetanus toxoid and Mycobacterium tuberculosis, in subjects supplemented daily with 1.23 g eicosapentaenoic acid and docosahexaenoic acid. Investigators have shown that feeding fish oil induces a decrease in pro-inflammatory neutrophil LTβ production and an increase in the less potent pro-inflammatory lipid mediator LTβ in human subjects with inflammatory diseases (Schmidt & Dyerberg, 1989).

Autoimmune disease

In mouse models of the human disease, systemic lupus erythematosus, fish oils rich in n-3 fatty acids increase the longevity and delay the onset of clinical manifestations of spontaneous autoimmunity (autoantibody mediated) in NZB × NZW F1; and MRL1pr mice (Kelley et al. 1985; Godfrey et al. 1986; Robinson et al. 1986). Feeding fish oil compared with maize oil delayed the onset of autoimmune disease in NZB × NZW F1; mice (Fernandes et al. 1994). This observation was associated with elevated IL-2, IL-4 and TGFB1, and lower c-myc and c-ras mRNA in the spleen, with protein products following the same pattern (Fernandes et al. 1994). The same group reported high kidney TGFB1...
mRNA for NZB × NZW F₁ mice fed on maize oil and low
kidney TGFβ₁ mRNA expression for NZB × NZW F₁ mice
fed on fish oil, the reverse of their findings in the spleen
(Fernandes, 1994). In contrast, antioxidant enzyme mRNA
expression in the liver was higher in fish oil-fed mice than
in maize oil-fed mice (Fernandes, 1994). These workers
suggested that these findings were important to the renal dis-
ease normally observed in the NZB × NZW F₁ mouse, and
also that dietary fatty acids regulate TGFβ₁ and antioxidant
enzyme expression in an organ-specific manner (Chandra-
skar et al. 1995). Interestingly, Kubo et al. (1997) reported
organ-specific susceptibility to lipid peroxidation and
organ-specific differences for antioxidants, and sug-
gested that the kidney, in terms of its fatty acid composition,
is more resistant to dietary n-3 fatty acid influences.
Fernandes et al. (1996) have also shown that feeding fish oil
to the NZB × NZW F₁ mouse increases programmed cell
death of lymphocytes, which may prevent the accumula-
tion of self-reactive immune cells in lymphoid organs.

Evidence for beneficial effects of n-3 fish oil fatty acids in
experimentally-induced T-cell-mediated models of auto-
immune arthritis appear conflicting. In the mouse, Leslie
et al. (1985) found fish oil to protect against experimental
collagen-induced autoimmune arthritis, whilst in the rat fish
oil was reported to augment the disease (Prickett et al. 1984).
We found that feeding fish oil augmented EAE in the rat
(Harbige, 1993), although suppression of EAE using lower
doses of fish oil has been described by Mertin (1983), but the
animals developed more severe clinical disease after discon-
tinuation of treatment. The mechanism(s) involved in fish
oil-induced augmentation of experimental autoimmune
disease in rats is not well understood.

Autoimmunity, immune functions and n-6 fatty acids

Animal studies

Erickson et al. (1983) concluded from data obtained using a
mixed lymphocyte reaction (alloantigens) system as a mea-
sure of lymphocyte function in mice that high dietary
levels of safflower oil (rich in linoleic acid) suppressed the
response whereas lower levels intensified the response. Sim-
ilarly Yaqoob et al. (1994) reported that high levels of dietary
linoleic acid-rich oil suppressed Con A-stimulated lympho-
cyte proliferation in rats. In contrast, De Deckere et al.
(1988) found no effect on spleen lymphocyte proliferation in
response to Con A in rabbits and rats fed on diets containing
a high amount of linoleic acid (35 % digestible energy as
sunflower oil) compared with palm oil. Studies by Kelley
et al. (1988) in rabbits suggest that a low intake of linoleic
acid-rich safflower oil does not affect spleen-derivied lympho-
cyte responses or peripheral-blood-derived lymphocyte
responses to PHA and Con A. Cantillon et al. (1990) also
reported no effect of feeding linoleic acid-rich oil on rat lympho-
cyte proliferation ex vivo. Spleen lymphocytes from rats
orally administered safflower-seed oil showed enhanced Con
A responses ex vivo compared with lymphocytes from rats
fed on the basal diet (Harbige et al. 1995). Kollmorgen et al.
(1979) reported that feeding rats on maize oil reduced the ex
vivo lymphocyte proliferative response to Con A; an impor-
tant consideration in the Kollmorgen et al. (1979) study is the
use of maize oil stripped of vitamin E. Young et al. (1987)
showed reduced spleen lymphocyte proliferation in response
to Con A in mice treated with a pure linoleic acid prepara-
tion at an estimated ten times higher dose than those used by other
workers; in addition, linoleic acid was administered by subcutaneous injection. Cinader et al. (1983) found loss of
'suppressor activity' to the tolerance inducibility of rabbit
γ-globulin in mice fed on a linoleic acid-rich diet. In
mice fed a γ-linolenic acid-rich diet high- and low-dose oral
ova tolerance induction reduced ova-specific proliferative
responses (but not in animals fed on borage oil only) in ova
immunized mice and decreased (high dose oral ova only)
ova-specific serum IgG₂a and IgG₂b (LS Harbige and BAC
Fisher, unpublished results). In summary, the effects of
dietary linoleic acid on immune functions in animals appears
inconsistent, and more information is required on other fatty
acids of the n-6 family.

Human studies

The effects of n-6 fatty acids on immune functions, particu-
larly the desaturated and elongated metabolites of linoleic
acid, have not been studied as much as the n-3 fatty acids in
human subjects. Supplementation with γ-linolenic acid-rich
borage oil (Borago officinalis) did not affect the lympho-
proliferative response to PHA and anti-CD3, but did increase
the production of mitogen-stimulated peripheral-blood
mononuclear cell TGFβ₁ and decreased the production of
IL-4 and IL-10 (Harbige & Fisher, 1997). These findings are
consistent with the effects of prostaglandin (PG) E₂ and
PGF₂α on IL-4 and IL-10 in human T-cell clones (Harbige
et al. 1997a). However, the effects of PGE on T-cell clones
reported by Harbige et al. (1997a) are not consistent with
previous findings obtained using murine and human T-cell
clones (Betz & Fox, 1991; Watanabe et al. 1994), possibly
due to differences in clones, mode of activation and
ecosanoid concentrations used. Membrane lipid-oxidation
products have been shown to increase TGFβ₁ expression and
production (Leonarduzzi et al. 1997). It is possible, there-
fore, that an increase in membrane unsaturation, leading to
an increased peroxidizability index, by feeding γ-linolenic
acid-rich borage oil might lead to increased production of
TGFβ₁. However, we found no change in plasma
malondialdehyde concentration, a marker of peroxidation, in
a γ-linolenic acid-rich borage oil supplementation study in
human subjects (LS Harbige, F Kelley, C Dunster and K
Ghebremeskel, unpublished results).

Autoimmune disease

In the NZB × NZW F₁ autoimmune mouse, linoleic
acid-rich oil appears to exacerbate the disease (Levy et al.
1982) or to have no effect (Hurd et al. 1981). Similarly, in the
MLR/Ip autoimmume-prone mouse, linoleic acid-rich oil
also appears to enhance the disease or to have no effect
(Kelley et al. 1985; Godfrey et al. 1986). In addition, in the
MLR/Ip autoimmune-prone mouse, Godfrey et al. (1986)
observed a greater survival rate for mice supplemented with
50 g evening primrose (Oenothera biennis) oil/kg diet (72 g
linoleic acid and 9 g γ-linolenic acid/100 g total fatty acids).
These findings suggest that linoleic acid, the parent n-6 fatty
acid, is unable to ameliorate antibody-mediated spontaneous autoimmune disease, whereas the desaturated n-6 metabolites can. Studies in the guinea-pig have shown linoleic acid to partially suppress the incidence and severity of EAE (Meade et al. 1978). Similarly, high levels of a linoleic-rich oil containing low levels of γ-linolenic acid (linoleic acid : γ-linolenic acid 7 : 1, based on total fatty acid content) partially suppressed the incidence and severity of EAE in the rat (Mertin & Stackpoole, 1978). Using γ-linolenic acid-rich oils from fungal or plant sources we demonstrated complete protection against EAE in both rats and mice (Harbige et al. 1995, 1997b). This series of investigations demonstrated important disease-modifying effects of linoleic and γ-linolenic acid on clinical and histopathological manifestations of EAE. Depending on dose, γ-linolenic acid is completely protective in acute rat EAE, whereas linoleic acid has a dose-dependent action on the clinical severity of EAE, although not abolishing it. Analysis of spleen-cell membranes from mice indicated no gross immunosuppression by the fatty acid treatment (Harbige et al. 1997b). However, on activation with myelin oligodendrocyte glycoprotein peptide, Con A, and protein purified derivative there was a non-specific increase in the production of TGFβ1 and PGE2 in γ-linolenic-acid-fed mice ex vivo, with no effect on the production of IL-2 and interferon-γ (Harbige et al. 1997b). Furthermore, there was higher TGFβ1 mRNA expression and increased membrane eicosanoid precursor fatty acids (PGE1 and PGE2) in the spleens of γ-linolenic acid-fed mice. These findings are consistent with reports that administration of TGFβ protects in acute and relapsing EAE (Racke et al. 1993; Santambrogio et al. 1993), and that PG inhibitors, such as indomethacin, augment EAE (Ovadia & Paterson, 1982). In addition, during the natural recovery phase from EAE, TGFβ-secreting T-cells can inhibit EAE effector cells, TGFβ is expressed in the central nervous system and, in oral-tolerance-induced protection in EAE, TGFβ and PGE2 are expressed in the brain (Karpus & Swanborg, 1991; Khoury et al. 1992). Feeding γ-linolenic acid can increase PGE2 production (Fan & Chapkin, 1992; Harbige et al. 1997b), and PGE2 has been shown to inhibit the production of Th1 but not Th2 cytokines in vitro (Phipps et al. 1991). Importantly, adoptive transfer experiments have shown EAE to be a T-cell-mediated autoimmune disease in which Th1-type cytokine-producing cells cause pathology (Liblau et al. 1995). On this basis we could propose that dietary γ-linolenic acid prevents T-cell-mediated autoimmune disease by altering the balance of cytokines from a Th1- to a Th2-type response. However, our findings suggest that the effects of dietary γ-linolenic acid on EAE are mediated through Th1-like mechanisms involving TGFβ1 (Harbige et al. 1997b). It is interesting to note that Vidard et al. (1995) suggested from studies of T-cell tolerance and site-specific lymphokine profiles that the type of Th subset cytokine pattern produced depends on the environment in which they are found. In relation to the observations made by Pond (1996) mentioned earlier, this could be one mechanism by which local fatty acids affect Th subset cytokines.

The antioxidant enzymes superoxide dismutase (EC 1.15.1.1) and catalase (EC 1.11.1.6) have been shown to beneficially modify the clinical course of EAE (Guy et al. 1989). Previously we have shown that feeding a γ-linolenic acid-rich oil to rats increases the activity of superoxide dismutase in rat tissues (Phylactos et al. 1994). Increased antioxidant activity may therefore be an important mechanism by which linoleic acid metabolites control EAE. Similarly, Fernandes (1994) has suggested this as a mechanism in fish oil protective effects in NZB × NZW F1 mice.

The nature of the autoimmune model appears to be important. The Th2 cytokines IL-4, IL-6 and IL-10 are pro-inflammatory in the NZB × NZW F1 model, which is antibody-mediated (Fernandes, 1994). In contrast, in EAE, which is T-cell-mediated, IL-4 and IL-10 are associated with remission (Kennedy et al. 1992; Khoury et al. 1992; Liblau et al. 1995). Consistent with the previous findings, in the antibody-mediated NZB × NZW F1 autoimmune model, animals fed on a high-fat diet consisting of equal amounts of lard and soybean oil (linoleic acid-rich) develop a more severe disease and have a shortened lifespan, which is associated with increased autoantibody, and a decreased Th1 and increased Th2 cytokine profile (Lin et al. 1996).

**Supplementation with n-6 and n-3 fatty acids in human autoimmune inflammatory disease**

In clinical studies significant benefits have been reported in patients with systemic lupus erythematosus following a low-fat diet plus an n-3 fatty acid-rich fish oil supplement (Walton et al. 1991). Controlled trials in patients with rheumatoid arthritis on diets high in n-3 fatty acids without background saturated fat manipulation have also shown clinically beneficial effects (Kremer et al. 1985; Cleland et al. 1988). Interestingly, Kremer et al. (1987) found a significant correlation between decreases in neutrophil LTβ4 production and decreases in the number of tender joints in individual patients supplemented with fish oil. In patients with rheumatoid arthritis, treatment with evening primrose oil enabled 73 % of patients to stop or reduce non-steroidal anti-inflammatory drug treatment (Belch et al. 1988). Using γ-linolenic acid-rich borage oil (23 g γ-linolenic acid and 62 g linolenic acid/100 g total fatty acids), Leventhal et al. (1993) managed to significantly reduce clinically-important signs and symptoms of disease activity in patients with active rheumatoid arthritis. Belluzzi et al. (1996), feeding a novel fish oil preparation in a double-blind placebo-controlled trial with patients with Crohn’s disease have reported a 60 % reduction in relapse rate. Double-blind trials to determine the therapeutic efficacy of diets supplemented with sunflower...
Summary and conclusions

Clearly there is much evidence to show that under well-controlled laboratory and dietary conditions fatty acid intake can have profound effects on animal models of autoimmune disease. Studies in human autoimmune disease have been less dramatic; however, human trials have been subject to uncontrolled dietary and genetic backgrounds, infection and other environmental influences, and basic trial designs have been inadequate. The impact of dietary fatty acids on animal autoimmune disease models appears to depend on the animal model and the type and amount of fatty acids fed. Diets low in fat, essential fatty acid-deficient, or high in n-3 fatty acids from fish oils increase the survival and reduce disease severity in spontaneous autoantibody-mediated disease, whilst linoleic acid-rich diets appear to increase disease severity. In experimentally-induced T-cell-mediated autoimmune disease, essential fatty acid-deficient diets or diets supplemented with n-3 fatty acids appear to augment disease, whereas n-6 fatty acids prevent or reduce the severity. In contrast, in both T-cell and antibody-mediated autoimmune disease the desaturated and elongated metabolites of linoleic acid are protective. Suppression of autoantibody and T lymphocyte proliferation, apoptosis of autoreactive lymphocytes, and reduced pro-inflammatory cytokine production by high-dose fish oils are all likely mechanisms by which n-3 fatty acids ameliorate autoimmune disease. However, these could be undesirable long-term effects of high-dose fish oil which may compromise host immunity. The protective mechanism(s) of n-6 fatty acids in T-cell-mediated autoimmune disease are less clear, but may include dihomo-γ-linolenic acid- and arachidonic acid-sensitive immunoregulatory circuits such as Th1 responses, TGFβ-mediated effects and Th2-like responses. It is often claimed that n-6 fatty acids promote autoimmune and inflammatory disease based on results obtained with linoleic acid only. It should be appreciated that linoleic acid does not reflect the functions of dihomo-γ-linolenic and arachidonic acid, and that the endogenous rate of conversion of linoleic to arachidonic acid is slow (Hassam et al. 1975, 1977; Phylactos et al. 1994; Harbige et al. 1995). In addition to effects of dietary fatty acids on immunoregulation, inflammation as a consequence of immune activation in autoimmune disease may also be an important mechanism of action whereby dietary fatty acids modulate disease activity.

In conclusion, regulation of gene expression, signal transduction pathways, production of eicosanoids and cytokines, and the action of antioxidant enzymes are all mechanisms by which dietary n-6 and n-3 fatty acids may exert effects on the immune system and autoimmune disease. Probably the most significant of these mechanisms in relation to our current understanding of immunoregulation and inflammation would appear to be via fatty acid effects on cytokines. The amount, type and balance of dietary fatty acids and associated antioxidant nutrients appear to impact on the immune system to produce immune-deviation or immunosuppressive effects, and to reduce immune-mediated inflammation which will in turn affect the susceptibility to, or severity of, autoimmune disease.

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