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PERINATAL PROGRAMMING OF ESSENTIAL FATTY ACIDS MODULATES IMMUNITY IN RATS

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SUMMARY

Recent studies have shown that besides the eicosanoids modulating the immunological response, also the peroxisome proliferator-activated receptor gamma (PPARγ) and its ligands can modulate both B and T lymphocytes and the dendritic cells. Fatty acids are potent ligands to PPARs and some of the effects might therefore be mediated via the PPAR systems and NF-κB pathways (*Appel* et al., 2005; *Jakobsen* et al., 2006). However, fatty acids can also influence dendritic cells independently of activation (*Zeyda* et al., 2005). Further studies have to consider the influence on gene expression and the modulation by different fatty acids, probably including the balance not only between the essential fatty acids, but also the balance to saturated and monounsaturated fatty acids. We are probably just in the beginning to understand the complex balance of the immune system with possible early programming, which might even include epigenetic aspects.

Our results indicate important physiological changes by fatty acids in the development of oral tolerance. Leptin might be involved in this development but also fatty acid products, the eicosanoids are probably important. PPARs, which also are influenced by fatty acids and other ligands, can further modulate the immune response via or independently of NF-κB. It is obvious that in animals, the composition of the maternal diet has direct and long-term influence on the immune system and it would not be too speculative to suggest that the complicated system also have similar impact in the humans. The complexity of the systems may explain the difficulties to get clear results in observational studies in the humans, and strongly implies that longitudinal studies from pregnancy on are urgently needed.

INTRODUCTION

There has been an increase of allergy in the Western world during the latest decades and much focus has been directed to both the "hygiene" hypothesis and diet (*Guarner* et al., 2006; *van Schayck* and *Knottnerus*, 2004; *Renz* et al., 2006; *Duchen* and *Björksten*, 2001). Several studies have reported abnormal fatty acid pattern in serum in patients with allergy but the results have not been uniform and a causal relation between an abnormal lipid

metabolism and allergy has remained puzzling (*Duchen* and *Björksten*, 2001; *Laitinen* et al., 2006a; *Oddy* et al., 2004). Despite that it is well known that bacterial growth can be modulated by fatty acids, there have been little interest to combine these hypotheses.

FATTY ACIDS AS MODULATORS OF IMMUNE SYSTEM

A possible link between allergy and abnormal fatty acid pattern is the fact that the relation between different fatty acids in diet has changed markedly during the latest decades (*Simopoulos*, 1999; *Sanders*, 2000; *Kris-Etherton* et al., 2000). By the general recommendation to decrease the intake of saturated fat and recommend increase of polyunsaturated fat, a marked displacement has taken place; essential fatty acids of the n-6 series have increased several fold but those of the n-3 series have remained low and even decreased (*Ailhaud* et al., 2006). Partly also this has occurred smouldering for the man in general, because the changed feeding of animals from natural sources to special forage have also markedly decreased the n-3 fatty acids in diary products and in the meat (*Ailhaud* et al., 2006; *Raes* et al., 2004). All these changes are reflected in the breast milk, which shows different ratios between the n-6 and n-3 fatty acids depending on mothers dietary intake, with big differences for different districts and countries and also by time in the Western countries, reflecting the general development (*Ailhaud* et al., 2006; *Chen* et al., 1997; *Fidler* and *Koletzko*, 2000). From this point of view, it is not surprising that investigations of breast milk in relation to allergy have given controversial results (*Laitinen* et al., 2006a,b; *Black* and *Sharpe*, 1997; *van Gool* et al., 2004).
Our interest in this subject is related to two factors; first that the n-6 and n-3 fatty acids have strong effect on immunity, like for instance different effects on Th1 and Th2 responses and influence on the maturation of dendritic cells (*Lee* et al., 2003; *Harizi* and *Gualde*, 2005; *Gosset* et al., 2005; *Zhang* et al., 2005), and second that essential fatty acids can influence gene expression (*Clarke* et al., 2002) and therefore might be especially interesting in the context of programming, i.e. the influence during early development of the foetus on diseases in adult life (*Lucas*, 1998).

Essential fatty acids contain unsaturated bindings starting at the carbons in position 3 (n-3) or 6 (n-6) from the methyl end of the fatty acid molecule. These fatty acids have to be supplied by food because they cannot be synthesised by the mammalians. Introduction of double bonds in other positions can be performed in the body, and occur both in the essential fatty acids and in fatty acids we can synthesize (Figure 1). There is a competition between enzymes to prolong the fatty acid molecules (elongases) and to increase the unsaturation (desaturases) between the essential fatty acid series and the newly synthesised fatty acids, and this competition is influenced by the access of substrate, i.e. it matters in which relation the diet supply the body with different kind of food and fat. Since the very long polyunsaturated fatty acids are important for many functions, like the long fatty acids from the n-3 series, the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for the brain and nervous system and the long fatty acid product of the n-6 series, arachidonic acid (ARA) for several meta-

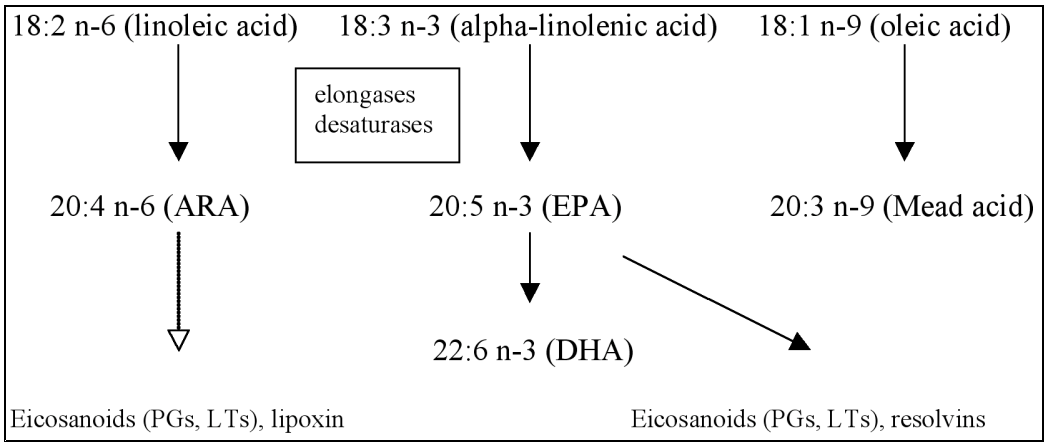

Figure 1: The major fatty acids of the n-6, n-3 and the endogenously (n-9) synthezised series. In deficiency of the essential fatty acids, especially the n-6 series, mead acid is compensatory increased and can therefore be used as an index of the essential fatty acid deficiency. The eicosanoids of ARA are inflammatory and those of EPA, lipoxins and resolvins are anti-inflammatory.

bolic processes and working as the substrate for very important eicosanoids, like PGE_2 and the cysteinyl-leukotrienes (Figure 1).

DEVELOPMENT OF ORAL TOLERANCE

The knowledge about the induction or breakdown of oral tolerance in the neonatal period is incomplete. In the development of oral tolerance the antigen-presenting cells, especially the dendritic cells, play a central role in the induction of adaptive immunity. Dendritic cells are activated by cytokines and eicosanoids and the balance between saturated and polyunsaturated fatty acids can reciprocally modulate the function of the dendritic cells through Toll-like receptors (*Weatherill* et al., 2005). Active suppression is important for and dependent on the induction and the maintenance of the regulatory suppressor cells (Treg/Th3) and their presence in the lymph nodes of the intestinal wall. These cells are triggered by a specific antigen and responsible for the release of the antigen-non-specific suppressive cytokine TGF-β (*Lundin* et al., 1999). As a consequence immune responses to other antigens in the close vicinity are decreased. If immunological tolerance is not developed, the immune response may lead to allergic sensitisation to food allergens. The dose and nature of antigen, as well as the maturation of the immune system, and the permeability of the intestinal wall are all factors of importance if an antigen induces tolerance or priming (*Strobel*, 2001). For the newborn most antigens are presented via the food, usually the breast milk, and the content of polyunsaturated fatty acids is dependent on the mother's diet. That means that the maternal diet has the potential to influence the development of immunological tolerance to food antigens.

Dietary polyunsaturated fatty acids have been shown to influence the tolerance induction in adult animals, and to influence the Th1 and Th2 responses to ovalbumin (*Cinader* et al., 1983; *Harbige* and *Fisher*, 2001).

EXPERIMENTAL PROGRAMMING OF ORAL TOLERANCE BY EFA

We have focused our interest on the possible potency of essential fatty acids to programme for diseases in the adult animal, and have been especially interested if they can influence the later development of oral tolerance, important in the context of allergy. Besides these studies, which will be reviewed in the following, we have also investigated whether the essential fatty acids might programme for bone mass (*Korotkova* et al, 2004a, 2005a) and the metabolic syndrome (*Korotkova* et al, 2005b). We have used two models, one providing the pregnant and lactating animal with essential fatty acid deficient diet (**A**) and one where the animals were provided three different diets, one rich in n-3 fatty acids (ratio n-6/n-3 of 0.4), one "control" diet with a so called balanced ratio of n-6/n-3 fatty acids (ratio n-6/n-3 of 9) and one with extremely high amount of n-6 fatty acids in relation to n-3 (corresponding ratio of 210) (**B**).

All diets had the same composition except that the quality of fat differed. Fat constituted 7 percent of all diets and in the diet free of essential fatty acids; the animals were given saturated fat except for trace of monounsaturated fat. In the diets with different ratios of essential fatty acids, 21-32 % of the fatty acids were monounsaturated and 13-20% was saturated fatty acids. The diet were introduced from the 10^{th} day of gestation and kept during lactation and till 7 weeks of age. The rats were subsequently exposed to ovalbumin either as pups via the milk at postnatal days 10-16, or as adults via the drinking water at 7-9 weeks of age.

A. For control one group of rats received the essential fatty acid deficient diet only as adults, from week 7 of age (31). They were immunized at 11 weeks with ovalbumin and delayed type of hypersensitivity (DTH) was tested at 13 weeks of age. Oral exposure of ovalbumin lead to suppression of the DTH response and also depressed response by IgG antibodies in both the animals deficient of essential fatty acids and the control group (31). The tolerance to ovalbumin was accompanied by reduction of DTH and IgG antibody responses to an unrelated antigen, human serum albumin, due to bystander suppression. Thus oral tolerance was developed and maintained by an active suppression mechanism in the adult animals of both the dietary groups.

In the adult offspring of the dams fed the deficient diet during the last half of pregnancy and during lactation, neonatal antigen exposure via the milk resulted in suppression of the serum antibody levels and DTH response against ovalbumin indicating induction of oral tolerance (31). In contrast, ovalbumin exposure of the dams fed the control diet did not result in suppressed ovalbumin responses of their offspring. Also the IgG and IgM antibody responses were only depressed in the animals on the deficient diet. Higher expression of TGF-β mRNA in the draining lymph nodes suggested that these effects were mediated via Treg cells. In the intestinal cells the essential fatty acid pattern was markedly abnormal at the time of weaning in the deficient animals and the CD8+ T-cells were increased. The expression of MHC class II was not different between the groups. Hence, these data indicate that the dietary content of polyunsaturated fatty acids was one factor of importance for the induction or failure of oral tolerance.

B. These data stimulated us to investigate the effects of different ratios of the n-6/n-3 fatty acids in the mater-

nal diet on the induction of the neonatal oral tolerance in the rat offspring (*Korotkova* et al., 2004c). Interestingly, the milk from the dams contained exactly the same ratio of essential fatty acids as the diet, but in serum of the pups at 3 weeks of age, the ratios were adapted, well into physiological range, being 3, 8 and 17, respectively. The serum fatty acid pattern was different between the pups reflecting the diets, as was the fatty acid composition of the adipose tissue. As described above, rat pups were exposed to ovalbumin via the milk at postnatal days 10-16. In the adult offspring from dams receiving the n-3 diet, exposure to ovalbumin via the milk resulted in lower DTH and antibody responses against both ovalbumin and human serum albumin, compared to those offspring on the same diet but not exposed to ovalbumin postnatally, indicating induction of oral tolerance. Also the antibody response followed the same pattern as the DTH reaction. Serum antibodies of the IgE class were also depressed in the n-3 animals exposed to ovalbumin. The lymph nodes draining the immunisation site were also less enlarged in the offspring exposed to ovalbumin via their dams, suggesting that in these animals the tolerance was mediated at least partly by an active suppression mechanism. In contrast, the adult offspring from dams receiving the n-6/n-3 diet did not show tolerance. Further increase of the n-6/n-3 ratio in the maternal diet was associated with induction of oral tolerance in the n-6 group of offspring. However, the bystander suppression was not observed in the offspring receiving the n-6 diet, suggesting that the oral tolerance probably was mediated by anergy in these animals. The results suggested that the ratio of the n-6/n-3 fatty acids in the maternal diet affected the mechanisms of neonatal oral tolerance and are in line with previous published data, demonstrating that dietary levels of the n-6/n-3 polyunsaturated fatty acids influence the mechanism of oral tolerance in adult mice (*Harbige* and *Fisher*, 2001).

We also investigated the mammary glands at the time of weaning (*Korotkova* et al., 2004c). There was no difference in the number of macrophages, T-cells or dendritic cells between the different dietary groups and although the number of activated dendritic cells differed numerically (3.4, 4.9 and 11.4 cells/mm^3, respectively), the differences were not statistically significant. The number of MHC class II positive cells in the mammary glands was significantly lower in the n-3 group of mothers ($p<0.05$). The results showed that the quality of fat ingested by the mother had effects on the development of immunological tolerance to dietary antigens in the offspring of the animals but the mechanisms have to be further studied. The relevance of our findings in understanding of allergy in the humans has thus to be determined.

POSSIBLE ASSOCIATED FACTORS IN PROGRAMMING OF ORAL TOLERANCE

There are many possible factors which might be involved in the development of oral tolerance. Leptin is widely distributed in the body, also with receptors in the gastrointestinal tract and in hypothalamus. It is known to regulate food intake and energy expenditure and immune responses. It is structurally similar to IL-6 cytokines and binds to receptors, which belong to the class I cytokine receptors. Leptin up-regulates monocytes/macrophage

functions (*Santos-Alvarez* et al., 1999) and modifies T cell responses with increasing Th1 (IL-2, IFN-g) and suppressing Th2 (IL-4, IL-10) cytokine production (*Lord* et al., 1998). In a recent study serum leptin in mice was increased related to enhanced metacholine responsiveness and IgE responses on sensitisation with ovalbumin (*Shore* et al., 2005). Leptin is secreted in breast milk and might play an important role in the induction and maintenance of immune and inflammatory responses, especially vital in the perinatal period. It has been shown that the quantity of dietary fat affects serum leptin levels perinatally. Increased maternal fat intake raises plasma leptin concentrations in neonatal rats and affects hypothalamus-pituitary-adrenal responsiveness in neonates and prepuberal rats (*Trottier* et al., 1998).

A. We found in our studies that the quality of the dietary fat modulated serum leptin levels in rat offspring during the suckling period, both in deficiency of the essential fatty acids and in studies of different ratios of the n-6 and n-3 series (*Korotkova* et al., 2001, 2002a,b). In the model with the essential fatty acid deficient diet, the weight of inguinal white adipose tissue depots and the serum leptin levels of the essential fatty acid deficient offspring were significantly lower than in the control pups during the whole suckling period, despite that milk leptin levels were higher in the deficient dams than in the control dams at 3 weeks of lactation. Furthermore, leptin receptor mRNA was significantly increased in mesenteric lymph nodes (*Palsdottir* and *Korotkova*, to be published), but the mRNA levels of leptin was decreased in inguinal adipose tissue compared with the control pups at 3 weeks of age (*Korotkova* et al., 2002a).

B. The different dietary ratios of n-6/n-3 fatty acids also influenced the serum leptin levels in the postnatal period (*Korotkova* et al., 2002b). Body weight, body length, inguinal fat pad weight, adipocyte size and serum leptin levels of the offspring receiving the n-3 diet were significantly lower during the whole suckling period compared with the n-6/n-3 fed offspring. The mean serum leptin levels of the n-6 offspring were between the other two groups, but not different from either group. Despite that the serum leptin levels were increased and the milk leptin content did not differ between the groups, the leptin mRNA in the adipose tissue was significantly lower in the n-6/n-3 group compared with the other two groups at 3 weeks of age (*Korotkova* et al., 2002b).

LITERATURE

Ailhaud, G., Massiera, F., Weill, P., Legrand, P., Alessandri, J.-M., and Guesnet, P.: Temporal changes in dietary fats: Role of n-6 polyunsaturated fatty acids in excessive adipose tissue development and relationship to obesity. Progr. Lipid Res. 45, 203-236 (2006).

Appel, S., Mirakaj, V., Bringmann, A., Weck, M.M., Grünebach, F., and Brossart, P.: PPAR-γ agonists inhibit toll-like receptor-mediated activation of dendritic cells via the MAP kinase and NF-κB pathways. Blood 106, 3888-3894 (2005).

Black, P.N. and Sharpe, S.: Dietary fat and asthma: Is there a connection? Eur. Respir. J. 10, 6-12 (1997).

Chen, Z.Y., Kwan, K.Y., Tong, K.K., Ratnayake, W.M., Li, H.Q., and Leung, S.S.: Breast milk fatty acid composition: A comparative study between Hong kong and

Chongqing Chinese. Lipids 32, 1061-1067 (1997).

Cinader, B., Clandinin, M.T., Hosokawa, T., and Robblee, N.M.: Dietary fat alters the fatty acid composition of lymphocyte membranes and the rate at which suppressor capacity is lost. Immunol. Lett. 6, 331-337 (1983).

Clarke, S., Gasperikova, D., Nelson, C., Lapillonne, A., and Heird, W.C.: Fatty acid regulation of gene expression. A genomic explanation for the benefits of the Mediterranean diet. Ann. NY Acad. Sci. 967, 283-298 (2002).

Duchen, K. and Björksten, B.: Polyunsaturated n-3 fatty acids and the development of atopic disease. Lipids 36, 1033-1042 (2001).

Fidler, N. and Koletzko, B.: The fatty acid composition of human colostrum. Eur. J. Nutr. 71, 31-37 (2000).

Gosset, P., Pichavant, M., Faveeuw, C., Bureau, F., Tonnel, A.-B., and Trottein, F.: Prostaglandin D_2 affects the differentiation and functions of human dendritic cells: Impact on the T cell response. Eur. J. Immunol. 35, 1491-1500 (2005).

Guarner, F., Bourdet-Sicard, R., Brandtzaeg, P., Gill, H.S., McGuirk, P., van Eden, W., Versalovic, J., Weinstock, J.V., and Rook, G.A.: Mechanisms of disease: The hygiene hypothesis revisited. Nat. Clin. Pract. Gastroenterol. Hepatol. 3, 275-284 (2006).

Harbige, L.S. and Fisher, B.A.: Dietary fatty acid modulation of mucosally-induced tolerogenic immune responses. Proc. Nutr. Soc. 60, 449-456 (2001).

Harizi, H. and Gualde, N.: The impact of eicosanoids on the crosstalk between innate and adaptive immunity: The key roles of dendritic cells. Tissue Antigens 65, 507-514 (2005).

Jakobsen, M.A., Petersen, R.K., Kristiansen, K., Lange, M., and Lillevang, S.T.: Peroxisome proliferator-activated receptor α, δ, γ1 and γ2 expressions are present in human monocyte-derived dendritic cells and modulate dendritic cell maturation by addition of subtype-specific ligands. Scand. J. Immunol. 63, 330-337 (2006).

Korotkova, M., Gabrielsson, B., Hanson, L., and Strandvik, B.: Maternal essential fatty acid deficiency depresses serum leptin levels in suckling rat pups. J. Lipid Res. 42, 359-365 (2001).

Korotkova, M., Gabrielsson, B., Hanson, L.A., and Strandvik, B.: Maternal dietary intake of essential fatty acids affects adipose tissue growth and leptin mRNA expression in suckling rat pups. Pediatr. Res. 52, 78-84 (2002a).

Korotkova, M., Gabrielsson, B., Lönn, M., Hanson, L., and Strandvik, B.: Leptin levels in rat offspring are modified by the ratio of linoleic to alpha-linolenic acid in the maternal diet. J. Lipid Res. 43, 1743-1749 (2002b).

Korotkova, M., Ohlsson, C., Hanson, L.Å., and Strandvik, B.: Dietary n-6:n-3 fatty acid ratio in the perinatal period affects bone parameters in adult female rats. Br. J. Nutr. 92, 643-648 (2004a).

Korotkova, M., Telemo, E., Hanson, L.A., and Strandvik, B.: Modulation of neonatal immunological tolerance to ovalbumin by maternal essential fatty acid intake. Pediatr. Allergy Immunol. 15, 112-122 (2004b).

Korotkova, M., Telemo, E., Yamashiro, Y., Hanson, L.A., and Strandvik, B.: The ratio of n-6 to n-3 fatty acids in maternal diet influences the induction of neonatal immunological tolerance to ovalbumin. Clin. Exp. Immunol. 137, 237-244 (2004c).

Korotkova, M., Ohlsson, C., Gabrielsson, B., Hanson, L.Å., and Strandvik, B.: Perinatal essential fatty acid deficiency influences body weight and bone parameters in adult male rats. Biochim. Biophys. Acta 1686, 248-254 (2005a).

Korotkova, M., Gabrielsson, B., Holmäng, A., Larsson, B.M., Hansson, L.Å., and Strandvik B.: Gender related long-term effects in adult rats by perinatal dietary ratio on n-6/n-3 fatty acids. Am. J. Physiol. Regul. Integr. Comp. Physiol. 288, R575-R579 (2005b).

Kris-Etherton, P.M., Taylor, D.S., Yu-Poth, S., Huth, P., Moriarty, K., Fishell, V., Har-

grove, R.L., Zhao, G., and Etherton, T.D.: Polyunsaturated fatty acids in the food chain in the United States. Am. J. Clin. Nutr. 71, 179S-188S (2000).

Laitinen, K., Hoppu, U., Hamalainen, M., Linderborg, K., Moilanen, E., and Isolauri, E.: Breast milk fatty acids may link innate and adaptive immune regulation: Analysis of soluble CD14, prostaglandin E2, and fatty acids. Pediatr. Res. 59, 723-727 (2006a).

Laitinen, K., Sallinen, J., Linderborg, K., and Isolauri, E.: Serum, cheek cell and breast milk fatty acid compositions in infants with atopic and non-atopic eczema. Clin. Exp. Allergy 36, 166-173 (2006b).

Lee, J.Y., Plakidas, A., Lee, W.H., Heikkinen, A., Chanmugam, P., Bray, G., and Hwang, D.H.: Differential modulation of Toll-like receptors by fatty acids: Preferential inhibition by n-3 polyunsaturated fatty acids. J. Lipid Res. 44, 479-486 (2003).

Lord, G.M., Matarese, G., Howard, J.K., Baker, R.J., Bloom, S.R., and Lechler, R.I.: Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 394, 897-901 (1998).

Lucas, A.: Programming by early nutrition: An experimental approach. J. Nutr. 128, Suppl. 2, 401-406 (1998).

Lundin, B.S., Karlsson, M.R., Svensson, L.A., Hanson, L.A., Dahlgren, U.I., and Telemo, E.: Active suppression in orally tolerized rats coincides with *in situ* transforming growth factor-beta (TGF-beta) expression in the draining lymph nodes. Clin. Exp. Immunol. 116, 181-187 (1999).

Oddy, W.H., de Klerk, N.H., Kendall, G.E., Mihrshahi, S., and Peat, J.K.: Ratio of omega-6 to omega-3 fatty acids and childhood asthma. J. Asthma 41, 319-326 (2004).

Raes, K., Demeyer, D., and De Smet, S.: Effect of dietary fatty acids on incorporation of long chain polyunsaturated fatty acids and conjugated linoleic acid in lamb, beef and pork meat: A review. Anim. Feed Sci. Techn. 113, 199-221 (2004).

Renz, H., Blumer, N., Virna, S., Sel, S., and Garn, H.: The immunological basis of the hygiene hypothesis. Chem. Immunol. Allergy 91, 30-48 (2006).

Sanders, T.A.: Polyunsaturated fatty acids in the food chain in Europe. Am. J. Clin. Nutr. 71, 1 Suppl., 176S-178S (2000).

Santos-Alvarez, J., Goberna, R., and Sanchez-Margalet, V.: Human leptin stimulates proliferation and activation of human circulating monocytes. Cell. Immunol. 194, 6-11 (1999).

Shore, S.A., Schwartzman, I.N., Mellema, M.S., Flynt, L., Imrich, A., and Johnston, R.A.: Effect of leptin on allergic airway responses in mice. J. Allergy Clin. Immunol. 115, 103-109 (2005).

Simopoulos, A.P.: Essential fatty acids in health and chronic disease. Am. J. Clin. Nutr. 70, 3 Suppl., 560S-569S (1999).

Strobel, S.: Immunity induced after a feed of antigen during early life: Oral tolerance v. sensitisation. Proc. Nutr. Soc. 60, 437-442 (2001).

Trottier, G., Koski, K.G., Brun, T., Toufexis, D.J., Richard, D., and Walker, C.D.: Increased fat intake during lactation modifies hypothalamic-pituitary-adrenal responsiveness in developing rat pups: A possible role for leptin. Endocrinology 139, 3704-3711 (1998).

van Gool, C.J.A.W., Zeegers, M.P.A., and Thijs, C.: Oral essential fatty acid supplementation in atopic dermatitis – a meta-analysis of placebo-controlled trials. Br. J. Dermatol. 150, 728-740 (2004).

van Schayck, C.P. and Knottnerus, J.A.: No clinical evidence base to support the hygiene hypothesis. Prim. Care Respir. J. 13, 76-79 (2004).

Weatherill, A.R., Lee, J.Y., Zhao, L., Lemay, D.G., Youn, H.S., and Hwang, D.H.: Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated through TLR4. J. Immunol. 174, 5390-5397 (2005).

Zeyda, M., Säemann, M.D., Stuhlmeier, K.M., Mascher, D.G., Nowotny, P.N., Zlabinger, G.J., Waldhausl, W., and Stulnig, T.M.:

Polyunsaturated fatty acids block dendritic cell activation and function independently of NF-κB activation. J. Biol. Chem. 280, 14293-14301 (2005).

Zhang, P., Smith, R., Chapkin, R.S., and McMurray, D.N.: Dietary (n-3) polyunsaturated fatty acids modulate murine Th1/Th2 balance toward the Th2 pole by suppression of Th1 development. J. Nutr. 135, 1745-1751 (2005).