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Review Article

Impact of PUFA on early immune and fetal development

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It has recently been reported that the increased prevalence in childhood allergy may be linked to deviations in fetal immune development. One reason may be impaired nutrient supply. Hence, a well-differentiated placenta together with an optimal fetal nutrition via the mother are important prerequisites for the establishment of a functional immune system with normal immune responses. Fatty acids and their derivatives can influence both the early immune development and immune maturation by regulating numerous metabolic processes and the gene expression of important proteins such as enzymes and cytokines. The present review summarises the impact of nutritional fatty acids on the development of the immune system as well as the fetal development. It describes the mechanisms of action of PUFA, *trans* fatty acids and conjugated linoleic acids in programming the fetus with regard to its risk of acquiring atopic diseases in childhood.

PUFA: *Trans* fatty acids: Fetal development: Immune development

Allergies are posing significant health problems in developed countries. Similar to other chronic diseases, they lead to an impaired quality of life as well as to an immense growth in costs for the health-care system. Thus, an early prevention of these diseases is becoming progressively important. Several studies point to a strong impact of unbalanced nutrition and lifestyle on the risk of developing chronic diseases. Hence, the development of these diseases during childhood or as an adult may be based on short-term survival adaptations *in utero*, which may, in turn, be induced by unfavourable environmental and nutritional circumstances. These influences, known as fetal or perinatal programming, are widely established and accepted for diabetes and obesity[1]. Conversely, little is known concerning the influence of nutrition and lifestyle during pregnancy on subsequent allergy development.

Allergy prevalence and fetal programming

Allergy prevalence has increased during the last decades. Today, in western societies, approximately one in three children suffers from an atopic disease. According to the International Study of Asthma and Allergies in Childhood, the 12-month prevalence of allergic rhinoconjunctivitis, eczema and asthma in children aged from 6 to 7 and 13 to 14 years in western European countries was between 5 and 20 %, 6 and 16 % and 7 and 30 %, respectively. In fact, a majority of study centres showed a trend towards an increase in the prevalence of allergy over the last 5–8 years[2]. While genetic predisposition is considered to be a main factor for the development of atopic diseases, genetic make-up is not likely to have undergone a dramatic change in the same period so as to lead to such an increase in allergy prevalence. Hence, the reason attributed for this substantial increase is mainly a westernised lifestyle defined by housing conditions, cigarette smoking and contact with environmental chemicals among which nutrition is considered to be a major element[3].

The molecular and cellular mechanisms leading to the development of allergy are a subject of controversy. It is assumed that in allergic conditions, a T-helper cell type 2 immune response (Th2; involving the synthesis of IL-4, IL-5, IL-6 and IL-13) predominates over the Th1 response, which is characterised by the expression of IL-1, IL-2, IL-12, interferon-γ (IFN-γ) or TNF-α. In order to prevent a rejection of the implanting and developing fetus by a predominance of Th1 cytokines, in pregnancy, there is also a strong Th2 response. However, a well-regulated placental balance between the Th1 and Th2 responses is important for a successful pregnancy outcome, although there is a slight shift in this equilibrium towards Th1 just before birth[4]. Thus, one of the approaches in allergy research concentrates on tracing the missing switch concerned with the physiological down-regulation of fetal Th1 to the 'normal' Th1-immune response after birth[5,6]. Although this change normally takes place during the first year of life, the switch might be determined during pregnancy. Several studies have, for instance, found an association between cytokine levels (high IL-4 and low IFN-γ)[7,8] in cord blood and an increased risk of developing

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; CLA, conjugated linoleic acid; COX, cyclo-oxygenases; IFN-γ, interferon-γ; LA, linoleic acid; LC-PUFA, long-chain-PUFA.

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atopy symptoms in childhood. In addition, various epidemiological and animal studies support the hypothesis that exposure to allergic conditions *in utero* lead to an enhanced disposition to acquiring allergies in later life[8–10].

Factors capable of modulating newborn immune responses and preventing allergy are being investigated[11,12]. It has also been suggested that an optimal physiological development of the fetus[13] and its immune system minimises the risk of allergy development[6,14].

Thus, in addition to the importance of genetic predisposition, both the environmental and dietary conditions *in utero* and the maternal immune system at the feto-maternal interface play a role in atopic outcome in childhood. Since an optimal development of the fetal immune system seems to be associated with an adequate physiological development of the fetus, early nutrition may have a crucial impact.

Nutrition and atopic diseases: an epidemiological view

Nutrition in pregnancy and breast-feeding

Maternal intake of margarine and plant oils appears to be positively correlated with atopic eczema in childhood[15]. While Ushiyama *et al.* [16] reported a negative correlation of proteins, carbohydrates and milk or milk products in the maternal diet with atopic manifestation in childhood, Calvani *et al.* [17] found no impact of butter or margarine intake. This can be explained by the low-level consumption of the two products by the study participants. Only 40–50 % had butter and approximately 15–20 % ate margarine more than once a month[17]. In addition to the afore-mentioned study, others have also described protective effects of habitual (more than once a week) fish consumption by pregnant women against both a sensitisation towards food allergens and an atopic disposition of their offspring[17–20].

After birth, breast-feeding offers optimal alimentation to the newborn and, in general, exclusive breast-feeding for a period of 4–6 months is recommended as a method of primary allergy prevention[21], although published data on the subject are somewhat conflicting. While most studies confirm preventive effects[22–26], several studies have found an increased risk for the development of atopic eczema or asthma for breast-fed babies[27–30]. In this context, the composition of breast milk regarding allergen content, immune mediators and fatty acids is important, though most studies lack this information. It has recently been shown that the maternal diet may influence breast-milk fatty acid and immune mediator composition[31,32]. Therefore, atopic mothers had significantly reduced the levels of transforming growth factor-β2, a factor that stimulates the development of the mucosal immune system and oral tolerance, than non-atopic mothers[33]. Interestingly, it correlates positively with the content of PUFA and negatively with SFA in the breast milk[32]. Several studies describe the lower levels of *n*-3 PUFA and the elevated concentrations of *n*-6 PUFA in serum phospholipids of atopic infants and in their mother's breast milk[34–36]. By contrast, in one study, a positive correlation between elevated *n*-3 long-chain (LC)-PUFA levels in the colostrum and the presence of food and aero-allergen sensitisation in infants at 6 and 24 months was found[37]. In the present study, a very high proportion of total *n*-6 PUFA was described, and a closer analysis revealed a ratio of linoleic acid (LA, 18 : 2*n*-6) to α-linolenic acid (ALA, 18 : 3*n*-3), which is nearly twice as high as that found by others[34]. This increased ratio may have a greater influence on the predisposition of newborns to atopy compared with the significant but slight difference in the *n*-3 concentrations between sensitised and healthy children. Furthermore, the LC-PUFA supply in breast milk is generally very low, in contrast to the selective transfer of LC-PUFA by the placenta known as biomagnification. Since preterm babies depend strongly on the supply of arachidonic acid (AA, 20 : 4*n*-6) and DHA (22 : 6*n*-3)[38], it is inconceivable that high levels of both *n*-3 and *n*-6 LC-PUFA in breast milk have a negative impact on the immune development and lead to the manifestation of allergic symptoms in childhood.

Several studies reveal a high dietary proportion of LA in atopic patients. A high ratio of LA to LC-PUFA or LA to ALA may, especially in genetically predisposed children, disturb fatty acid metabolism, and thereby influence the immune development leading to an increased prevalence in atopic diseases.

Nutritional fatty acids and their metabolites

Synthesis and intake of essential fatty acids and long-chain-PUFA

Most fatty acids present in the daily human diet can be synthesised endogenously by fatty acid synthetase, Δ9-, Δ6- and Δ5-desaturases and/or elongases. Since mammals lack enzymes such as Δ12- or Δ15-desaturases, which introduce double bonds at position C6 or C3 (counted from the methyl end of an 18-carbon acid), respectively, the intake of the so-called parent fatty acids (LA and ALA) is essential for the synthesis of LC-PUFA[39]. LC-PUFA, such as AA, EPA (20 : 5*n*-3) or DHA, can be synthesised endogenously from LA and ALA[40] (Fig. 1 (a)). However, this process is not very effective in human adults[41]. Compared with men, women seem to have a slightly higher capacity for LC-PUFA synthesis[42]. Thus, an adequate intake of LC-PUFA seems to be necessary, especially during the periods with increased requirements such as during pregnancy.

In central Europe, the daily intake of *n*-6 PUFA is recommended at approximately 2·5 % of the daily energy intake for adults and 4 % for infants. The intake of *n*-3 PUFA for both adults and children should be 0·5 % of the daily energy intake[43]. The WHO recommends a ratio between 5:1 and 10:1 for *n*-6:*n*-3[44]. While anthropological data suggest a ratio below 3:1 (at best 1:1), in societies with a westernised lifestyle, this ratio has changed drastically over the past 100 years, and is today estimated at 15:1 to 17:1[45]. This ratio could be decreased by consuming more green vegetables, flaxseed, rapeseed oil or nuts that have a relatively high content of ALA, as well as marine fish rich in *n*-3 LC-PUFA. The increase in *n*-6 PUFA intake is predominantly due to an elevated proportion of LA. Because people use more vegetable oils, the intake of LA has intensely increased during the last 40 years[46], and currently approximates 10–20 g per capita and day[47]. These alterations in the concentration of PUFA in the common daily diet may be a reason for the changes observed in the functioning of the immune system among western populations.

Long-chain-PUFA, their metabolites and biological properties

Various LC-PUFA are precursors of important bioactive compounds, known as eicosanoids, lipoxins, resolvins or

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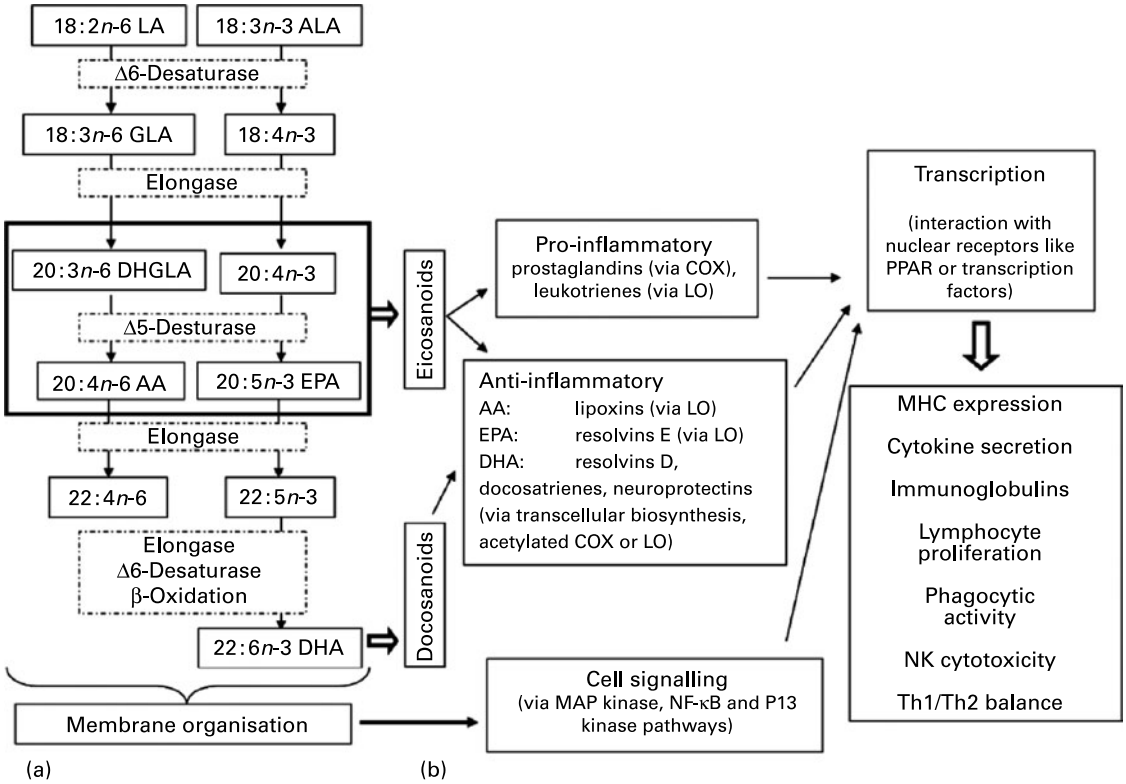

Fig. 1. (a) *n*-3 and *n*-6 fatty acid families and modifying enzymes and (b) their derivatives and physiological effects. LA, linoleic acid; ALA, α-linolenic acid; GLA, γ-linolenic acid; DHGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; COX, cyclo-oxygenase; LO, lipoxygenase; MAP kinase, mitogen-activated protein kinase; PI3 kinase, phosphatidylinositol 3-kinase; MHC, major histocompatibility complex; NK, natural killer; Th1(2), T-helper cell type 1 (type 2).

docosanoids (Fig. 1 (b)). The classical eicosanoids are classified according to their oxidation status and their transforming enzymes (e.g. cyclo-oxygenases (COX1 and COX2) or 5-lipoxygenase) into PG, thromboxanes and leukotrienes, as well as into subgroups (e.g. PGE). Different series of PG or leukotrienes are further classified according to the number of double bonds present, which, in turn, depends on the predecessor LC-PUFA molecule, e.g. PGE_2, leukotriene B_4, deriving from AA. Eicosanoids deriving from dihomo-(γ-linolenic acid and EPA, also substrates of the afore-mentioned enzymes, generally have lower inflammatory properties than those deriving from AA. In addition to their molecular structure, the different membrane receptors (e.g. PGE receptors 1 and 2 for PGE) and the nuclear receptors (such as PPAR), which mediate their effects in tissue, modulate the properties of these derivatives.

Independent of their inflammatory properties, LC-PUFA and their oxygenated derivatives are involved in several other physiological processes (Table 1). In fact, they can also function as growth factors. Hence, LC-PUFA may directly or indirectly mediate actions that play a wide-ranging role in the human body beginning at the embryonic stage, as discussed later.

Furthermore, eicosanoids may not only act as immune mediators in both children and adults, but also in the fetal immune development[48]. The latter phenomenon has been the subject of increasing interest.

Effect on the immune system

The functioning of the immune system is highly complex and, as already mentioned previously, the exact mechanisms of allergy pathogenesis are not yet clear. To date, a disturbance in the Th1:Th2 ratio is believed to be the main cause of atopic diseases. It is assumed that during allergic sensitisation, B-lymphocytes are stimulated by IL-4-secreting Th2 cells and switch from synthesising IgM and IgG to IgE. Subsequently, IgE binds to mast cell receptors, where cross-linking through allergens induces the release of histamine, which together with the Th2 cytokines IL-4 and IL-5 triggers an inflammatory reaction involving the chemotaxis of, for example, eosinophils and Th1 cells. Hence, the anti-inflammatory Th2 cytokines of the first phase of allergic reactions make way for the inflammatory Th1 cytokines. LC-PUFA derivatives can enhance or attenuate this process at various points in the cycle.

AA enhances inflammatory processes via its derivatives PGE_2 and leukotriene B_4. Moreover, PGE_2 can itself bring about a reduction in the Th1:Th2 cytokine ratio by decreasing IL-2 and IFN-γ secretion[49,50], as well as an induction of IgE class switching, and may thus promote the development of allergies. Leukotriene B_4, on the other hand, boosts immune responses by inducing proliferative effects on a macrophage cell line[51]. The anti-inflammatory effects of *n*-3 PUFA, seen in epidemiological studies, may be mediated by a reduced NF-κB-DNA-binding activity and activation of PPARγ. These cellular mechanisms result in a decreased gene expression and secretion of the highly inflammatory cytokines IL-1β, IL-6 and TNF-α in monocytic cells[52]. Other authors found a reduction in IL-2 secretion by a T-cell line[53], a decreased major histocompatibility complex I and II expression[54] and natural killer cell activity[55] due to *n*-3 LC-PUFA. Both EPA and AA concentrations were negatively correlated with proliferation and

Table 1. Some biological properties of arachidonic acid-derived eicosanoids

	Immune system	Smooth muscles	Neurons
PGD_2	Role in asthma	Bronchoconstriction (asthmatics!)	Regulation of temperature and sleep (antagonises PGE_2)
PGE_2	Strong inflammatory, vasopermeability (from macrophages and monocytes); maturation	Bronchoconstriction; constriction of longitudinal and dilatation of circular muscles in vascular and reproductive systems	Pain (stimulation of non-receptors in inflammatory sites and in spinal marrow), fever (hypothalamus)
$PGF_{2\alpha}$		Uterus contraction (initiation of birth); bronchoconstriction (asthmatics!)	
PGI_2 (= prostacyclin)	Highly inflammatory	Vasodilatation, bronchodilatation; constriction of longitudinal and dilatation of circular muscles of fallopian tubes	Pain (stimulation of non-receptors in inflammatory sites)
TXA_2 (antagonist of PGI_2)		Vasoconstriction, bronchoconstriction	
LTB_4	Chemoattraction of leucocytes in inflamed tissue; vasopermeability		
Cysteine leukotrienes	Anaphylactic reactions	Bronchoconstriction, vasodilatation	

TXA_2, thromboxane A_2; LTB_4, leukotriene B_4.

IFN-γ secretion following the stimulation of cord blood lymphocytes with common allergens[56]. By contrast, in supplementation studies with healthy adults, the effects of *n*-3 LC-PUFA on immune functions are controversial[57,58].

To control inflammatory reactions, immune responses are regulated physiologically. Lipoxins, resolvins (E or D series) and docosatrienes, derived from AA, EPA or DHA, and DHA, respectively, may be involved in these feedback processes[59]. These rather anti-inflammatory metabolites are synthesised via platelet–leucocyte interactions in a complex pathway catalysed by acetylated COX and lipoxygenase[60]. Lipoxins decrease the synthesis of TNF-α[61] and leucocyte chemotaxis[62]. Resolvin E1 inhibits leucocyte infiltration and synthesis of pro-inflammatory cytokines[63] and interacts directly with cell-surface receptors that induce anti-inflammatory functions[64,65]. Docosatrienes are capable of blocking T-cell migration[66].

Thus, the immune-modulating effects of LC-PUFA are indeed complex. Derivatives of EPA and DHA lead not only to an attenuated acute-phase reaction, but also to a general suppression of inflammation. By contrast, AA and its classical eicosanoids boost immune reactions, whereas lipoxins, which derive likewise from AA[59], can regulate inflammation.

Long-chain-PUFA and immune development

During immune maturation, naive Th0 cells are able to synthesise both Th1 and Th2 cytokines as a response to antigens. The predominating expression of a Th1- or Th2-like cytokine pattern can be modulated by numerous eicosanoids and cytokines synthesised by antigen-presenting cells in the vicinity of the Th0 cell. For example, PGE_2-secreting antigen-presenting cells can switch the Th0 cell to an increased synthesis of IL-10 and a decreased synthesis of IL-12, and hence towards a rather Th2-like pattern[50].

Some supplementation studies on atopic pregnant women reported immunosuppressive effects of EPA and DHA on the fetal immune system[67–69], in terms of a reduced IL-13 synthesis or a secretion of IL-10 after allergen stimulation of cord blood. This demonstrates that LC-PUFA and their derivatives can influence the Th1 and Th2 balance.

Trans *fatty acids: all bad fatty acids?*

In general, double bonds of nutritional unsaturated fatty acids are in *cis*-conformation, but approximately 5 g of *trans* fatty acids per day are included in a westernised diet[70]. Nowadays, the dietary uptake of *trans* fatty acids results primarily from consuming industrially hydrogenated vegetable oil products, such as margarine or snack food. The most common isomer introduced through processing is *trans*-elaidinic acid (18 : 1 *t*9). The second dietary source of *trans* fatty acids is ruminant fats found in beef and in butter. These *trans* fatty acids, mainly *trans*-vaccenic acid (18 : 1 *t*11), are synthesised by microbial hydrogenation of fatty acids. In contrast to industrial hydrogenisation, products resulting from microbial hydrogenisation generally contain only traces of *trans*-elaidinic acid.

Trans fatty acids from industrially hydrogenated foods[71,72] (e.g. margarine) are known to be positively correlated with diseases such as asthma, atopic eczema or allergic rhinitis in children[72–78] and adults[79]. By contrast, other data show a negative correlation between bovine milk-fat consumption

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and the incidence of atopic diseases[25,80,81], a fact that may be due to preventive factors in ruminant fat or to a lower consumption of industrially hydrogenated fat. Since vegetable oils, such as sunflower oil, used for industrial hydrogenation usually contain high proportions of LA and positive associations between LA and atopy have been described[36,82], further investigations to identify the exact causal relationship between LA and *trans*-elaidinic acid and pathogenesis of atopy are necessary. Interestingly, it has been shown that the impact of *trans*-elaidinic acid on the secretion of PGE_2, leukotriene C_4 and IgG in rats is linked to the *trans*-elaidinic acid and LA ratio, or to ALA intake[83]. The content of *trans* fatty acids in erythrocyte membranes is also positively correlated with atopic eczema[84]. Data on fatty acid composition of cord blood reveal an inverse correlation between *trans* fatty acids and LC-PUFA[85–87]. This finding may be linked with the inverse correlation found between high cord plasma levels of *trans* fatty acids and birth weight and the length of gestation[88], and the enhanced risk for pre-eclampsia due to increased *trans*-elaidinic acid levels in maternal erythrocyte membranes[89]. To date, data regarding the impact of *trans*-vaccenic acid on pregnancy outcome and on the fetal immune system are still lacking.

A special group of *trans* fatty acids contain conjugated *cis* and *trans* double bonds in varying numbers and positions. These conjugated linoleic acids (CLA) have been the subject of several studies. First found to be synthesised in ruminants by micro-organisms[90], CLA are now known to be formed by the conversion of *trans*-vaccenic acid in a membrane-associated complex containing Δ9-desaturase[91]. Nevertheless, the main source of CLA for human adults is ruminant fat, especially milk fat. The daily intake of CLA depends on the local diet. In the USA, it is estimated to be approximately 140 mg/d for women and 190 mg/d for men[92]. In Europe, values between 250 and 330 mg/d are reported[93] for young women.

Although a few studies relating to the role of *n*-6 and *n*-3 LC-PUFA in fetal development and allergy exist, at present, very little is known regarding the effects of CLA on human fetal, immune or allergy development. Anti-inflammatory and allergy preventive effects similar to *n*-3 LC-PUFA are also attributed to CLA, although data are still controversial[94].

A mixture of *cis*-9,*trans*-11 CLA and the synthetic isomer *trans*-10,*cis*-12 CLA has been studied in animal models, predominantly in young rats and mice. The CLA mixture decreased the secretion of PG, especially PGE_2[95] and histamine in mast cells[95,96], and normalised the secretion of IFN-γ and IL-10 in various tissues[97]. Moreover, a decreased synthesis of IL-4 using the mixture has been observed *in vitro*[97,98]. Furthermore, reduced TNF-α levels[52] have also been found. However, since differences between the physiological properties of both isomers are suspected, current investigations use single isomers.

On analysing the mechanisms for *trans*-10,*cis*-12 CLA, it was shown that the level of expression of COX2 and PGE_2 decreased on reducing NF-κB activation[99]. In pigs, the synthesis of IL-8[100] increased after the diet was supplemented with *trans*-10,*cis*-12 CLA. Other studies investigating the properties of *trans*-10,*cis*-12 CLA also found adverse effects such as the induction of an inflammatory and fibrotic phenotype in the mouse mammary gland stroma[101].

With respect to the immune system, *cis*-9,*trans*-11 CLA decreased IL-12 synthesis[102]. In other studies, the isomer increased the apoptotic rate and IL-2 synthesis in a T-cell line[103]. Furthermore, in a co-culture of eosinophils and a human bronchial epithelial cell line, the surface expression of either cluster of differentiation (CD) 69 or CD13 on eosinophils was suppressed after supplementing with *cis*-9,*trans*-11 CLA[98].

In summary, *cis*-9,*trans*-11 CLA seems to reveal general immune-suppressing and -regulating properties. In contrast to the technically synthesised *trans*-10,*cis*-12 CLA, no adverse effects were reported for the *cis*-9,*trans*-11 CLA isomer. CLA may lower polarisation of naive T-cells towards Th2 cells by decreasing PGE_2, and hence decrease the IL-4 and IgE secretion. Thus, CLA tend to down-regulate mechanisms that precede allergic reactions. By contrast, *trans* fatty acids, especially isomers such as *trans*-elaidinic acid, probably interfere with the physiological processes and fetal maturation, and hence may predispose for chronic diseases.

Molecular mechanisms of fatty acids and their derivatives

Fatty acids and their derivatives are involved in cellular physiological processes through several mechanisms. First, PUFA and their derivatives directly modulate the gene expression of enzymes (e.g. desaturases and COX) and cytokines by the activation of transcription factors, e.g. PPARγ[52,104–107]. Second, they modulate gene expression indirectly via cell signalling pathways, as, for instance, through the mitogen-activated protein kinase cascade or by preventing the activation of NF-κB via an inhibition of inhibitor of NF-κB ubiquitination[52,53,63,102], as well as by means of their membrane-bound receptors. While the binding of membrane-bound receptors has only been observed for eicosanoids[108] and resolvins[63], nuclear receptors and signalling cascades interact with both fatty acids and their derivatives. Furthermore, the function of membrane-bound receptors can be modulated when fatty acid composition in lipid rafts is modified[109].

Beside modulating gene expression, single groups of fatty acids compete for enzymes, such as Δ6-desaturase[39], phospholipase A or COX2[110]. Thus, a low ratio of *n*-6:*n*-3 LC-PUFA may attenuate inflammatory reactions by the competitive inhibition of COX and 5-lipoxygenase by EPA, thereby generating less highly inflammatory metabolites. A high *trans* fatty acid content in the diet not only decreases the incorporation of DHA in membrane lipids, but also interferes with the Δ6-desaturase function[111].

An impaired lipid metabolism in atopics has been suspected for some time now[112]. A recent study demonstrates that variants in the human Δ5- and Δ6-desaturase genes fatty acid desaturase (FADS) 1 and FADS2 are linked to the fatty acid composition in serum phospholipids and the prevalence of allergic rhinoconjunctivitis and atopic eczema[113]. Here, a high percentage of LA *v.* a low level of AA in breast milk may favour atopic sensitisation of the child since fatty acids, first, have a direct effect on the immune system[114] and, second, modify the immune system indirectly by influencing gut maturation[32,115].

Thus, especially in genetically predisposed families, particularly when the possible polymorphisms in genes coding for signal molecules or enzymes involved in fatty acid metabolism as well as cytokines are considered, an optimal dietary

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supply of eicosanoid precursors, such as AA or EPA, seems to be the clue for the prevention of allergy.

PPARγ

The various PPAR isoforms (PPARγ, PPARα and PPARβ/δ) belong to a family of ligand-activated nuclear hormone receptors that regulate physiological and cellular differentiation, fat and glucose metabolism, as well as inflammatory responses[106,116,117].

By interacting with transcription factors, fatty acids and their derivatives influence a wide range of physiological processes including metabolism and immune functions, and they have a high impact on the entire course of pregnancy (Fig. 2). This effect begins with the synthesis of PGE_2 and PGI_2 in the fallopian tube involved in conveying the embryo into the uterus[118] and ends with the synthesis of PGE_2 and $PGF_{2\alpha}$ in the placenta, responsible for the induction of labour. Hence, the strong correlation between the effects of fatty acids and their derivatives on the fetal development, in general, and on the fetal immune system shall be exemplified by means of the nuclear receptor PPARγ, for which fatty acids and their derivatives act as ligands[119].

PPARγ and placenta

The placenta denotes the central organ in pregnancy. It is responsible for anchoring the fetus in the uterus, forming an anatomical barrier between maternal and fetal circulation, and allowing an exchange of gases, nutrients and metabolic products of degradation between mother and fetus. In addition, it provides a means of mediating hormonal signals and inducing immunological tolerance. Thus, a well-differentiated placenta is significant for mammalian fetal development. Interestingly, PPARγ plays a crucial role as a regulating factor in the placenta[120]. In animals, ablation of PPARγ leads to embryonic death at a point in time when the placenta takes over embryonic nutrition[121]. Although it is ubiquitous in the human body, in the placenta, PPARγ is expressed predominantly in invading trophoblast cells[122–124]. The latter invade the decidua in early human pregnancy, substitute endothelial cells in maternal placental blood vessels and perform vasculogenesis[125]. This invasion of trophoblast cells is regulated by a variety of extra- and intracellular factors[126–129]. It is essential for a stable blood supply to the fetus. Activated PPARγ down-regulates the invasiveness of cytotrophoblast cells[130], accelerates their differentiation[124] and thus assists towards the growth of a healthy placenta. The dysregulation of PPARγ is involved in the pathogenesis of pre-eclampsia[131], which is accompanied by the constriction of placental spiral arteries and hence an impaired nutrient supply to the fetus. The regulation of fatty acid transport and accumulation in trophoblast cells[132], as was discovered in adipocytes, is also attributed to PPARγ. Lipid droplets in murine trophoblast cells were only found in wild-type embryos, but not in PPARγ-null mutants[121]. In human trophoblasts, PPARγ ligands increase the uptake of fatty acids[122,132], via special fatty acid transport or binding proteins[133,134]. This transport is important for two reasons: first, the developing fetus requires fatty acids to build cellular membranes and maintain their fluidity, permeability and conformation; second, as bioactive metabolites. Thus, large amounts of LC-PUFA, in particular, AA and DHA, need to be transferred to the fetus. Finally, LC-PUFA is essential as a precursor for steroid hormone synthesis in the placenta.

Uterine contractions are triggered by pro-inflammatory mediators, such as PG and cytokines. By antagonising the NF-κB pathway and down-regulating COX2 and labour-inducing cytokines, activated PPARγ may have a preventive function against preterm labour and delivery[135–137]. This may explain why a large intake of *n*-3 LC-PUFA by the mother results in a delayed onset of delivery[138,139]. In addition, the biomagnification of LC-PUFA in the placenta

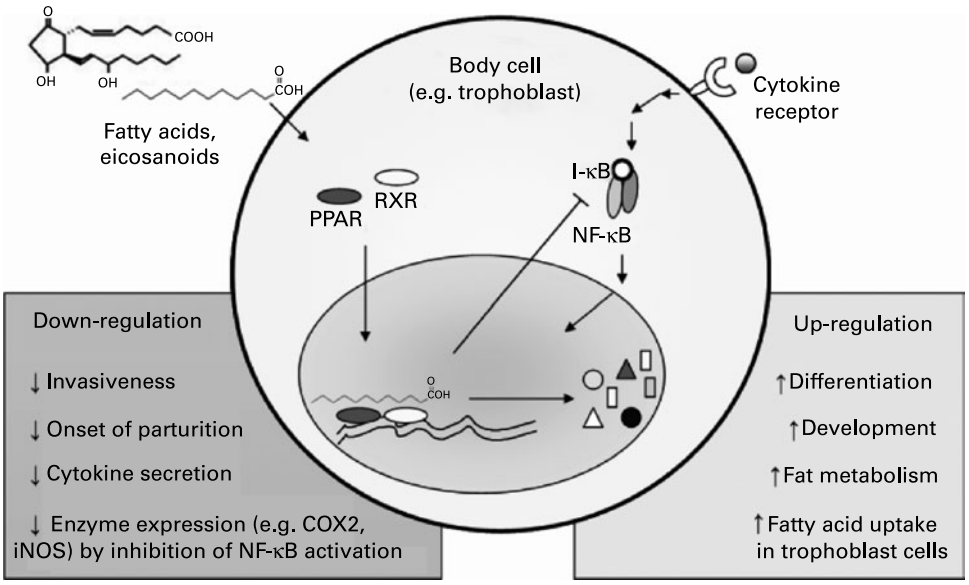

Fig. 2. Fatty acids or their metabolites can activate PPARγ. The receptor then forms a heterodimer with retinoid X receptor (RXR), thereby regulating the transcription of target genes in the trophoblast and other cells and thus influencing the physiological functions and processes. I-κB, inhibitor of NF-κB; COX, cyclo-oxygenase; iNOS, inducible NO synthase.

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is influenced by the proportion of nutritional fatty acids. Therefore, a high proportion of *trans* fatty acids may disturb the bioaccumulation of LC-PUFA in the placenta, for instance, by competing for nuclear receptors such as PPARγ. Thus, a deficiency in LC-PUFA is directly linked to a poor fetal development, and consequently to a defective fetal immune maturation and finally predisposes to a later atopy.

Conclusion

The concept of 'fetal programming' implies that non-optimal conditions during fetal development could lead to deviations in physiological feedback mechanisms resulting in the manifestation of chronic diseases. Thus, counteractive measures should commence during the prenatal period. These should not be limited to the immune system or individual metabolic processes, but rather focus on the entire course of the pregnancy and the complete fetal developmental process.

The activation of PPARγ in trophoblast cells leads to the initiation of invasive and differentiation processes, the promotion of transplacental fatty acid transport and placental PUFA accumulation. Moreover, by inhibiting the NF-κB pathway, it also decreases the synthesis of labour-promoting mediators. Thus, PUFA play a crucial role in placental development and the maintenance of pregnancy via an interaction with PPARγ. Furthermore, it is conceivable that the interaction of LC-PUFA with the almost omnipresent PPARγ leads to 'cell priming' during the fetal maturation process.

Fetal immune development commences midterm. Since a physiological balance between Th1, Th2 and regulatory T-cells is a prerequisite for an adequate immune response, an imbalance here due to inadequate priming of the cells during maturation may enhance a predisposition for allergic diseases. However, very little data dealing with this particular subject are available in the literature. While several studies have confirmed the immunomodulatory effects of PUFA in animal models, results from human adults are controversial. Moreover, only a few reports on the impact of fatty acids on human immune development exist. Of these, most have shown a negative correlation of *n*-3 LC-PUFA supplementation of pregnant women and Th2 cytokine secretion in cord blood. Studies of the effects of CLA or *trans* fatty acids on fetal immune development are, as far as we are aware, lacking.

The impact of *n*-6 PUFA on allergy development is, today, still controversial. However, since AA and DHA are essential for the placenta and the fetus, a negative effect of AA on fetal immune development is not conceivable. The relationship between dietary LA and AA, the intake of *n*-3 PUFA and the modifications in enzyme expression and activity appear to have a substantial impact on allergy manifestation.

Long-term follow-up studies on children are needed to unravel the relationship between the availability of *n*-3 and *n*-6 LC-PUFA in pregnancy and the manifestation of allergic symptoms in childhood. Since health risks related to industrially hydrogenated *trans* fatty acids are well known, products containing hydrogenated fat should be consumed with caution. Finally, numerous further studies are necessary to thoroughly investigate the effects of naturally occurring *trans* fatty acids, as well as CLA present in milk and milk products on the fetal development.

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