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Development of the Immune System - Early Nutrition and Consequences for Later Life

JoAnn Kerperien¹, Bastiaan Schouten², Günther Boehm^{2,3},
Linette E.M. Willemsen¹, Johan Garssen^{1,2},
Léon M.J. Knippels^{1,2} and Belinda van't Land^{2,4}

¹*Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS),
University of Utrecht,*

²*Danone Research – Centre for Specialised Nutrition, Wageningen,
The Netherlands and Friedrichsdorf,*

³*Sophia Children's Hospital, Erasmus University Rotterdam,*

⁴*Wilhelmina Children's Hospital, University Medical Center, Utrecht,
The Netherlands*

1. Introduction

The immunological interaction between mother and fetus during pregnancy causes the fetal immune system to avoid excessive and destructive immunological reactions. This particular physiologic situation coexists with an immature immune system, which makes the infant very vulnerable for infections and susceptible to the development of immune system related disorders. At birth, the immune system of the infant is particularly characterized by a not fully developed non-specific immune system. In addition, a suppressed capacity of antigen-specific T cells, a deletion of activated T cells, and the presence of high amounts of regulatory T cells (Treg) hamper proper immune responsiveness. During the first months of life the antigen-specific immune response has to be developed in parallel to the maintenance of immune tolerance against compounds commonly found in the environment of mother and infant. There is evidence that disturbances of these complex developmental processes will have impact on the function of the immune system during lifetime causing immunological disorders such as allergy and autoimmunity.

Human milk contains several immunological active compounds which protect the infant from infection. Many of them such as antibodies are individually adapted to the maternal environment which is similar to the environment of the infant thus providing individual protection to the infant. Apart from this protection activated immediately after birth, human milk modulates also the described developmental processes. Although the mechanisms of this modulation are not fully understood there is evidence that human milk can transfer “immunological memory of the mother” to the infant. This concept of the role of human milk underlines the importance of quality of nutrition during first months of life for total development of the immune system. Individual human milk analyses will provide insight in components that are important modulators. Immunologic active peptides, long chain

polyunsaturated fatty acids, several glycolipids and non-digestible oligosaccharides have already been identified as such modulators. The interaction of these active components with different parts of the immune system is very complex allowing a graduate and balanced development of the immune system.

One problem of studies in animals and humans is the fact that no single biomarker exists which describes completely the developmental status of the immune system. Although the question which biomarkers are of relevance is still a matter of intensive research there is evidence that many “classical” biomarkers are not useful. Many of these “classical” biomarkers are only sensitive in case the immune system is out of balance but not during a normal development. Consequently, research to identify relevant biomarkers characterizing healthy development is strongly required. There are many questions still open. However, first results are promising indicating that the quality of nutrition early in life might support development of the immune system for lifetime. Acceptance of such a concept might provide opportunities for new ways of primary prevention of immune related diseases later in life.

This chapter will summarise the newest and some specific insights of the mechanisms and impact of nutrition on the development of the immune system early in life.

2. Influences prior life

The nutritional status in early life has an important influence on human immune development, for example, a positive association is clearly observed between birth weight and antibody response to certain vaccines later in life (McDade, Beck et al. 2001). The precise relationship however between nutritional exposures during critical periods of development and later immune function warrants further investigation. The early postnatal environment is a vital determinant of adult health. An environmental exposure, like nutritional modulation of the evolving intestine during early infancy makes an impact on the development and function. A concept like this (as illustrated in *Figure 1*) will provide opportunities for primary prevention from immune related diseases later in life.

In order to understand the impact of nutrition on immune development early in life it is of key importance to know which steps in immune development are subjective to change and depend on specific nutrition. During embryogenesis, stem cells start to differentiate into specific progenitor stem cells, creating a pool of more specific and less totipotent stem cells. Hematopoietic stem cells (HSC) are the progenitor cells for our whole immune system (*Figure 2*). Identification of the first HSC is still difficult, because these regions don't contain many HSC and unique markers are lacking (Medvinsky, Rybtsov et al. 2011). After these few first HSC have colonized the human fetal liver, these cells expand and will relocate under influence of adhesion molecules and chemo-attractants to thymus, spleen and bone marrow (Mazo, Massberg et al. 2011). The bone marrow will start to produce immune cells from the hematopoietic lineage at four to five months of gestation in human pregnancy. Upon stimulation with ‘early acting cytokines’ a HSC will proliferate and differentiate into a myeloid or a lymphoid precursor cell depending on their surroundings (Grassinger, Haylock et al. 2010).

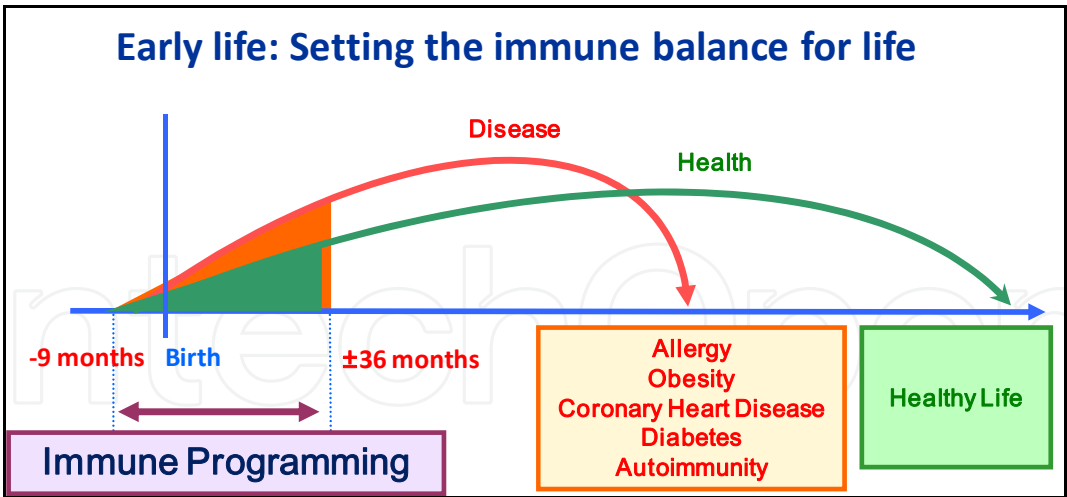


Fig. 1. Disturbances of immune developmental processes will have impact on the function of the immune system during life causing immunological disorders such as allergic disorders and autoimmunity. Although there are many questions still open first results are promising indicating that feeding early in life might support the development of the immune system for lifetime.

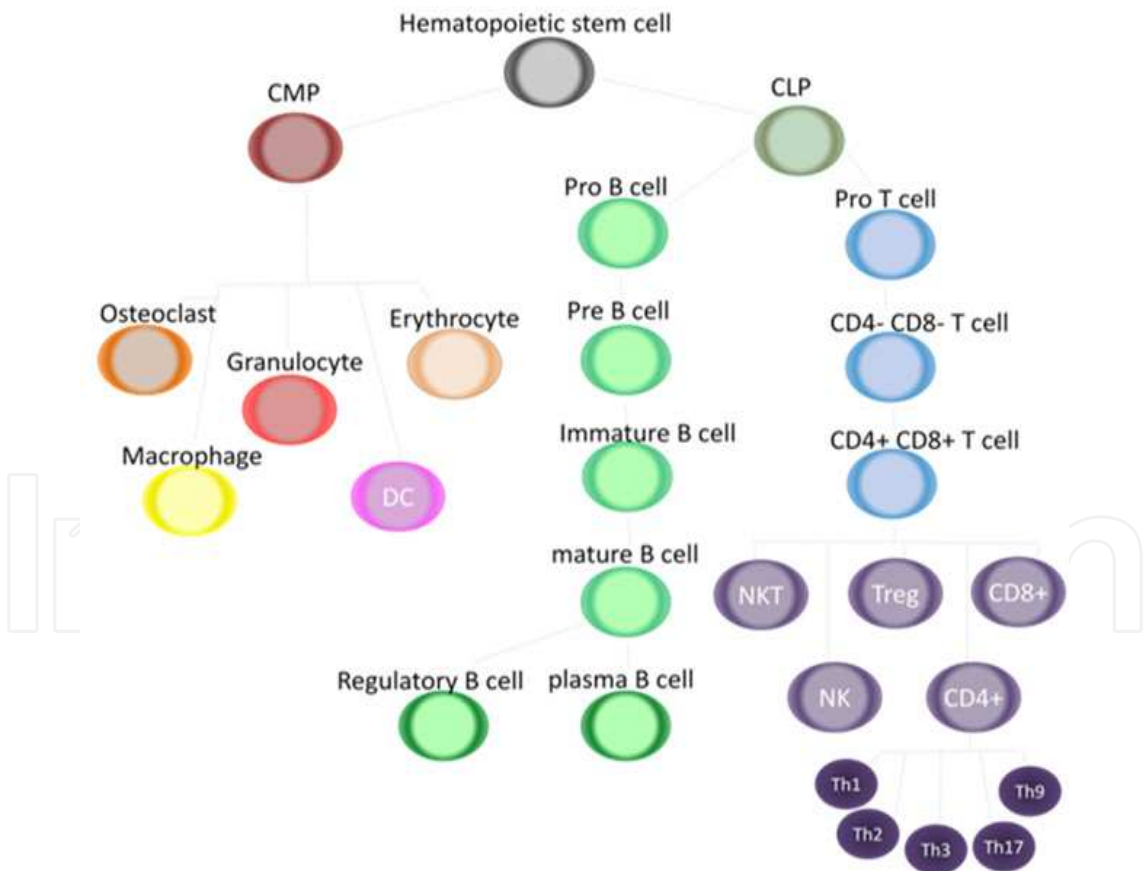


Fig. 2. Hematopoiesis/ immune cell development; From the hematopoietic stem cell the different immune cells develop, including; CMP, common myeloid precursor; CLP, common lymphoid precursor; DC, dendritic cell; NKT, natural killer T cell; NK, natural killer cell; Treg, regulatory T cell; CD8+, cytotoxic T cell; CD4+ Th, T helper cell.

2.1 Lymph node formation

Recent investigation showed that during lymph node development retinyl hydrogenase (RALDH) 2 is one of the enzymes essential in initial cross talk between different cell types (van de Pavert and Mebius 2010). RALDH-2 converts retinaldehyde to retinoic acid (RA). In absence of this enzyme proper lymphoid follicles are not developed. Retinoic acid is the active form of vitamin A and is important during embryogenesis, when axial patterning and organ formation take place (Campo-Paysaa, Marletaz et al. 2008). RA is involved in nerve development and expression of RALDH is found in nerve fibers near the lymph node anlagen, where RA can influence stromal cells to produce specific chemokines. Because RA is produced and used for different developmental processes, other factors should be present to direct lymph node development. One of these factors is CXC chemokine ligand 13 (CXCL13) produced by lymph node surrounding stromal cells. After a small cluster of pre-T- and -B cells is formed, more cells are attracted to this specific site for example via CC chemokine receptor (CCR) 7 and CC chemokine ligand (CCL) 19 and CCL21. When there are enough cells in the cluster, differentiation into lymph nodes occurs. Lymph nodes in the intestine are essential for priming of the whole immune system; therefore detailed development of the intestinal tract and intestinal immune tissues are described in *Box 1*. Peyer's patches (PP) are the local small intestinal lymph nodes and mesenteric lymph nodes (MLN) are the collecting lymph nodes for small and large intestine. In essence these lymph structures develop very similar but there are some differences. For the development of PP the CD11c⁺ cells are required. In addition there are differences in essential transcription factors which are necessary to develop lymph nodes or PP, like interleukin (IL) 7 and RANK (Chappaz, Gartner et al. 2010). Using mice deficient for IL7 or Kit or both they showed that IL7 is important for lymph node anlagen but not for PP development whereas both Kit and IL7 are important for MLN anlagen (Chappaz, Gartner et al. 2010). But growth factors needed for lymph node development still remain poorly understood. The influence of vitamin A on the development of lymphoid structures is already a strong indication that nutritional components are of key importance at the base of infant's immune system.

A human embryo consists two weeks after fertilisation of three layers, called ectoderm, endoderm and mesoderm. Ectoderm forms the nervous system and the exterior, endoderm forms among others the gastrointestinal tract and the mesoderm forms for example connective tissue and the cells of the immune system. In the fourth week of embryogenesis the flat tissue folds lateral and folds from head to toe, via which the endoderm is enclosed by the ectoderm and a foregut, midgut and a hindgut are being formed, surrounded by mesoderm. At the end of the fourth week the liver is also beginning to form. From one of the pouches in the foregut, thymus will be formed, between 3rd and fourth month during pregnancy.

The loop of the midgut remains in contact with the yolk sac via the vitalline duct. In the same period that the definitive duodenum is formed, the midgut elongates and the hindgut becomes enlarged. When these changes in the pre-intestinal tract occur, the midgut migrates to the umbilical cord and returns in the embryo before the 4th month. During retraction the gut rotates to its final position. Throughout the whole gut enlargement of the surface is initiated via formation of crypts, villi and microvilli. The villi and microvilli start to develop after 9 to 10 weeks and at a later stage the colon loses it's villi. After birth the intestine needs approximately one week to organize it's lymph nodes with specific T- and B-cell regions and six months to acquire a tight epithelial barrier.

Box 1.

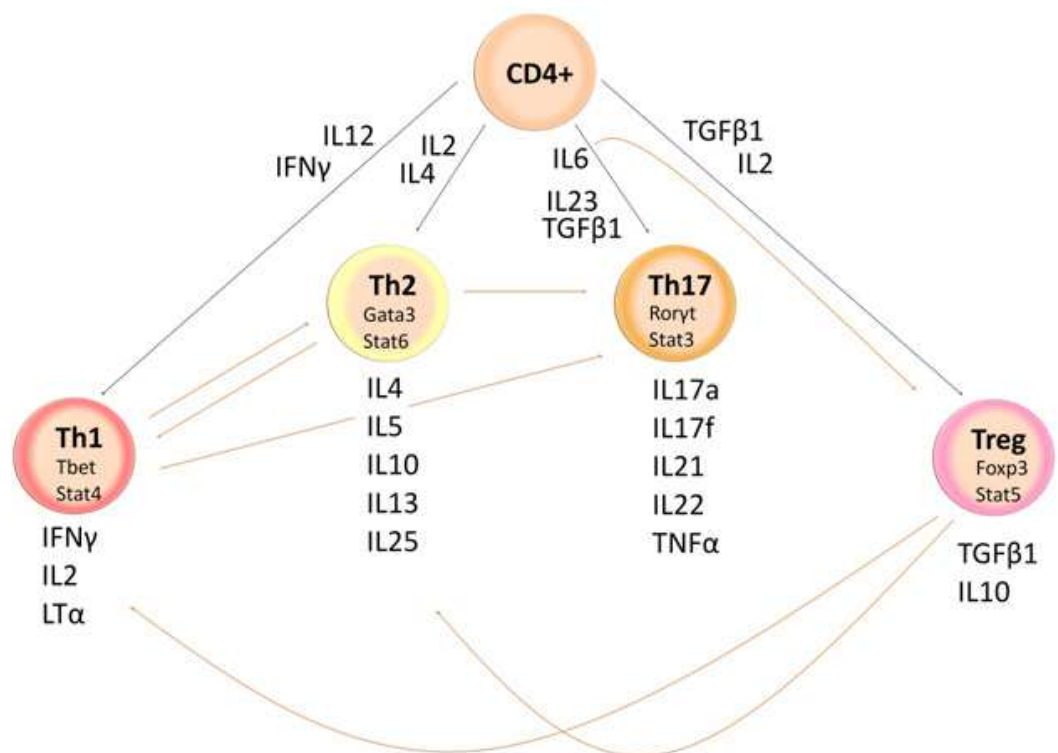


Fig. 3. Immune cell plasticity; Upon antigen encounter and T cell activation, naïve CD4+ T cells mature into several subsets. Several factors including cytokines, as described above determine the type of immune response, including Th1, Th2, Th17 and regulatory T cells. For example Th1 cell differentiation Interleukin (IL)12 and interferon gamma (IFN γ) is needed (blue arrow indicates stimulation). These cytokines help up regulate specific transcription factors like Tbet and Signal transducer and activator of transcription 4 (Stat4). These transcription factors activate certain genes to produce other cytokines like, IL2, LT α and IFN γ . When these cytokines are produced they help inhibit the differentiation of other Th-cells (red arrows indicate inhibition).

2.2 Immune cell development

The fetal common lymphoid progenitor cells (CLP) differ from the adult CLPs. The fetal CLPs have the ability not only to differentiate into all lymphoid cell types but also into macrophages. It is currently not known whether adult CLP are restricted to the division in myeloid and lymphoid progenitors or whether it is a gradual loss in lineage commitment (Chi, Bell et al. 2009). Via complex processes involving, a positive and negative selection, a lineage specific development in the thymus occurs. Only naïve T cells, intermediately recognizing the Major Histocompatibility Complex (MHC)-self-peptide and expressing CD4 or CD8, are allowed to migrate to their target organ (Singer, Adoro et al. 2008). CD4+ T cells form a subset of T cells called T helper (Th) cells and these cell types help to activate the B cells and CD8+ T cells. Th cells need binding of CD4 and CD28 to become activated Th cells and dependent on a specific set of cytokines, CD4+ T cells mature into different kinds of effector T cells, memory T cells or regulatory T (Treg) cells [Box 2]. Many factors are important for the development of both B and T cells, IL7 is of uttermost importance for both lymphocyte lineages (Kang, Der, et al. 2004). Recently it was shown that IL7 helps establish B cells, producing IgM, in the marginal zone of the spleen (Willems, Li, et al. 2011). Directly

after birth maternal IL7 increases T cell production in the thymus and supports survival of T cells in other lymphoid structures in offspring, underlines the importance of IL7 during lymphogenesis (Aspinall, Prentice, et al. 2011).

The thymus is critically sensitive to malnutrition, with protein nutrition deficiency causing atrophy of the thymus (Savino and Dardenne 2010). This suggests that the thymus is a putative target for early-life programming effects. Most immune defence mechanisms are impaired in malnutrition, even in moderate nutritional deficiency. Protein-energy malnutrition is accompanied by deficiencies of micronutrients such as vitamin A, vitamin E, vitamin B6, vitamin C, folate, zinc, iron, copper, and selenium. Rapid proliferating T cells are especially affected by the lack of essential nutrients. Severe and chronic malnutrition may even lead to thymus atrophy affecting the basis of our immune system. The potential of adding certain nutrients, like vitamin C, D, or E, at levels above recommended dietary allowances (RDA) to the diet may improve immune function, is subject to increasing research.

Naïve CD4⁺ T cells are activated upon encountering an antigen presenting cell expressing MHC class II and the co-stimulatory signal CD28. They mature into effector, memory- or Treg dependent on which cytokines are produced by their APC. Already in 1986 two subsets were discovered by Mosmann and Cofmann (Zhu and Paul 2008) and now many more are well characterized. For Th1 Tbet and Signal transducer and Activator of transcription (Stat)1 are the initiating transcription factors, producing IFN γ , then Stat4 is amplifying the Th1 response. Th2 differentiation is activated by IL4, which induces Stat6. Stat6 in turn will activate the transcription factor Gata3. For Th17 ROR γ t is crucial, it is induced by transforming growth factor (TGF) β with IL6, then Stat3 and IRF4 are expressed. The transcription factors Foxp3 and Stat5 are needed, but without RA Tregs aren't formed. After the infection is cleared most cells die by apoptosis and some cells become memory cells to establish a faster response upon another infection (Zhu and Paul 2008; Zhu, Yamane et al. 2011).

Box 2.

The B cell lineage develops from HSC at the same sites as T cell development occurs. A major difference in lymphocyte development is that B cell development starts earlier, already in the pre-aorta gonad mesonephros region, which is also the most potent site for B cell development in the fetus (Dorshkind and Montecino-Rodriguez 2007). The HSC that migrate into the bone marrow are post natal responsible for B cell production. When B cells are activated they start to produce immunoglobulins, soluble and cell surface products to neutralize pathogens. Follicular B2 cells respond to microbial infections, they will present processed bacterial peptide to their CD4⁺ T cell partner. Because of this interaction B cells will undergo isotype switching and mature into plasma cells secreting antibodies to clear the infection. Some of these mature cells become memory B cells in peripheral lymphoid organs. Marginal B cells respond to bacterial polysaccharides without T cell stimulation. Recently it has been found that regulatory B cells can negatively influence the immune response via IL10 and transforming growth factor (TGF) β secretion (Vaughan, Roghanian et al. 2010). There are T cell independent B cell activators as mentioned above, but there is also T cell dependent B cell activation. Th1 type of CD4⁺ T cells are capable of helping B cells redirect to IgG2a in mice and IgG2 in humans. Th2 type of environment can induce switching towards IgE and IgG1 in mice and IgE and IgG4 in humans. At first the B cells will start with producing IgM and IgD. Upon stimulation they can switch towards an IgA,

IgE or IgG, depending on their surroundings and seem to be influenced by dietary components as discussed later. Neonatal B cells are capable of switching to IgG1 and IgG3 during the first 2 years of life, but the switch to IgG2 and IgG3 is inadequate during this period. To compensate the lack of protection in fetus and newborn, microbe-specific maternal IgG antibodies move across the placental barrier to provide some vital protection. During the last trimester of pregnancy IgGs are transferred intrauterine to the infant, because new-borns memory T cells capable of generating IgG and isotype switching aren't present yet. IgG1 and IgG4 are most effectively transported across the placenta compared to IgG3 and IgG2. Transfer of maternal antigen-specific IgG regulates the development of allergic airway inflammation early in life in a neonatal Fc region (FcRn)-dependent manner (Nakata, Kobayashi et al. 2010). This active transfer of IgGs from mother to child starts at week 17 and continues until birth. Moreover, just before birth, IgG levels of prenatal infants are even higher than levels present in the mother. The transfer and amount of pathogen specific IgGs is dependent on vaccinations and diseases the mother acquired during life. Many factors influence the IgG transportation processes which are described in a review by (Chucuri, Monteiro et al. 2010). IgA IgD, IgM are the only known antibodies acquired after birth via breast feeding, covering the lack time during increasing antibody productions of infant's immune system itself. When the infant can produce the different B-cell antibodies, the activation, isotype switching and survival of B cells is for example under influence of B - cell activating factor (BAFF), TGF β 1, IL-6, -7 and -10 produced by PP stromal cells (Finke, 2009). Not much is known about the involvement of Ig free light chains (IgLC) in humoral immune response early in life. However the release of antigen specific IgLC by B-cells/plasma cells like for example IgE may have implications for the health status of the newborn (Redegeld Nat Med 2003, Schouten JACI 2010). Furthermore compromised immune status may result in enhanced production and secretion of IgLC at the cost of other immunoglobulins (van Esch CEA 2010).

Whereas T and B cell lineage experienced an in dept research into their origin, the origin and differentiation of dendritic cells (DC) is in its initial phase. One problem is to define specific precursor DC types (Liu and Nussenzweig 2010). Microbial exposure is one of the key developing factors for DCs (Plantinga, van Maren et al. 2011). The lamina propria (LP) contains mostly fractalkine positive DCs which sample the gut lumen with protrusions across the epithelial barrier, and are able to induce a Th17 response. Furthermore, in addition to the non-migrating DC population in PP there is a majority of DCs which will migrate to specific sites after encountering an antigen. For example the intestinal LP derived CD103+ DC subtype will migrate towards the MLN and is known for its capability to elicit a regulatory response, in the presence of RA and TGF β . However if other factors are present a Th1 or a Th2 response can be induced. The activated T cell in the MLNs will migrate to the site of inflammation for instance in the intestine to initiate a proper immune response (Figure 4). Intestinal development is already influenced during pregnancy by the amniotic fluid as intestinal epithelial cells of the fetus can react to components in the amniotic fluid by different receptor expression (Drozdzowski, Clandinin et al. 2010). So during gestation the gut can readily react to its micro-environment, but still much is unknown about the influence of maternal status on infantile gut development.

An increasing number of studies have identified interesting links between early nutrition, epigenetic processes and disease development later life (Boehm and Moro 2008). As the plasticity of growing and developing tissues shapes, the base of the responses to later

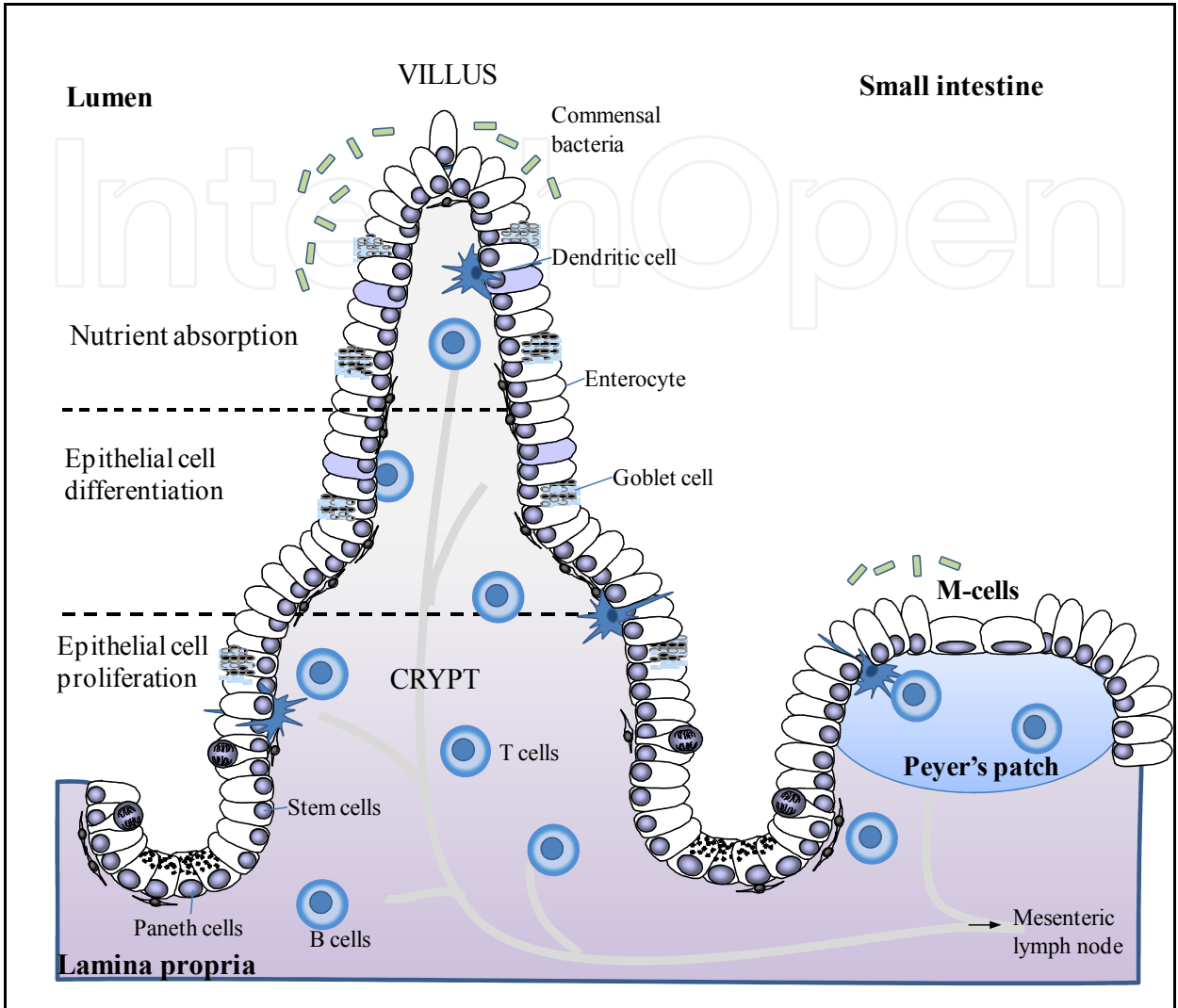


Fig. 4. Intestinal structure and development is already influenced during pregnancy and reacts to its micro-environment. The complex structure includes a variety of cross talk between different cells including epithelial cells, dendritic cells and lymphocytes. The lamina propria contains mostly dendritic cells which sample the lumen with protrusions across the epithelial barrier; in addition, the CD103+ DC subtype will migrate towards the mesenteric lymph nodes (MLN), after which the activated T cell in the MLNs will migrate back to the site of inflammation to initiate a proper immune response.

challenges is established, therefore the exposures during early life may be critical. Folate deficiency during pregnancy is associated with increased risk for aberrant reprogramming of DNA methylation inducing neural tube defects. Dietary folate intake can restore these deficiencies and neural tube defects. Folate is however not the only determinant of DNA methylation. Other methyl donor nutrients like betaine, vitamins B2, B6 and B12, and methionine, and choline, can also change DNA methylation status and therefore have an impact on development early in life (Niculescu and Lupu 2010).

3. Postnatal immune development in the gut

After birth a newborn changes from a sterile environment of the uterus into a world of constant challenges. In the first months of life newborns are more dependent on their innate immunity and immunoglobulins derived from the mother as described before. IgG is already acquired intrauterine but IgM and IgA are ingested via human milk to have an early defence against pathogens. Triggering the innate immunity repeatedly to microbial challenges after birth helps establishing a normal Th1 response postnatal. But the immune response is still less adequate compared to the adult response, possibly due to a general lower number of immune cells present. To build up an effective and balanced immune system interaction with germs and bacteria is needed (van't Land, Schijf et al. 2011). It is important that the immune balance is restored properly because a deregulation early in life could trigger an adverse reaction leading to an allergic reaction. The gut is the main processing site of food and, here immune tolerance against new food particles is established. But an improper chemical barrier and weak mucosal barrier integrity will complicate acquiring immune tolerance. There are some factors positively influencing development of the gut and immune system during pregnancy and after birth, of which only few of them will be discussed in detail below.

3.1 Influence of vitamins during and after pregnancy

Vitamin A has been recognized for its importance in lymphoid structure formation during embryogenesis. Sources of vitamin A are carrots, liver, sweet potatoes and butter. For example vitamin A supplementation before, during and after pregnancy using restricted dosages, results in long term positive effects on lung function which could be measured nine to thirteen years later.(Checkley, West et al. 2010). Shortly after the recognition of vitamin A essence during pregnancy, the teratogenic effect of excess vitamin A was shown. Malformations of the central nervous system, the eye and the thymus were found due to excessive use of vitamin A (Gutierrez-Mazariegos, Theodosiou et al. 2011). The teratogenic danger of vitamin A can also be induced via extra prolonged ingestion of this vitamin because it is stored in fat cells in the liver. It was already mentioned that RA could increase the progression from HSC into myeloid cell lineage. When RA is lacking from the diet CD4+ and CD8+ T cells and IgA+ B cells aren't found in the LP of the intestine, whereas CD4+ T cells were still present in lung tissue (Iwata 2009). Recently it was shown that stromal cells and DCs in the MLN induce high levels of RALDH expression postnatally, dependent on vitamin A and not on toll like receptor (TLR) signalling (Molenaar, Knippenberg et al. 2011). They compared MLN with other lymph nodes at different postnatal weeks and found an increased expression of RALDH only in the MLN residing DC, almost exclusively in CD103+ MHC-II+ CD11c+ DC cells. Vitamin A deficiency reduces this RALDH expression significantly. In addition, RA skews DC towards tolerance induction via instruction of Foxp3 Treg in the mother during pregnancy and in the infant just after birth (Coombes, Siddiqui et al. 2007; Duriancik, Lackey et al. 2010). Also vitamin A is necessary for the intestinal homing properties of activated T cells, Treg and certain B cells. *In vitro* it was shown that naïve CD4+ cells induce gut homing receptors when they are activated by CD3 and CD28 together with RA, this combination simultaneously down regulates skin homing receptors (Iwata 2009). *In vitro* DC from the gut associated lymphoid tissue could also induce activated IgA secreting B cells more effectively when RA was present in the medium,

however the intracellular mechanism needs to be determined (Mora and von Andrian 2009). Not only RA is important for IgA secreting B cells, IL5 is essential for IgA production and TGF β increases IgA secretion *in vitro*. There is also a positive feedback loop, IL6 stimulates IgA induction by DC and IL6 is induced by RA. Synergistic effect on IgA induction could be obtained by the aforementioned cytokines and therefore immune protection of the infant could be achieved (Mora and von Andrian 2009; Duriancik, Lackey et al. 2010). This indicates that also during early infancy the level of vitamin A is of importance for proper immune functioning, which may have profound consequences later in life.

An additional vitamin of interest for immune development is vitamin D. Worldwide there is no consensus on the healthy levels of vitamin D intake before and during pregnancy. Already during the first trimester of pregnancy vitamin D could be of importance for the development of the fetus. The 25-hydroxy vitamin D-1 α -hydrolase CYP27B1), which converts vitamin D into its more active metabolite 1,25 (OH) $_2$ D, can be detected in the placenta. There is some speculation about vitamin D deficiency and reduced fertility, this fertility problem may be caused by a reduced down regulation of the Th1 response by high levels of vitamin D as well as circumstantial evidence pointing at a relation between gestational diabetes and preeclampsia in correlation to circulating vitamin D levels (Dror and Allen 2010). In addition, vitamin D is important for the clearance of certain infections (Hoyer-Hansen, Nordbrandt et al. 2010).

Vitamin D is linked to monocyte activation via activation of TLR2 and TLR1 (Lagishetty, Liu et al. 2011). Recently it was shown that IL4 and IFN γ are involved in the regulation of vitamin D expression (Edfeldt, Liu et al. 2010). IL4 promotes expression of CYP24A1, which down regulates active vitamin D, and IFN γ positively influences the expression of CYP24B1 in monocytes. Then it is suggested that vitamin D could skew the balance between Th1 and Th2 towards a Th2 phenotype directly or indirectly via monocyte activation, which however may be much more complex *in vivo* (Adams and Hewison 2008). Low vitamin D levels during pregnancy are suggested to be related in the development of food allergy (Nwaru, Ahonen et al. 2010). It was recently shown that active vitamin D can suppress DC maturation and inhibit T cell proliferation. Mature DC have high levels of vitamin D converting enzymes, suggesting that upon Vitamin D addition, mature DC can inhibit the development of immature DC. Suppression of DC maturation could then via vitamin D promote tolerance. Research with vitamin D receptor (VDR) and CYP27B1 knockout mice showed abnormal lymph node development due to the presence of more mature DC and increased DC trafficking (Hewison 2011).

There is still debate about the healthy amount of vitamin D intake during pregnancy (West, Videky et al. 2010). Indeed some studies show that vitamin D intake is associated with diminished wheeze, asthma and eczema in offspring (West, Videky et al. 2010). For vitamin D it is clear that lymphocytes are influenced, but to what extent this affects function later in life remains to be established. Increasing evidence from observational studies in infants at older ages, indicate that vitamin D insufficiency and deficiency might increase the risk of chronic diseases such as type 1 diabetes and multiple sclerosis. However, clear randomized trials on this association need to be conducted to confirm these findings. In the last decades, observations accumulate that vitamin D deficiency leads to more often and more serious respiratory infections than in individuals with sufficient vitamin D plasma levels. This

illustrates the importance of the nutritional status early in life, to set the proper immune balance (Karatekin, Kaya et al. 2009).

3.2 Human milk

It is well established that breastfeeding reduces the incidence of gastrointestinal and non-enteric infections in infants, due to its antimicrobial activity against several viruses, bacteria, and protozoa (Chirico, Marzollo et al. 2008). In addition, it was shown that infants, breastfed for more than 4 months experienced significant reduced incidences of respiratory tract infection requiring hospitalization, as compared to infants who were not breastfed (Bachrach, Schwarz et al. 2003). Moreover, other studies showed that breastfeeding provides protection against urinary tract infections and otitis media and it reduces the development of inflammatory conditions like allergy (Fiocchi, Martelli et al. 2003), Crohn's disease and ulcerative colitis (Hanson 2007). This, moreover, emphasizes the diversity of activity and active components present in human breast milk. Although it is clear that allergy development is influenced by breast milk as well as atopy related disorders, still some controversy exists regarding the beneficial length of breastfeeding (van Odijk, Kull et al. 2003). These protective effects of human breast milk seem to persist at least during the first decade of life.

Fortunately prenatally the infant is supplied with maternal immunoglobulins, for the first protection against infections. It takes at least one year before an infant can produce about 60% of its IgG levels on its own. After birth the child can be supplied with essential IgG, IgM and IgA via human milk. For example, IgA is necessary as the first line of defence against microorganisms. This immunoglobulin also controls commensal (also called beneficial) bacteria all without activation of an inflammatory response. Because infants do not have an optimized Treg response and no memory cells, B cells cannot be directed to produce the right amount of Ig antibodies quickly as a first defence. IgM helps to eliminate the pathogen before IgGs are produced. As earlier mentioned IgM is normally produced by naive B cells before isotype switching occurs. The B cell response needs time after birth to be fully functional, so acquiring this component via human milk strengthens the first line of defence. Not only antibodies are factors present in human milk, other immune modulating components are present, including cytokines, non digestible oligosaccharides and poly unsaturated fatty acids (PUFA), which are discussed in more detail below.

3.3 Cytokines

TGF β and IL10 are held responsible for the induction of oral tolerance in the intestine (du Pre and Samsom 2010). They educate the immune system locally not to respond to harmless antigens. In human milk TGF β 2 is the predominant isoform of the three existing mammalian isoforms. Addition of TGF β 2 to infant formula, can skew the Th2 allergic effector response towards Th1 in rat pups exposed to β -lactoglobulin, a cow's milk allergy protein (Penttila 2009). Not TGF β 2 but TGF β 1 is the major player to establish immune tolerance to food in the adult system. To guarantee the uptake of TGF β , TGF β receptors are abundantly expressed in the neonatal intestine, even the soluble TGF β 2 receptor is present in breast milk. But in addition it was found that TGF β is not essential for tolerance induction when milk born-IgG antigen immune complexes are present (Verhasselt, Milcent et al. 2008). Moreover it is known that high levels of TGF β together with RA skew the immune system

towards a regulatory suppressive function, a low dose of TGF β combined with IL6 or IL21 or IL23 will result in inflammatory Th17 activation instead of Treg upregulation (Konkel and Chen 2011). Recently Hering et al (2009) showed that *in vitro* TGF β probably helps forming the intestinal epithelial barrier via exerting its effect on the reinforcement between the epithelial cells (van't Land, Meijer et al. 2002; Hering and Schulzke 2009). The production of IgA is also positively influenced by TGF β (Cazac and Roes 2000; Borsutzky, Cazac et al. 2004). This indicates that the immune modulating components have their function alone, but this needs to be further investigated in combination.

3.4 Nondigestible oligosaccharides

There are different types of soluble dietary fibres e.g. (hemi)cellulose, lignin, β -glucans, pectins, gums, inulin and oligofructose. In addition different non-digestible oligosaccharides with specific properties are obtained or manufactured from natural sources (Calder, Krauss-Etschmann et al. 2006). Human milk contains approximately 7-12 g/L oligosaccharides (Hopppu, Kalliomaki et al. 2001). At least 130 different oligosaccharides have been isolated from human milk and the two main categories are neutral and acidic oligosaccharides (Lara-Villoslada, Olivares et al. 2007; Greer, Sicherer et al. 2008). These oligosaccharides are non-digestible carbohydrates that have many different properties and are believed to act on the microbiota in the gut (Host, Koletzko et al. 1999; Halken, Hansen et al. 2000; Hill, Murch et al. 2007; Niggemann and Beyer 2007). Due to physicochemical properties of non-digestible carbohydrates the absorption of minerals and fecal consistency improves. Some of these have specific properties and can be used as prebiotics as a dietary supplement. Prebiotics are defined as "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health" (Host and Halken 2004). Prebiotics enhance defense mechanisms of the host by stimulation of growth of Bifidobacteria and Lactobacilli. As the intestinal microbiota plays a critical role in the establishment and maintenance of healthy immune responses, the delayed colonisation of the infant gut with commensal bacteria are suggested to be a risk factor for the development of immune mediated chronic disorders such as allergic and autoimmune diseases. Short-chain fatty acids, released by these bacteria upon fermentation of prebiotics, are essential nutrients for intestinal epithelial cells and support gut function (Gibson and Roberfroid 1995; Nakhla, Fu et al. 1999; Boehm and Stahl 2007). *In vivo* and *in vitro* studies have shown beneficial effects of prebiotics on the innate as well as the adaptive immune system (Boehm, Fanaro et al. 2003). Short-chain galacto-oligosaccharides (scGOS), long-chain fructo-oligosaccharides (lcFOS) and pectin-derived acidic oligosaccharides (pAOS) are some examples of non-digestible oligosaccharides that mimic the functionality and molecular size distribution of human milk oligosaccharides.

The effects of scGOS and lcFOS (9:1)(Immunofortis®) have been studied in a murine vaccination model (Vos, Haarman et al. 2006), in an allergic asthma model (Vos, van Esch et al. 2007) and a cow's milk allergy model (Schouten, van Esch et al. 2009). The response to vaccination of mice fed the scGOS/lcFOS diet was significantly enhanced, as well as the fecal Bifidobacteria and Lactobacilli proportions. pAOS enhanced the murine vaccination response and the combination (scGOS/lcFOS/pAOS) was even more effective (Vos, Haarman et al. 2007). To stimulate the entire microbiota a great variation in the oligosaccharide structures will exert this effect, as human milk oligosaccharides comprise of many different oligosaccharides. The pAOS are not only another group of oligosaccharides,

they act very specifically to their acidity. Based on this they are able to interact with surfaces and might prevent the adhesion of pathogens on the intestinal epithelium. In infants pAOS showed no difference in stool characteristics, pH, growth, crying, vomiting and regurgitation patterns as compared to control formula. In addition pAOS alone did not affect intestinal microecology (Fanaro, Jelinek et al. 2005). Furthermore, systemic Th1 dependent immune responses were enhanced using the prebiotics without inducing autoimmunity, as Th1 is low in newborn infants. In addition, in a murine model for cow's milk allergy dietary intervention with scGOS/lcFOS showed significant decrease of the allergic response and increased specific IgG2a levels (Meyer 2004; Schouten, van Esch et al. 2009).

Recently it was found in mice that dietary intervention with scGOS/lcFOS/pAOS reduces the development of an acute allergic response upon antigen challenge, although specific immunoglobulins levels remain high. *Ex vivo* depletion of CD25⁺ Treg abrogated the diminished acute allergic response, combined with adoptive transfer studies, imply crucial involvement of antigen specific CD25⁺ Treg cells in the suppression of the allergic effector response (Schouten, van Esch et al. 2010; van't Land, Schijf et al. 2010; Schouten, van Esch et al. 2011). Furthermore, clinical trials have been performed with the scGOS/lcFOS mixture in children at high risk for allergies. A reduction in the incidence of atopic dermatitis (AD) (Moro, Arslanoglu et al. 2006) and the incidence of allergic manifestations during the first 6 months of life (Arslanoglu, Moro et al. 2007) was observed, furthermore this reduction lasted at least until 2 years of age (Arslanoglu, Moro et al. 2008).

Recently, it was also shown, in a multicenter trial, that the scGOS/lcFOS/pAOS mixture could reduce the incidence of AD in healthy not at risk children (Gruber, van Stuijvenberg et al.). In another clinical study, using the scGOS/lcFOS mixture, fecal secretory IgA was increased in healthy infants (Bakker-Zierikzee, Tol et al. 2006). Also in healthy infants there is cumulative evidence that prebiotic mixtures might beneficially affect the host in both Th1 as well as Th2 prone settings as it might prevent food allergy (Th2) and enhances the vaccination response (Th1). Although it is believed that prebiotics exert their effect via stimulation of growth of selective bacterial species that beneficially improve host health, there is debate about this mechanism and there are potentially microbiota-independent mechanisms as well (Boehm, Fanaro et al. 2003; Vos, M'Rabet et al. 2007). As it was shown that epithelial cells can transport scGOS, lcFOS and pAOS across from apical to the basolateral side (Eiwegger, Stahl et al. 2010), this illustrates that besides a prebiotic immune modulating effect the oligosaccharides also come in direct contact with immune cells themselves, making it possible to act directly on the immune cells.

3.5 Poly unsaturated fatty acids

Omega-3 and omega-6 poly unsaturated fatty acids (PUFA) are essential for humans and have to be provided via the diet especially found in seafood. PUFA are incorporated into the cellular membrane and are eicosanoid precursors hereby affecting the immune response. In this regard in particular n-3 long chain (LC)-PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are regarded to be anti-inflammatory while n-6 LCPUFA, like linoleic and arachidonic acid, are able to boost inflammatory responses. Arachidonic acid, for example can be converted into 2 series prostaglandins, these are able to increase IL4 and

decrease IFN γ , and 4 series of leukotrienes, which are able to induce endothelial permeability and production of inflammatory cytokines (Moreno 2009).

In westernized countries the n-3 fatty acid ingestion is no longer favoured over n-6 PUFA which may have implications for immune homeostasis. It has been stated that the original diet of the human race had an n-6 : n-3 ratio of approximately 1:1 and that this has changed over the past decades to a ratio of at least 15:1 (Simopoulos 2008). This shift is suggested to be explanatory for the increased incidence of cardiovascular diseases, chronic inflammatory diseases, obesity and also allergic diseases. Therefore pre-clinical as well as clinical trials are performed in order to investigate this hypothesis. It has been reviewed that n-3 LCPUFA intake reduces the incidence of allergic disorders, e.g. AD, less sensitization to egg in the clinical trials (Blumer, Pfefferle et al. 2007). Two studies by Dunstan *et al.* show reduced sensitization to egg and less AD in offspring when pregnant woman were supplemented with fish oil, which contains EPA and DHA (Dunstan, Mori et al. 2003; Dunstan, Roper et al. 2004). They found a positive influence of n-3 LCPUFA on TGF β mRNA levels in maternal peripheral blood and cord blood. This could imply a regulatory function of n-3 LCPUFA, but mRNA still needs to be processed towards an active component. Recently, it was shown that maternal n-3 LCPUFA intake decreased the risk of food allergy and IgE-associated eczema in children at risk for allergy (Furuhjelm, Warstedt et al. 2009). This shift in the decrease of allergy can be explained since n-3 LCPUFA is incorporated in the membrane of immune cells at the cost of n-6 LCPUFA as arachidonic acid, skewing towards a less inflammatory cytokine surrounding. In contrast, in a clinical study by Almqvist et al., (Almqvist, Garden et al. 2007) it is shown that supplementation of n-3 PUFA, starting at a maximum of six months of age, did not prevent children with a family history of asthma from developing atopy, eczema nor asthma at the age of 5 years. Hence discrepancy on effects of n-3 PUFA in prevention of allergic disease exists. There are also discrepancies between studies in the preparation of fish oil, influencing EPA and DHA content (Prescott and Calder 2004). Of concern is the dosage in human studies, this is often much lower than used in animal studies, which makes it difficult to extrapolate the outcome and could explain differences observed. However interventions using dietary factors like LCPUFAs are under-explored and that there is a need for additional research. One of the strategies that are proposed is the use of selected LCPUFA in the formula feeding of young children at high risk for allergies (Vanderhoof 2008). Another strategy could be to supplement a novel LCPUFA during pregnancy; LCPUFA maybe has its largest positive effect on an infant health status when primary immune responses are still developing. In addition novel synthetic LCPUFA may reveal to be potent in the reduction of the allergic burden (Prescott and Calder 2004).

4. Consequences later in life conclusion

During the different phases of life, several nutritional factors influence our immune system and immune responsiveness in collaboration with endogenous immune modulating mediators like humoral factors, lipids and oligosaccharides. A vast amount of literature is available on the role that nutrients and human milk (as reviewed in this article), have on the development of the immune system; a lot less is known about the exact requirements in the phases thereafter, in toddlers, during adolescence, and in the later stages of life. Moreover, as no single biomarker exists able to determine a proper functioning immune system, it is

almost impossible to describe completely the developmental status of the immune system and the important influences of nutrition. Although it is clear that each phase in life puts specific requirements on nutrition, no clear statement can be made based on literature as to what the exact dietary requirements are in order to fully support the immune system during these stages in life. But food as a beneficial dietary component is currently under very active scientific investigation, so more information about nutrition will be available soon.

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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