**Development and Regulation of Immune Responses to Food Antigens in Pre- and Postnatal Life**

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**Abstract**

Food antigens are harmless environmental components. The physiological response is the development of clinical and immunological tolerance. It is now well appreciated that tolerance development is the result of active immunoregulation and depends on a close interaction between the innate and adaptive immune system resulting in the development of tolerance-mediating T-cell responses. Programming of the immune system, particularly with regard to tolerance development, already starts before birth and stays under close control of the maternal immune system. Therefore, the pre- and postnatal period represents an important ‘window of opportunity’ for immunoprogramming. Underlying mechanisms include maternal cell transmission, antibody transfer, transfer of mediators/cytokines, and transmission of antigens and allergens. Immunoprogramming is fostered and augmented in the context of microbial components. Recently, several microbes have been identified which possess the capacity of immunoprogramming early in life. Epigenetic regulation represents an important novel mechanism in this regard. This concept opens new avenues for the development of preventive strategies to avoid inappropriate immune responses against food antigens.

**Introduction**

The development of immune responses to food antigens is of great relevance and interest. Food antigens belong to the first group of antigens which are encountered by babies after birth. The foods are digested within the gastrointestinal tract and fragments pass through the gut barrier and are transported through the bloodstream to the various target organs in the body.
The key responsibility of the immune system is to distinguish between dangerous and harmless environmental antigens and to organize the appropriate immune response to protect the body. In this regard, most common food antigens clearly belong into the category of harmless environmental antigens and the appropriate immune response is the development of clinical and immunological tolerance.

The development of tolerance is dependent on the close interaction between the innate and the adaptive immune systems. As an outcome of this regulatory pathway, certain T-cell subsets develop which have distinct anti-inflammatory, immunosuppressive or tolerance-maintaining activities. Since this is an active immune process, regulation is required. Many data indicate that tolerance development depends on antigen-specific mechanisms. This implies that initiation of this immunological process starts already before birth in order to ensure the readiness of antigen-specific tolerance-inducing mechanisms at the time of first antigen exposure.

Immunoprogramming is controlled by gene–environment interaction. Since programming starts already before birth, the maternal status in terms of genetic background and environmental exposure must be considered in this regard. Immunoprogramming and immunoregulation of the fetal immune system is controlled to a large extent via cellular and molecular transfer mechanisms by the mother. Since at least parts of this process are genetically determined, it is relevant to distinguish between atopic and non-atopic mothers. In terms of environmental living conditions, the qualitative and quantitative load of food antigen exposure must be considered as well as exposure to a number of co-regulatory and co-modulatory factors, including smoking, alcohol and hormones. Recently, bacterial components received great attention as potentially potent immunoregulators.

Development of T-Cell Responses

It is now well accepted that antigen-specific T cells are readily detectable in cord blood. The presence of T-cell responses is per se independent of the allergic or atopic status of both mother and child. Therefore, it seems to be a normal mechanism of regulation that a baby is born with a repertoire of antigen-specific T cells. What antigens do these T cells recognize? This has been extensively investigated and the results indicate that T-cell responses to food antigens are most frequently detectable in cord blood. Specifically, highest frequencies were observed for T-cell responses to cow's milk and hen's egg protein [1, 2].

T cells are identified as early as 12–14 weeks of gestation. The development of antigen-specific T cells may occur at several sites. Antigen exposure via amniotic fluid allows swallowing of the antigen and, therefore, the antigen–immune interaction in the fetal gut is of relevance. Alternatively, and
even occurring in parallel, antigen exposure also occurs via transplacental uptake. In this case, the antigen enters the fetal circulation and may trigger antigen-specific immune responses in various lymphatic organs.

Some time ago, the fetal immune system of the gut was described to initiate adaptive immune responses [3]. Therefore, antigen-presenting cells as well as cells expressing co-stimulatory molecules are present in the fetal gut. Indeed, major histocompatibility complex class II (MHC-II)-positive cells are also detectable in the fetal gut from week 11 of gestation onwards. Antigen-presenting cells, like CD68+ macrophages, CD20+ B cells or CD83+ dendritic cells, are also detectable in the fetal gut. CD83+ dendritic cells are considered to be functionally mature dendritic cells ready for antigen presentation. The co-stimulatory molecule CD40 as well as its T-cell ligand CD40L are detectable in the fetal gut as well as other co-stimulatory T-cell molecules like CD28 or CTLA-4. The constitutive expression of CTLA-4 has been identified as a characteristic of regulatory T cells indicating the development of self-tolerance at this stage [4]. The presence of this molecule in the fetal gut, together with the occurrence of antigen allergen exposure of the fetal gut might, therefore, favor the development of either tolerance or Th2-biased immune responses (table 1).

We have recently developed a model of food allergy in mice. BALB/c mice were intraperitoneally sensitized to ovalbumin (OVA) followed by repeated

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<th>Table 1. Development of different cell types in human fetal gut</th>
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APC = Antigen-presenting cell; NK = natural killer. Data from Jones et al. [1] and Gunther et al. [5].
intragastric (OVA challenges). The highest levels of OVA-specific IgE antibody levels were detected in OVA-sensitized and OVA-challenged mice. Throughout the lower intestinal tract, a marked infiltration with eosinophils was observed, and goblet cell numbers as well as goblet cell area were significantly increased. Furthermore, the villus/crypt ratio was decreased compared with controls. We then transferred CD4+ T cells from the mesenteric lymph nodes of OVA-sensitized and OVA-challenged mice and analyzed the development of asthma in the recipients. Airway hyperreactivity and eosinophilic airway inflammation in recipients was observed when they were aerosol-challenged with OVA, but not with PBS. These data indicate that CD4+ T cells from the mesenteric lymph nodes of mice with food allergy are able to transfer the phenotype of experimental asthma [6].

**Development of Early T-Cell Responses under Maternal Influence**

In contrast to adults, immune responses elicited in early life are predominated by antigen-specific CD4+ T cells producing Th2 cytokines together with a reduced frequency of IFN-\(\gamma\) production, particularly within the CD8+ subset. This tendency towards generation of Th2 biased immunological memory response has been observed in both neonatal mice and humans, even in responses to infectious agents [7–9]. Recent data provide new insights into the potential mechanisms underlying these effects. The profile of maternal immune responses impacts the development of Th2 immunity in the progeny. This has been elegantly demonstrated recently [10]. The investigators induced an OVA-specific Th1 or, alternatively, Th2 immune response in mother mice. The offspring were then sensitized to and challenged with OVA following weaning. They found that the progeny of mothers with Th1-biased immunity to OVA had reduced anti-OVA-specific IgE antibodies and airway eosinophilia following sensitization and challenge. In contrast, this was different in the progeny of mothers with Th2-biased immunity to OVA or naïve mothers. Importantly, the progeny of mothers with Th1-type immunity to a heterologous antigen were not protected from developing OVA-induced airway disease. These findings demonstrate that maternal transfer of protection from development of allergic airway disease to offspring was achieved in an antigen-specific manner and requires antigen-specific Th1 immunity in the mothers. In contrast, the allergic status of the mothers has the potential to negatively affect the immune response of the offspring. Th1 immunity, IgG production and the presence of regulatory T cells is characteristic of the physiological responses to food antigens. The consequence of these observations would be that a maternal Th1 and/or Treg (food) antigen-specific immune response would be the ideal prerequisite in order to prevent the development of a Th2 and, therefore, pro-allergic response in the next generation.
What might be the underlying mechanism for this phenomenon? Recently, several mechanistic aspects received attention, including antibody transfer and antigen/allergen transmission.

**Allergen Transfer**

The transfer of allergens from different origins via placenta or breast milk has long been recognized. Two possible routes of intrauterine allergen transfer have been postulated: passage of allergens from the maternal vasculature of the decidua across the amniochorionic membranes into the amniotic fluid, and across the placenta from the maternal to the fetal circulation [11]. Of these, transplacental transport offers the greater reservoir of antigens due to the placenta’s primary function in enabling the exchange of nutrients and vast materials between the mother and fetus. The transplacental passage of common dietary allergens, cow’s milk β-lactoglobulin and hen’s egg OVA is described to occur from week 26 of gestation using an ex vivo model of placental perfusion [12–14]. The same has authors have shown that the main part of the allergens accumulate in human placental tissue, providing an explanation for the missing dose-related cell reactivity in cord blood cells. A human study that followed the food allergen OVA in the serum of pregnant woman also investigated the dietary egg intake and the antigen amount in the cord blood of children and 3 months postpartum in breast milk. This study revealed that the amount of OVA in cord blood and breast milk was not related to maternal dietary intake or atopic predisposition. The authors concluded that a rigorous dietary egg exclusion cannot exclude egg allergen transfer via the placenta and breast milk [15]. These studies have recently been extended to research on lactating mice. It was investigated whether the exposure of lactating mice to an airborne allergen effects asthma development in progeny. The investigators found that airborne antigens were efficiently transferred from the mother to the neonate through milk and that tolerance induction did not require the transfer of immunoglobulins. Breastfeeding-induced tolerance relied on the presence of TGF-β during lactation, was mediated by regulatory CD4+ T lymphocytes, and was depending on TFG-β signaling in T cells. The authors concluded that breast milk-mediated transfer of an antigen to the neonate results in antigen-specific tolerance induction leading to antigen-specific protection from allergic airway disease. It is tempting to speculate that such mechanisms may also apply to food antigens [16].

From these and other experimental data it is clear that allergen exposure is necessary to develop (oral) tolerance. This is contradictory to earlier studies suggesting that sensitization, e.g. against peanut, milk and egg, may occur via breast milk and is responsible for allergic reactions to antigens on a presumably first direct encounter [17–20]. In the same studies, however, it was noted that mothers of sensitized children did not consume significantly different
amounts of the respective food during pregnancy and, more importantly, children of mothers avoiding certain foods were not protected against sensitization [18]. A recent Cochrane analysis assessed the effects of prescribing an allergen avoidance diet during pregnancy or lactation or both on maternal and infant nutrition and on the prevention or treatment of atopic disease in the child. Based on the data review, it was concluded that prescription of an antigen avoidance diet to high-risk women during pregnancy is unlikely to substantially reduce their children’s risk of atopic diseases. However, prescription of an antigen-avoidance diet to high-risk women during lactation may reduce their children’s risk of developing atopic eczema. However, the authors require better and larger trials for this recommendation [21].

From the literature and data discussed above, several important aspects might be concluded. Development of clinical and immunological tolerance is T-cell-dependent and antigen-specific. To induce tolerance regulating T-cell subsets, antigen contact during pregnancy is required. Due to the accumulation of antigens within placental tissues even elimination of respective foods during pregnancy cannot prevent accumulation of antigen in the placenta. Finally, antigen transfer via the placental barrier is now well established.

**Antibody Transfer and Immune Regulation by Antibodies**

The antigen transfer across the placental barrier is facilitated to some extend by binding to immunoglobulins. Of particular relevance to the field of allergy is the specific transport of IgG. Maternal IgG transfer begins at about 16 weeks of gestation. From 22 weeks of gestation, fetal IgG levels increase rapidly reaching maternal serum concentration by 26 weeks and exceeding those of the mother at birth [22]. However, this relationship is isotype-specific with fetal IgG1 exceeding, IgG3 and IgG4 are equivalent to, and IgG2 levels are less than maternal levels, reflecting the transfer preference of IgG1 > IgG3 ≥ IgG4 > IgG2. Transfer is mediated by IgG receptors on various cell types within the placenta. An important receptor for IgG transport is the neonatal Fc-receptor (FcRn), an MHC class I-like Fc receptor expressed by syncytiotrophoblasts [23]. The syncytiotrophoblast is bathed in IgG-containing maternal blood. IgG binding occurs at a pH of 5–6.5 which is below the neutral pH of the intervillous space. Therefore, the proposed model is the uptake of IgG from the fluid phase by endocytosis which enables binding to FcRn within vesicles at the appropriate pH. In this way, IgG is delivered to the basal membrane where it dissociates from the receptor at the responsible neutral pH of the stromal fluid [23–25]. Other FcRns are probably also involved in regulating the transfer of maternal IgG including FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), all of them are expressed on placental macrophages (Hofbauer cells) playing a scavenging role in the clearance of immune complexes. Finally, IgG must pass fetal epithelial cells. A candidate transport molecule expressed there is FcγRIIb [26].
In mice, IgG is also transferred via breast milk and uptake by FcRn in the gut, whereas human breast milk contains very low amounts of IgG. In a recent study [27] it could be demonstrated that the protection of mouse neonates from helminthic infections is dependent on IgG antibodies from primed (helminth-exposed) mother mice.

Transferred antibodies play not only a role as passive protectors against microbes and pathogens, but also an active immunomodulatory role in the progeny. With regard to allergy development, we have examined this in a mouse model where allergic Th2 immune responses to OVA were induced in pregnant mice by sensitization and aerosol allergen challenges. Allergen-specific IgG1 and IgG2 antibodies passed the placental barrier as well as free antigen. Free allergen was detected in serum and amniotic fluids in the offspring. As a functional consequence of antibody transfer, the progeny demonstrated a suppressed Th1 response as reflected by lowered frequencies of IFN-γ-producing cells paralleled by reduced levels of IFN-γ production. Development of an IgE response against the same allergen was completely prevented early in life. Experiments with antibody-reconstituted immune-compromised SCID animals proved that this Th2 and IgE-protective effect was mediated by transferred IgG antibodies. This protection was antigen-specific since sensitization to an unrelated allergen early in life resulted in even accelerated Th2 responses in these animals [28].

This is in line with previous observations indicating that maternally derived IgG antibodies suppress postnatal IgE production [29]. This suppression is antigen-specific [30] and depends on the Fc portion of the antibody. The proposed mechanism of this phenomenon is co-cross-linking of FcγRIIb and the B-cell receptors which are both simultaneously present on B cells (fig. 1). Cross-linking of both receptors at the same time by IgG and/or antigen-antibody complexes terminates B-cell responses and provides a negative antibody feedback mechanism [31, 32].

It is not a novel observation that IgE does not cross the placental barrier. However, a transamniotic transfer of intact maternal IgE into the amniotic fluid or even into breast milk of humans has been described. Whether this passive sensitization is of clinical relevance needs to be determined [33].

**Window of Opportunity – Immunoprogramming under the Control of Microbial Compounds**

The risk of development of allergic disease is greatly influenced by environmental factors. Western lifestyle conditions have in particular been associated with an increased risk of developing IgE responses. The hygiene hypothesis represents an attractive paradigm to explain the impact of environmental factors on the development and maturation of immune responses. In this regard, it has been proposed that certain microbes and their compounds...
play an important role in shaping the development of normal non-pathogenic immune responses. This concept also applies to the development of (oral) tolerance.

Among the environmental factors that modulate oral tolerance, the bacterial flora in the gut is thought to be one of the most important. It was demonstrated that oral treatment with bacterial LPS of germ-free mice, which have no indigenous bacterial flora in the gastrointestinal tract and are resistant to oral tolerance induction compared with specific pathogen-free mice, rendered these mice susceptible to the subsequent challenge for oral tolerance induction when estimated by the antigen-specific IgE, IgG and IgA responses [34]. This initial observation has been investigated in more detail by Japanese investigators [35] who showed the requirement of intestinal bacterial flora for oral tolerance induction. They investigated germ-free mice and exposed them orally to a high dose of OVA followed by systematic challenge with the same antigen. In the course of this protocol, the Th2 response was maintained whereas the Th1 response was abrogated. When the intestinal flora of germ-free mice was reconstituted with *Bifidobacterium infantis*, oral tolerance to both Th1 and Th2 responses was achieved. However, this was only effective when such reconstitution was performed in neonates but not in older mice. These data indicate that early life represents a window of opportunity for the induction of oral tolerance. Furthermore, intestinal flora with at least one bacterial strain is required to achieve Th2-related tolerance.

**Fig. 1.** The concept of pre- and postnatal regulation of immunity: atopy could be considered as a persistent lack of inhibition.
The innate immune system is the first line of immunological recognition and responsiveness to microbes. Toll-like receptors (TLRs) have not only been shown to play an important role in the immune defense against a majority of pathogenic structures but were also reported to be involved in the early programming of the developing immune system. Thus, loss of TLR signaling, e.g. in germ-free animals or MyD88 knockout mice that lack a central molecule necessary for signal transduction of most TLRs, resulted in an improper immune maturation mainly of the CD4+ T-cell compartment which finally leads to increased susceptibility of the respective animals to infections. Moreover, recognition of the commensal microflora by TLRs under normal steady-state conditions was demonstrated to be required for the development and maintenance of intestinal epithelial homeostasis [36] and, moreover, for establishing a proper maturation of the immune system in- and outside the gut [37, 38]. Mazmanian et al. [39, 40] demonstrated that monoclonization of germ-free mice with a single bacterial species, in their case the ubiquitous gut microorganism Bacteroides fragilis, was sufficient to correct the CD4+ T-cell deficiency in the spleens of otherwise germ-free animals. Taken together, all these observations indicate that an early interaction of innate immune mechanisms with components of an environment rich in microbiological structures is necessary for the proper maturation of the adaptive immune system (fig. 2).

Along this line, epidemiological studies have elucidated that, to a large extent, pre- and early postnatal exposure to a stable farm environment and consumption of non-pasteurized milk protect children from the development of respiratory allergies [41]. Therefore, the investigation of the role of perina-
tal exposure to certain microbial components on the development of allergic responses has been in the focus of recent studies.

We recently developed a murine model in which LPS was applied intranasally to pregnant mice [42]. At birth, T cells from the offspring of those LPS-treated mothers showed an elevated IFN-γ production. Following sensitization to OVA as the model allergen, these mice developed reduced levels of antigen-specific IgE and IgG1, whereas anti-OVA IgG2a levels remained unaltered. In addition, a selective suppression of Th2 reactivities was observed as in vitro re-stimulated T cells produced significantly less IL-5 and IL-13 while the IFN-γ response was not affected. Following airway provocation by allergen aerosol, the inflammatory reaction within the airways was less pronounced when compared to the offspring of untreated mothers; however, airway hyperresponsiveness to methacholine remained unaffected. Comparable results were obtained by Wang and McCusker [43] and Gerhold et al. [44]; both groups demonstrated significant allergy-preventing effects of endotoxin exposure in neonatal mice. These data clearly show that perinatal exposure to microbial components such as LPS may potently reduce the risk of offspring developing allergic immune responses later in life.

From an experimental point of view, LPS is an ideal molecule since biochemistry, biology and immunological responses are well defined. On the other hand, LPS also represents a potentially dangerous molecule since it is closely related to septicemia when present in peripheral blood. Therefore, there is a need to expand investigations on tolerance induction to other bacterial products and/or strains. In our subsequent experiment BALB/c mice received intragastric *Lactobacillus ramnosus* GG (LGG) during pregnancy and lactation or during pregnancy only. The progeny was then sensitized and challenged to OVA in order to induce the phenotype of experimental asthma. Our data suggest that *L. ramnosus* GG may exert beneficial effects on the development of experimental allergic asthma when applied in a very early phase of life. Immunological effects are, at least in part, mediated via the placenta through yet unknown mechanisms [45].

**Conclusion**

Immunoprogramming is an area of immunoregulation which is becoming more and more appreciated. It now becomes clear that immunoprogramming is an important prerequisite for the development of normal immune responses. The normal immune response to environmental antigens including food antigens is the development of clinical and immunological tolerance. The immunological regulation of tolerance depends on a close and complex interaction between the innate and adaptive immune system. A result of this interaction is the development of tolerance-regulating T-cell effector populations including regulatory T cells. The pre- and postnatal period represents
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an important ‘window of opportunity’ for immunoprogramming. This also implies that immunoprogramming stays under close control of the maternal immune system. Regulation of the fetal and neonatal immune response pattern depends, at least to some degree, on maternal cell transmission, antibody transfer and antigen/allergen transmission. The antigen-nonspecific mechanism of tolerance regulation depends on the recognition of microbial compounds by the innate immune system. Molecular sensors of such compounds are pattern recognition receptors including TLRs. Signaling through these receptors triggers a cascade of immune response mechanisms which then foster and augment antigen-specific tolerance development. Recently several microbial compounds have been identified which bear the capacity for early and efficient immunoprogramming. These novel aspects will open a new field of immunoprevention. It will be also applied in the area of food allergy prevention.

Acknowledgement

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References

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Discussion

Dr. Björkstén: You mentioned that allergens pass transplacentally and you pointed out that it is predominantly in foods and also in inhalants. Has it been excluded that it could be anti-idiotypic IgG antibodies rather than true antigens? We could never conclusively prove the point and Dehlink et al. [1] also have not been able to do this with mites.

Dr. Renz: Both are possible, absolutely. There are several mechanisms of how antigens can pass the placental barrier. One is free antigen and this could go via the blood or amniotic fluid, but the other mechanism is clearly immune complexes, antigen antibody complexes. Dehlink et al [1] in Vienna have done some recent experiments where they actually generated immune complexes and showed that they pass through, and even the antigens pass through. But I think the important issue here is not so much the mechanism, it's the amount of antigen which is passing through, and the amount passing through with immune complexes is much less, much lower than the free antigens.

Dr. Björkstén: Yes, but it's also a superb antigen if it is an immune complex. We showed some years ago that there are IgG complexes in cord blood.

Dr. Thornton: You mentioned that fetal allergen exclusion would be virtually impossible. What wasn't clear is whether you are advocating the exclusion of allergen at this time or not as a disease prevention strategy. To get the fetus to exclude allergen, the mother has to exclude allergen. We know from work done by Vance et al. [2] that egg-specific IgG decreased in mothers who excluded eggs from their diet from 6 weeks of pregnancy, so there was less IgG going to babies. I am not sure that it has been published, but we have anecdotal evidence that this had a negative clinical impact on these children. So are you suggesting allergen avoidance for the fetus or not?

Dr. Renz: The answer can only be given by clinical studies. From an experimental point of view I am quite doubtful that really strict allergen avoidance during the entire course of pregnancy can be achieved. It might be possible to do that for some unique antigens, unique foods where exclusion can be controlled quite well. But for common
basic foods like milk, egg and others, it is impossible to achieve really sufficient complete antigen exclusion during pregnancy. I think the colleagues who are closer to the clinical side are better able to comment on that.

Dr. Thornton: About 10 years ago the Department of Health in the UK advocated that allergic women avoid peanut during pregnancy. Now they are going back and looking whether that actually had a detrimental impact on the incidence of peanut allergy over 10 years, much as we saw this morning with gluten in celiac disease. My major concern is that we give conflicting advice to women during pregnancy: for 5 years we said avoid allergen and over the next 5 years we say I am sorry that was wrong, but the children already have allergic disease.

Dr. Björkstén: Twenty years ago Kjellman et al. [3] followed a group of children whose mothers had strict elimination of cow’s milk, egg and fish during the first trimester of pregnancy. At age 5, there were 4 of 220 children who were still food-allergic clinically. All of them were children of mothers who had been on an exclusion diet during pregnancy. So I really want to caution and reiterate what Dr. Thornton is saying.

Dr. Tang: In the model using immunodeficient mice, you very nicely illustrated the antigen-specific approaches to tolerance induction but also the nonspecific approach to generating immune responses. I am interested to know whether you have actually undertaken experiments where Th1 cells were transferred into immunodeficient mice or T-regulatory cells?

Dr. Renz: We have not done regulatory T cell studies so far, but they are of course on the agenda. In terms of Th1, Th2 transfer we have used antigen-specific clones and cell lines and in both systems the transfer of these signals from the mother to the fetus can be observed. In both cases it is a Th2- or Th1-specific immunoregulatory component which we see in the fetus.

Dr. Tang: Are you suggesting that any form of activation in the fetal setting will assist in generating immune responses whether they be of the Th1 or Th2 type in the newborn?

Dr. Renz: I think it depends very much on the situation of the mother. If a mother has a Th2 response to this particular antigen then we observe the regulatory issue on that level, but if a mother has a Th1 immune response as in autoimmunity, which is a very common and classical example in this regard, we observe the Th1-related immunoregulatory component in the fetus.

Dr. Tang: Do you think that if you transferred ovalbumin-specific Th1 cells, for example, you might be able to prevent ovalbumin-induced allergic disease in the murine offspring?

Dr. Renz: On an experimental level yes, but this might be difficult to achieve under real-life conditions because we have this Th2 predominance on the placental side. So unfortunately, this is probably preventing us from using this approach as a new mode of prevention, maybe even in clinical conditions.

Dr. Shao: Could you give some advice for pregnant mothers regarding food avoidance?

Dr. Renz: If you look at all of the data available and all the clinical studies there, avoidance of certain foods during pregnancy has been attempted. It is very difficult to achieve and very difficult to see really strong significant clinical outcomes. So from my perspective, but I need more comments from my clinical colleagues, allergen avoidance cannot really be achieved during pregnancy.

Dr. Shao: What about the avoidance of inhalant allergens such as exposure to cats?

Dr. Renz: With the inhalant allergens, even from a mechanistic point of view, we face a different mechanism here. With inhalant allergens we mainly have uptake
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through the respiratory tract and the concentrations which are being taken up are very low, several magnitudes lower than what we observe with the food allergens. This might even be the reason why we see seasonal differences, and it has been attempted to correlate the presence of inhalant-specific T cells to the month of conception, and this might be a dosing phenomenon. I doubt that by avoiding these exposures during pregnancy will lead to anything really clinically significant later in life.

Dr. Sennhauser: You showed that prenatal sensitization of the mother might protect the antigen reaction in the offspring. That seems to reflect an active transplacental isotope-specific antibody transfer. Is there anything known about the functionality of these antibodies so the transferred antibodies may be more avid or more affine to the antigen or to the allergen therefore protecting the offspring even in a more efficient way than in the mother?

Dr. Renz: Thank you for this very important question because it refers to avidity, affinity, and maturation of the antibody responses. Of course this depends on how strong the interaction between the antibody and the antigens are, e.g. the higher the avidity of the maternal antibodies, the better the inhibitory effects observed later in life. I didn’t go into that.

Dr. Brandtzaeg: Thank you for pointing out that tolerance is an active process; we tend to forget about that and also that antigens are needed. After my talk yesterday there was discussion suggesting that perhaps it makes sense that it takes time after birth to establish an intact epithelial barrier in the gut because you may need that window to have a good access of antigens. I mentioned in my talk that there are a couple of models, including our polymeric Ig receptor knockout mouse, where enhanced tolerance induction is actually seen because there is a slight decrease in barrier function – giving rise to more uptake of antigen. But it is very dose-dependent as you alluded to. However, avoidance of antigens during pregnancy doesn’t make sense, although perhaps pregnant women should be advised not to eat too much of the strong allergens like egg and peanut. Avoidance is one thing but if you are a big egg eater or a big peanut eater I think that might be dangerous by actually promoting allergy in a susceptible baby. What are your views on that?

Dr. Renz: That is a very interesting topic. From an immunological point of view I think there are two windows in terms of dosing where you can induce tolerance by different mechanisms. One is low-dose tolerance induction and the other is high-dose tolerance induction. But we don’t actually know what the doses are for which antigen.

Dr. Brandtzaeg: High-dose tolerance is an experimental situation.

Dr. Renz: Why is it only experimental? An experiment of nature is provided by the data from Lau et al. [4] showing that increasing numbers of cats at home means increasing concentrations of cat allergen with a decreasing prevalence of cat allergy. So from an immunological point of view, this is high-dose tolerance induction. But this might be a unique situation related also to the antigen.

Dr. Brandtzaeg: You stated that there is intolerance and then augmentation. In the first models you mentioned, you said that cytokines are transferred to promote augmentation, but why not Th2 cells through the placenta or through breast milk?

Dr. Renz: I want to be careful. We have some preliminary data also on this but they are really preliminary. I personally think that, as you stated, there is also cellular uptake and cellular transfer from the mother to the fetus, actually in both directions. We can even detect fetal T cells in the maternal circulation. So there is something going on at that level, but I think this level has not been very extensively studied so far. I don’t feel comfortable about putting that up here, but there is certainly another level of regulation which we need to understand.
Dr. Björkstén: With regard to prevention, we have a strong ethic responsibility not to give advice unless we are very sure of what we are doing. With regard to the high dose, this study has also been done in Sweden where the mothers had at least half a liter of milk and 2 eggs a day, and again there were no clinical effects.

Dr. Renz: Yes, but we need to do more studies.

Dr. Du Toit: May I quickly draw your attention to a paper we published comparing Jewish children in Israel to genetically similar Jewish children in the UK [5]. In Israel they eat peanut very early on, and in the UK, certainly for the last 10 years, most people have been avoiding peanut. In the paper we cross-sectionally show very low rates of peanut allergy in Israel and extremely high rates in the UK, nearly 2% of children now are peanut allergic. At the end of the paper we challenged the recommendations. The recommendations, which are often blamed in the UK, say you may wish to avoid, but not you should avoid, peanut, and obviously people take great umbrage at this because we are not sure who is at risk. Most peanut-allergic children are born to non-allergic parents so it has become a little chaotic. As you said, the only way to sort this out is with interventional studies. I am very lucky to be working on the LEEP study which is such an ongoing interventional study where we expose children to very high-dose peanut at the time of weaning or not. It will take some 5 years until the first results are released but there are over 500 children in the study now. I agree with you that we need to be cautious in this regard because we simply do not know at present.

Dr. Renz: Thank you for this very important comment. I think your study is really a landmark in this whole field, and I am really looking forward to reading the paper and seeing the follow-up.

Dr. Isolauri: I wanted to comment on the elimination diet. If we eliminate cow’s milk, cereals and other nutrients from pregnant mothers’ or lactating mothers’ diet, do we then know what their diet is composed of? Diet is always a combination of many foods and nutrients, and their interaction may be more important than previously understood.

Dr. Renz: Thank you very much; this is a very important point. I didn’t go into the issue of polyunsaturated fatty acids, but they also play an immunoregulatory role in themselves.

Dr. Prescott: I think we might need to make the clinical message very clear and unambiguous at this point. There is currently no evidence to support an elimination diet of any kind in pregnancy and we are also now just questioning delayed allergen introduction in the postnatal period as well. Just in answer to some of the other questions earlier, I think we need to make that very clear. I refer to the work of Thornton et al. [6] showing that the T-cell responses in cord blood are somewhat promiscuous; they are not the same sort of memory responses that we see in adult memory responses; they are not necessarily long-lived, and we don’t know what role they subsequently play in tolerance or memory responses.

Dr. Renz: Regarding your first comment in terms of the recommendation, I think it fits very nicely with the experimental animal data, and in both humans and animals, exclusion cannot be achieved as we would like from the conceptional point of view. The other thing is, what are the consequences of having all these immunoregulatory issues in terms of developing clinical phenotypes? This can only be answered by the prospective long-term investigations of such issues you are doing here in Australia and others are doing elsewhere. This is very important work because we need to understand the role of these regulatory T cells, Th1, Th2, and even the longevity of these T-cell responses is not so clear. They disappear from the blood I agree but that does not necessarily mean that they disappear completely from the immune system.
References


