

Perinatal Events Affecting the Onset of Allergic Diseases

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Abstract: The prevalence of asthma and related allergic disorders has increased considerably over the last several decades. Since the genetic makeup of humans has not changed during this time, it is likely that environmental factors may have influenced this rise in allergic diseases. Furthermore, there is increasing evidence to suggest that many aspects of health and disease are determined during the perinatal period and that alterations in lifestyle and diet later in life are secondary to the effects of the immunological programming that occurs during pregnancy and early infancy. This is directly applicable to allergic disease where immune responses at birth implicate intrauterine exposure as a primary sensitization event. Moreover, infants who experience allergy early in life already have an altered immune response at birth and most therapeutic approaches focus on altering the expression of the disease. Therefore, a better understanding of the underlying mechanisms that shapes the immune response towards allergy development is fundamental to strengthening "natural" protective stimuli or developing preventative rather than treatment therapies.

Keywords: Perinatal, pregnancy, fetal, allergy, Th1/Th2 cells, tolerance, probiotics, gut.

INTRODUCTION

The worldwide prevalence of allergic diseases, such as asthma and atopic dermatitis, has dramatically increased during the past decades [1]. It is well-established that both genetic polymorphism at multiple sites in the genome as well as the immediate environment plays a crucial role in the development, maintenance and severity of allergic diseases such as asthma and atopic dermatitis. Because the genetic background of populations has not markedly changed during the past few decades, the increased prevalence of allergic diseases may be related to altered environmental and lifestyle conditions. Over the last decade an association has been clearly established between various risk factors, such as air pollutants, smoking and indoor allergen exposure, and the onset and promotion of allergic diseases. However, recent research has highlighted the importance of environmental factors in providing protection from the onset of allergies (reviewed in [2]). The concept of exposure to microbes playing a role in shaping the immune system in a beneficial manner was originally referred to as the hygiene hypothesis and is supported by several epidemiological studies [3-5]. The proposed underlying mechanism focuses on the critical balance between T-helper (TH-1) and T-helper 2 (TH-2) cell activity and/or the generation of T-regulator cells in protecting against the development of allergic diseases. Recent epidemiological and experimental findings extend the concept of the hygiene hypothesis to other diseases such as Crohn's disease and autoimmune diseases such as type 1 diabetes and multiple sclerosis [6].

However, these studies provide only indirect evidence that the decreased exposure to microbes and/or microbial antigens might be inversely associated with an increase in the prevalence of immunological disorders. The mechanistic explanation for this hypothesis is based on an imbalance of

cytokine profiles elicited by TH-1, TH-2 and TH-reg T-cell subpopulations (reviewed in [7]). TH-1-dominated responses are induced during exposure to microbial products, and may work to down-regulate the allergic TH-2 responses. However, it appears critical that this exposure to non-pathological microbes occur during pregnancy and/or the early postnatal period, since accumulating evidence suggests that exposure during this period, programs long-term outcomes in human health. These mechanisms are not only important in disease-related conditions but also in the maintenance of pregnancy and avoiding rejection of the fetus. This review focuses on recent work in animal and human studies that provides evidence that cellular and antibody-dependent processes act perinatally to impact the long-term outcome of the neonate.

T-HELPER CELLS PLAY A CENTRAL ROLE IN ORCHESTRATING THE IMMUNE RESPONSE

The T-helper cell sub-populations are critical in discriminating between harmful and beneficial immune responses. Three subpopulations of T-cells have been identified (TH-1, TH-2; TH-reg), based on cytokine profiles elicited by appropriate stimuli. TH-1 cells are credited with driving a type-1 pathway to fight viral and bacterial infections and also orchestrating specific inflammatory immune responses. TH-2 type dominance is the major underlying process that allows tolerance of xenografts and the fetus during pregnancy, but also result in allergic sensitization and allergic inflammation (e.g. bronchial asthma). The recent characterization of TH-reg cells have received much attention since this T-cell subpopulation might regulate and control TH-1 as well TH-2 type immune responses.

The initial event believed to be responsible for the development of allergic diseases is the generation of allergen-specific CD4 T-helper type 2 cells. These TH-2 type effector cells produce IL-4, IL-5, IL-6, IL-9 and IL-13 and play a central role in the immunopathogenesis of allergic disease, since they regulate the class-switch of B-cells to

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produce high amounts of allergen-specific IgE and induce recruitment of eosinophilic granulocytes into the site of allergen exposure (e.g. lung tissue). On the other hand, it is well-known that TH-1 type cells, which are characterized by their IFN- γ , TNF- α , IL-2 and IL-12 production, are central to cellular immunity against intracellular antigens, attenuating the production of IgE by B-cells, and down-regulation of the inflammatory immune response. The differentiation of naive T-cells into TH-1 or TH-2 cells is influenced by cytokine exposure during and after antigen presentation. The current view is that naive T-cells activated by antigen presenting cells are influenced by IL-2 and IL-4 to differentiate into TH-2 type effector cells. Recently, a third T-cell subset has been discovered, which is known as regulatory T-cells (TH-reg). TH-reg cells actively control or suppress the function of other cells, generally in an inhibitory fashion. Regulatory T-cells appear to control the development of autoimmune disease and transplant rejection, and may also play a critical role in controlling asthma and allergy. The specific mechanisms by which these regulatory cells function, and the specific characteristics of these cells, is still not completely defined. Based on their cytokine expression pattern, four major subsets of CD4+ regulatory T-cell types have been described; TH-3, T_R -cells, CD4+CD25+ and natural killer T-cells (NKT). TH-3 cells produce TGF- β and varying amounts of IL-4 and IL-10. TGF- β plays an important role in immune activation (e.g. upregulation of adhesion molecules, enhanced chemotaxis and enhanced production of IgA) as well as in immune deactivation. TGF- β expression has been observed in mucosal tissues of the gut and nose and is directly involved in the regulation and maintenance of tolerance [8,9]. Treg-cells have a low proliferative capacity and produce high levels of IL-10, low levels of IL-2 and no IL-4. CD4+CD25+ appear to constitutively express CD25+ and suppress immune response through direct cell-cell contact in a process that is dependent on signaling *via* cytotoxic T lymphocyte antigen 4 (CTLA-4) as well as the secretion of TGF- β . NKT cells comprise a population of T-cells that express cell surface markers characteristic of both NK cells and conventional T cells. Upon activation, NKT cells produce IL-4 and IL-13 which accelerates the action of TH-2 type T-cells, which drive the allergic phenotype. Therefore, the type of immunological response to antigens may be altered by time or as a result of external influences, resulting in changes in patterns of predominant cytokines produced by antigen-specific T-cells. Studies have demonstrated the importance of the intrauterine microenvironment, when the immature immune system is first exposed directly to environmental allergens, in the establishment of long-term patterns of allergen responsiveness.

TH-2 TYPE IMMUNITY DURING PREGNANCY

The concept of TH-1/TH-2/TH-reg immune deviation also has implications to the condition of pregnancy. It has been revealed during the last few years that the feto-maternal interface represents an immunologically highly active site of regulation. Since fetal tissue is regarded as a classical allo-transplant expressing histocompatibility antigens (HLA) from the father, successful pregnancy depends upon tolerance of a genetically incompatible fetus by the maternal immune

system. The immune system has developed several strategies to prevent recognition of paternal HLA antigen and the subsequent development of cytotoxic T-cell responses against these cells. These strategies include the lack of expression of classical major histocompatibility complex (MHC) alloantigens on the trophoblastic surface [10]. Another major strategy relates to the TH-1/TH-2/TH-reg concept. In recent years, the immunology of the feto-maternal interface has been studied in greater detail and has revealed an unique pattern of immunodeviation at the feto-maternal interface. To prevent fetal rejection, it seems critical that the local environment at the fetal-maternal interface is dominated by TH-2/TH-reg immune responses. In fact, high level expression of IL-4, IL-10 and TGF- β has been demonstrated at the fetal-maternal interface, which supports fetal survival and engrafting [11,12]. Changes that favor a TH-1 dominated immune pattern results in a negative outcome of the pregnancy [13]. This might provide one explanation why TH-1 immunity, as reflected by the production of IFN- γ , is extremely low in neonates and even lower in neonates derived from allergic mothers (see below) [14-16]. The unanswered question is still whether this TH-2 type skewed immunity at birth predisposes to the development of allergic diseases later in life. The differences between genetic predisposition to atopy may reflect the tendency for immune development to deviate towards a TH-1 type response after birth.

T-CELL RESPONSIVENESS AT BIRTH AND THE IMPACT ON THE DEVELOPMENT OF ALLERGIES

The first step in the development of allergies is the development of an allergen-specific immune response. A proliferative response of cord blood mononuclear cells to aero- and food-allergens is common, and occurs regardless of whether the mother exhibits an allergic phenotype or not [17]. This immune response is mediated by fetal T-cells, as opposed to maternally-derived contaminants [18], and depends on antigen-exposure of the mother beyond the first trimester of pregnancy [19]. The presence of an allergen-specific immune response at birth itself does not determine the allergic outcome. Recent data indicate that neonatal T cell responses to allergens differ markedly from those occurring in later life. In contrast to allergen-responsive adult CD4+ T cells, allergen-specific neonatal T cells display high levels of apoptosis and express CD45RA and CD38 on cell surfaces, markers of recent thymic emigrants. These findings suggest that a significant component of the reactivity of human neonatal CD4+ T-cells, toward allergens (and other antigens) represents a default response by recent thymic emigrants [20]. However, the presence of IgE at birth indicates the prenatal development of functional B-cell interactions and implies that the allergen-responder phenotype may be determined during the fetal period by immune deviation and/or allergen-driven T-cell selection [21]. Clinical studies indicate that the development of chronic manifestations such as asthma follow a typical sequence of sensitization events, followed by symptoms. Those with early development of IgE sensitization to cow's milk or hen's egg proteins have an increased risk for later development of allergic diseases [22].

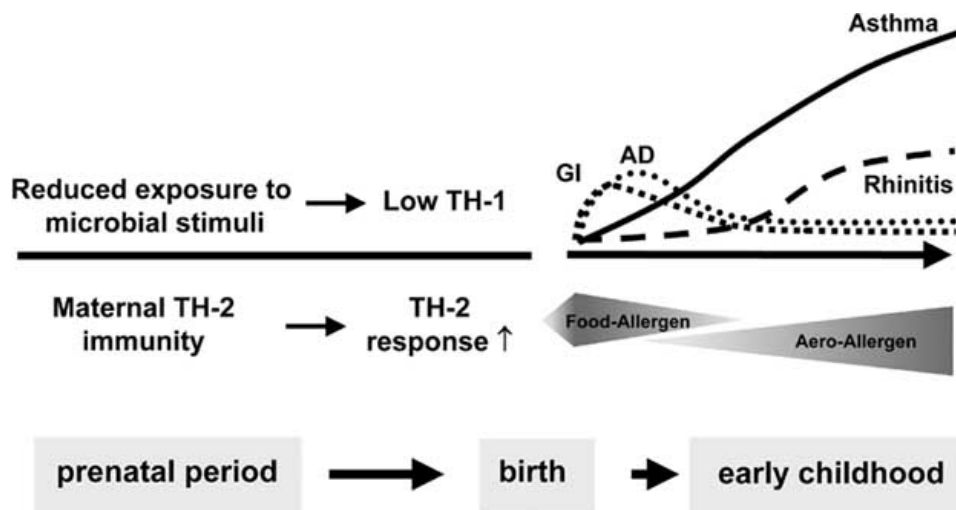


Fig. (1). Concept of pre- and early postnatal events influence the development of allergy and asthma.

Modern public health practices have led to the relative sterilization of living environments in developed countries. This reduced exposure to non-pathological microbial stimuli during pregnancy together with the maternal TH-2 type immunity of an allergic mother might bias the developing immune system towards the onset of allergic diseases.

DECREASED CAPACITY OF TH-1 IMMUNITY AT BIRTH

Several studies have shown that both atopic and non-atopic individuals display immune responses to allergens early in life, although the type of response differs in the level of IFN- γ production. At birth, the level of IFN- γ production by full-term, healthy neonates is markedly reduced as compared to later in life. However, an even lower capacity to secrete TH-1 cytokines has been related to the risk and development of allergies, particularly in the first few years of life. There is evidence to suggest that in normal healthy neonates at birth, allergen-induced mononuclear cell responses are skewed toward a TH-2 type phenotype, possibly because of placental-derived TH-2 type factors, and IFN- γ responses are particularly low [14,15,23]. Furthermore, IFN- γ responses gradually increase in magnitude in normal infants, whereas in allergic infants IFN- γ responses are both lower at birth and more slowly developed. As a result, this reduced IFN- γ generation causes a TH-1 / TH-2 imbalance that might be a risk factor for the subsequent development of allergic diseases such as asthma (Fig. 1). Although these observations are of considerable interest, it is important to note that until now there is no direct experimental evidence in humans that this TH-1 type imbalance at birth affects the development of allergies later in life. Among the environmental factors that modulate T-cell immunity during the perinatal period, the bacterial flora that the neonate is exposed to might be another important factor. The infant GI tract plays a key role, since it is the primary mucosal site of exposure to microbes and two-thirds of the immune system is organized in the gut associated lymphoid tissue (GALT).

EXPOSURE TO INTESTINAL MICROBES AFFECTS IMMUNE BALANCE

The colonization of the gut with non-pathogenic bacteria plays a critical role in the development of the gut immune system by mechanisms related to the maturation of both the intestinal epithelium and the immune compartment [24].

The gastrointestinal (GI) tract of a newborn baby is essentially sterile at birth. Immediately following birth the newborn is exposed to maternal vaginal and fecal bacteria, along with bacteria from other environmental sources, which leads to colonization of the intestinal tract in a characteristic pattern during the early weeks of life [25]. This highly complex mixture of bacteria becomes the indigenous flora, which undergoes significant changes during the first year of life and represents the single most important source of microbial stimulation for development of the host immune system.

The GI tract of the newborn infant is exposed to a wide variety of food and microbial antigens following birth. While the human intestinal immune system is immature at birth, it must learn very quickly how to discriminate between potential disease-causing microbes and harmless antigens, such as food proteins and commensal bacteria. This physiological event leading to controlled response to harmless gut antigens is known as induction of local and systemic immunological tolerance, or oral tolerance [26,27]. The mechanisms underlying oral tolerance are not completely understood, but they likely involve a complex interplay between intestinal epithelial cells, antigen presenting cells (APCs), and specialized lymphoid cells located in the vast lymphoid tissue lining the intestinal tract (e.g. gut-associated lymphoid tissue, GALT). In addition, the host has evolved various mechanisms of tolerance which allows a productive coexistence with commensal bacteria while allowing it to remain responsive to pathological bacteria. In this regard, the intestinal epithelial cell seems to play a pivotal role through the expression of Toll-like receptors on their apical surface that enable them to detect bacterial products and to initiate an innate immune response. Recent studies provide insights into potential regulatory mechanisms that control the intestinal immune response [28,29]. These mechanisms rely on negative signaling pathways that provide cross-talk to the Toll-like receptor signaling cassette, or the ability of non-pathogenic bacterial strains to abrogate the synthesis of inflammatory cytokines by the intestinal epithelium cells. The bacteria accomplish

this by blocking degradation of $\text{I}\kappa\text{B}$ an inhibitor of the master transcription factor NF- κB . In contrast, certain invasive pathogens and intact antigens are known to bind to M cells associated with Peyer's patches [27]. M cells are believed to pass on intact antigens to professional antigen presenting cells (APCs) and thereby activating the innate immune response.

The intestinal microflora of the host can also influence the immune responses to ingested antigens in a number of other ways. For example, intestinal bacteria produce enzymes that can further reduce the immunogenicity of food antigens beyond the degradation that occurs from proteolytic secretions in the stomach and small intestine [30]. Intact bacteria may also come in contact with intestinal epithelium or specialized cells located in the vast lymphoid tissue lining the intestinal tract (e.g. GALT), which in turn elicit various immune responses. Finally, breakdown products from dead intestinal microbes, including both intracellular and cell wall components, may be taken up by immune cells and trigger immune activation. For example, lipopolysaccharides (LPS, endotoxins) are derived from the cell wall of Gram-negative bacteria and are potent inducers of a TH-1 type cytokine profile by cells of the innate immune system.

The acquisition of commensal flora is believed to affect upregulation of TH-1 activity and thereby cause down-regulation of TH-2 type, allergy-promoting responses. This assumption is supported by animal studies showing that antigen exposure in a germ-free environment favors the development of TH-2 responses and abrogates TH-1 responses or induces immunological tolerance to bacterial antigens [24,31]. The capacity to mount a TH-1 immune response could be restored by reconstituting the gastrointestinal flora of the germ-free animals with *Bifidobacterium infantis*, an organism common to their normal commensal flora. This effect was only seen when reconstitution occurred during the neonatal period.

The first evidence in humans for a link between early bacterial exposure and subsequent development of allergies was the original observation by Strachan and co-workers of an inverse relationship between family size and both hayfever and eczema in two birth cohorts [3]. This observation was followed by a number of other studies which provide further indirect evidence that the recent rise in allergic diseases might be related to the reduced exposure to the total microbial burden during the neonatal period [4,32]. This issue was addressed in further detail in studies showing that a difference in the indigenous flora might affect the development and priming the immune system in early childhood. In a prospective study, the development of allergy was related to the colonization of the intestinal gut during early childhood [5,33]. This study provides evidence that infants colonized with *Lactobacilli* had a decreased risk for developing allergic diseases later in life, compared to infants with high levels of aerobic microorganisms, particularly coliforms or *Staphylococcus aureus*. However, the nature of the microbes responsible for this effect remain undefined.

It seems that the beneficial effect of microbial exposure in the prevention of allergic diseases is not limited to the intact intestinal microflora. Recent data from

epidemiological studies indicate that growing up on a farm confers significant protection against the development of allergies. In particular, these findings point to the importance of exposure to endotoxin (LPS) in dust [34]. Early and regular contact with high concentrations of endotoxin was identified as an important protective factor [4]. However, the role of LPS exposure in the development of allergies and asthma continues to be controversial. LPS is also recognized as a potent inducer of pro-inflammatory cytokines such as TNF- α . Various animal studies provided evidence that timing of exposure is an important factor in determining a protective versus accelerating role of LPS in the development of an allergic phenotype [35]. LPS exposure prior to sensitization suppresses allergic immune responses and hinders the development of airway hyper-reactivity, whereas animals exposed to LPS after sensitization showed greater allergic inflammatory immune responses. The suggestion that the time window of exposure is critical in mediating this protection is supported by results from other epidemiological studies. Children living in farming environments were only protected from onset of allergic diseases if the exposure to stables and consumption of raw milk occurred within the first year of life including the prenatal period [4]. This suggests that primary prevention efforts should start during infancy. This concept of exposure to immune stimuli during critical periods in early life having lifelong consequences is termed immune programming. Such programming stimuli can be from indigenous or environmental sources. Early exposure to microbial antigens, including the prenatal period, may be an important environmental programming stimulus (Fig. 1). However, additional studies are needed to clarify which microbes or microbial antigens and which immunological pathways are involved in either promoting or protecting from the onset of allergies. Several models have now been established to elucidate the significance of perinatal events regulating the immune response to allergens [36-40].

ANIMAL STUDIES OF PRECONCEPTION MATERNAL EXPOSURE TO ALLERGENS AND THEIR IMPACT ON THE NEONATAL IMMUNE RESPONSE

In these animal models, the impact of maternal allergy on the development of an allergic immune response in early life was assessed. Mice were sensitized to ovalbumin (OVA) prior to conception followed by allergen-aerosol exposure during pregnancy. At the end of pregnancy, mice developed allergen-specific TH-2 immunity and immediate-type hypersensitivity responses to OVA. These studies showed that maternal-derived antibodies of the subclasses IgG1 and IgG2a, but not IgE, cross the placental barrier. Another important feature of this murine model is that free allergen also crosses the placental area and was detected in serum and amniotic fluids of neonatal. Offspring from normal healthy mice were characterized by impaired IFN- γ production at birth, comparable to the situation in the human [41]. Neonates from allergen-sensitized mothers demonstrated an even further reduced level of IFN- γ production compared to offspring from non-sensitized mice. This further suppression was the result of a lowered frequency in IFN- γ secreting cells and was mediated by maternal CD-4 and allergen

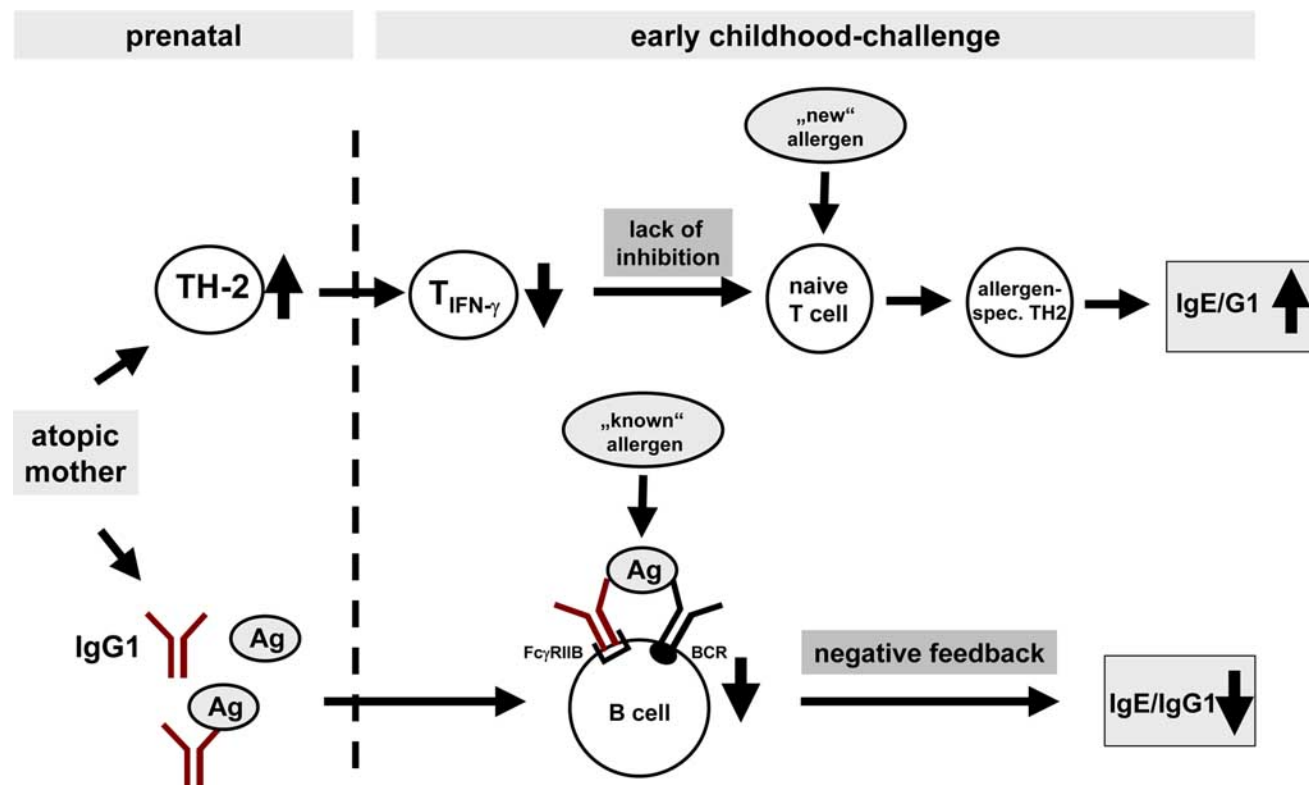


Fig. (2). Concept of pre- and postnatal regulation of immunity.

Maternal immunity may protect or promote the development of allergies in the neonate.

specific TH-2 type T-cells. However, the average level of IFN- γ production per cell remained the same, suggesting some type of regulatory effects that act possibly during pregnancy and/or early childhood. Neonatal T-cells are intrinsically capable of reaching an adult level of function, but only if an apparent increased requirement for co-stimulatory signals is provided [42,43].

MATERNALLY DERIVED IgG ANTIBODIES SUPPRESS IgE RESPONSE IN OFFSPRING

To assess whether prenatal allergen exposure favors postnatal onset of a TH-2 type immune response, these offsprings were exposed to a "known" allergen (pre-natal exposure) or to a "novel" antigen (to which the mother had not been exposed). Development of an IgE-mediated allergic immune response against the "known" allergen was completely prevented early in life. In contrast, neonates from sensitized mice developed an accelerated allergic phenotype after exposure to a "novel" allergen. We proposed that this contradictory phenotype in these offspring is caused by two mechanisms operating in parallel [40]. The protective effect may be mediated by maternally derived allergen-specific antibodies, while the promotion of the allergic response to a novel allergen may depend on the maternal TH-2 type immunity. To test whether maternal allergen-specific antibodies protect from the onset of an allergic immune response, immuno-compromised mice (SCID) were reconstituted with allergen-specific IgG1 antibodies during the prenatal period. Offspring from these mothers developed no allergic immune response after allergen-exposure,

indicating that the protective effect is mediated by maternally derived antibodies. The ability of maternal IgG antibodies to inhibit the induction of humoral immune responses is a well-known phenomenon [39,44]. As shown recently, type I hypersensitivity preconceptional maternal immunization inhibits the type I hypersensitivity responses of offspring [37]. This effect is mediated by passively acquired maternal antibodies and relates to binding of IgG1 to Fc γ RII receptors (review in [45]). Antigen exposure causes cross aggregation between IgG1 antibodies bound to these Fc γ RII receptors and surface immunoglobulin expression by the B-cell receptor. This cross aggregation induces a state of negative intracellular signaling, which prevents these cells from switching towards IgE production (Fig. 2). However, it was demonstrated that suppression of IgE production by maternally transferred IgG antibodies no longer occurs after 3 months of age [39]. A number of studies have suggested that IgG may have a role in modulating the fetal immune response to allergen. In humans this phenomenon has probably been best studied in diaplacental and breast milk transmission of antibodies. These antibodies not only provide passive protection against infections, but they might also actively shape childhood immunity and tolerance induction by providing the fetus and the infant with the mother's immunological experience [46]. This capacity to modulate the neonatal immune response might lead to a strategy in which the mother is actively immunized against certain environmental allergens to protect the offspring from allergic sensitization. Indeed, there are some reports which showed that children from allergic women who received grass pollen immuno-therapy during pregnancy, were

protected from development of immediate hypersensitivity reactions to the same allergen [47]. More recently, epidemiological studies indicate that the presence of high titers of cat-specific IgG antibodies is inversely related to the risk to develop cat allergies [48]. Along this line, increased levels of maternal anti-Bet v 1 antibodies at birth have been associated with a reduced prevalence of allergies at 18 months of age [49].

In contrast, allergic sensitization against the “new” allergen early in life was accelerated in these mice. Adoptive cell-transfer experiments indicated that this effect was mediated by maternal CD4 and OVA-specific TH-2 cells induced by allergic sensitization during pregnancy (Fig. 2) [40]. Maternal CD4 TH-2 cells may act *via* different pathways in this context. Maternally derived T-cells have been previously detected in fetal/neonatal circulation. It might also be possible that cytokines including IL-4, IL-13 and others derived from these T-cells may pass the placental barrier and provide a local cytokine milieu which favors the development of TH-2 type immune responses. However, the underlying mechanism has not been defined. These data indicate a critical role for maternal T- and B-cell response in shaping pre- and postnatal maturation of specific immunity to allergens. Recently, it was demonstrated that treatment with neutralizing anti-IL-4 antibodies during the prenatal period, or reduction of maternal allergen exposure abrogated the maternal effect, suggesting a critical mechanistic role for IL-4 and an additional benefit of allergen avoidance [36].

CONCLUSION

There is growing evidence to suggest that early programming of the immune system during the perinatal period is critical in shaping the overall immune responsiveness. The exposure of the neonatal intestinal mucosa to microbial antigens appears to be a critical factor in such immune programming events, which has implications for protective immunity as well as the development of allergic and other chronic diseases. Definition of the microbial antigens and immune cells that are important in this process may represent new intervention strategies for avoiding allergic disease. However, the safety of such intervention strategies for influencing TH-1 / TH-2 balance needs to be carefully considered, since TH-1 type immune responses can affect loss of the developing fetus, protection from infectious disease, and the development of autoimmune diseases such as type-1 diabetes.

ABBREVIATIONS

APC	=	Antigen-presenting cell
CTLA-4	=	Cytotoxic T lymphocyte antigen 4
GALT	=	Gut-associated lymphoid tissue
IFN- γ	=	Interferon-gamma
IL	=	Interleukin
LPS	=	Lipopolysaccharide
OVA	=	Ovalbumin
TH	=	T-helper cell

TNF- α	=	Tumor necrosis factor-alpha
TGF- β	=	Transforming growth factor-beta

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