Human milk research group

Avenues to Allergy Prevention in the Neonate

Content

Introduction

Current research is investigating the health benefits of human milk and its preventative role in allergy. Based on numerous studies, food allergy affects up to 10 % of children in developed countries and is one of the most common diseases in childhood, with evidence indicating an increase in prevalence. Thus, effective primary allergy prevention strategies are important steps to influence positively the infant's 'early window of opportunity'.

Among others, breastfeeding has been suggested as an optimal tool to prevent allergy although evidence is inconsistent. Nutritional and non-nutritional interventions can be used for primary prevention of allergic diseases. For instance, farm life has been shown to effectively protect children.

Imbalances in the microbiome profiles are believed to impair the immune system maturation and thereby increase the risk of allergic diseases. These changes may occur as a result of environmental factors typical of the western lifestyle or different food components which are thought to be responsible for the pandemic of allergic diseases, like food allergy.

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According to the EuroPrevall (The prevalence, cost and basis of food allergy across Europe) birth cohort study, 3.5 % of children born in the United Kingdom (UK) between 2005–2007 developed food allergy [1]. In the opinion of Professor Alessandro Fiocchi (Rome/Italy), chair of the 2019 human milk research meeting, food allergy incidence is increasing. This observation is also based on the fact, that the even higher prevalence (7.1 %) in UK children born from 2009–2011 observed in the EAT (Enquiring About Tolerance) Study indicated that food allergy is increasing [2].

A global increase in food allergy

In other parts of the world, the situation is similar. For instance, in China, South Korea, and Thailand the prevalence of food allergy is comparable to Europe. In Australia >10 % of the 1-year old children were reported to exhibit challenge-proven, clinical food allergy [3]. In less developed countries, however, the prevalence tends to be lower.

The food allergy pandemic appears to be mainly attributable to egg allergy, increasing in the UK from 2.2 % in children born 2005–2007 to 5.3 % in children born from 2009–2011 [1, 2]. Since egg sensitization is already present at birth, this increase points to a possible role of early or prenatal factors. In contrast, cow's milk allergy does not appear to be increasing in prevalence. This is shown by the fact that the prevalence of cow's milk allergy in children born 2005–2007 and 2009–2011, was largely identical (0.8 % vs. 0.7 %) [2, 4].

Low contribution of genetics

Ethnicity does not have a strong influnece on food allergy risk, though rather environmental factors seem to be important. For example, infants of Chinese ethnicity born in Australia exhibit an increased risk of nut allergy as compared to Chinese infants born in China [5]. However, few genetic determinants of pediatric food allergy, e.g. filaggrin muations, have been identified so far [6]. Overall, the contribution of genetics to food allergy is low, concluded Fiocchi [6]. Noteworthy, environmental factors play an important role in the genesis of food allergy and food allergy epidemics. That's why more emphasis should be put on allergy prevention strategies.

Environmental factors modify the microbiota and allergy risk

In a cross-sectional study, the higher prevalence of allergic diseases in children from a Chinese community in Australia was associated with a significant lower microbiota diversity (alpha diversity) in oropharyngeal and fecal samples as compared to Chinese children born in China [7]. The authors concluded that western environment or lifestyle changes microbiome profiles and

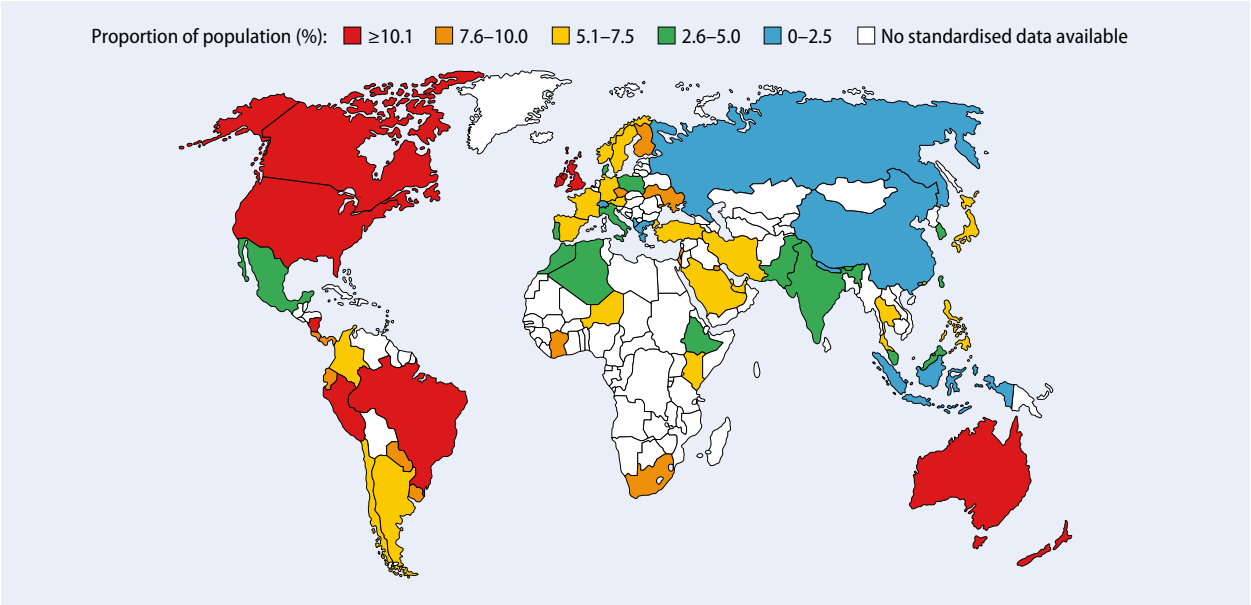

Fig. 1 ▲ The world allergy map (modified after [10])

that these changes are increasing the risk of developing food allergy or other allergic diseases. In children aged ≥5 weeks, fecal microbiota composition was found to be associated with the development of atopic dermatitis, allergic sensitization, and asthma [8]. However according to a recently published longitudinal study in children, richness and diversity of the gut microbiota at age 2–4 years were not predictive of preschool wheezing or future asthma development at age 6 [9].

According to Fiocchi, several early-life environmental factors have been shown to shape the gut microbiome. Many of these factors have been associated with the development of allergy in epidemiological studies, such as low quality of outdoor air, rare contact with farm animals or soil, indoor factors like dampness, dust or mold, as well as lifestyle (e.g. early use of antibiotics) and nutritional factors [10, 11].

A disease of educated and small families

Food allergy, and in general allergic diseases, are diseases of developed countries (**fig. 1**), countries with high gross national product per capita, urban environment, wealthy people, and educated or small families. Furthermore, sibship size or birth order correlate with the risk of atopy. Food allergy could be labelled as a "modern plague of the firstborn", concluded Fiocchi. Epidemiologists generated a series of hypotheses in order to explain the pathogenesis of food allergy and the emergence of the food allergy epidemic [12]. Dietary (e.g. vitamine D status) as well as non-dietary factors (e.g. maternal stress and immune status) have been blamed to be involved.

The hygiene hypothesis is postulating that reduced exposure to specific microorganisms in early childhood leads to Th (T helper cell) 2 skewing, thereby predisposing to allergic diseases [12]. While this could explain the majority of the epidemiological observations, according to Fiocchi this may no longer be regarded as hypothetical.

HiPP initiative: Human Milk Research Group

Human milk has always been considered the natural model for the production of infant milk formula, as human milk optimally supports infant's natural development. Therefore, the "Human Milk Research Group" – initiated by HiPP – has been extensively exploring the composition of human milk and its positive effects on human health for years.
The research group has met for thematic workshops on a regular basis.
Representatives of HiPP's nutritional science division discussed the issue of "allergy prevention" together with Professor Alessandro Fiocchi, Department of Allergy at the Pediatric Hospital Bambino Gesú in Vatican City (Rome/Italy), Professor Isabella Annesi-Maesano, EPAR (Epidemiology of Allergic and Respiratory Diseases) Department at the INSERM (Institut National de la Santé et de la Recherche Médicale) and Sorbonne Universités (Paris/France), Professor Mathias Hornef, Institut für Medizinische Mikrobiologie at the Universitätsklinikum of the RWTH (Rheinisch-Westfälische Technische Hochschule) Aachen (Germany), Professor Oliver Pabst, Institut für Molekulare Medizin at the Universitätsklinikum of the RWTH Aachen (Germany), and Professor Erika von Mutius, Dr. von Hauner Kinderklinik at the Ludwig-Maximilian-Universität (Munich/Germany).

Allergy prevention in high-risk infants

Preventive measures may be indicated in children who have a high risk of developing allergy, because they have a biological parent or sibling with existing (or a history of) allergic rhinitis, asthma, eczema, or food allergy. The WAO (World Allergy Organization)-McMaster University Guidelines consider probiotics as preventative measure in pregnant as well as in breastfeeding women if their children are at high risk for allergy [13]. Probiotic supplementation is also regarded as useful for infants at high risk. Furthermore, the WAO guidelines advocate prebiotic supplementation in not exclusively breastfed infants [13].

However, recent guidelines particularly in the UK and Australasia have generated scepticism regarding the usefulness of probiotic supplementation for pregnant mothers and their infants. Therefore, further studies will be necessary to confirm first studies with protective effects [14].

Non-familial risk factors

It has become increasingly clear that, in countries experiencing a rapid rise in food allergy prevalence, allergic children born to families without history of allergy may be more numerous than allergic children born to families with mono- or biparental allergy risk [15]. Many (pre-, peri- or postnatal) risk factors are not included in the definition of the at-risk child. For instance, pollen or food exposure in pregnancy may increase food sensitization in the offspring [16, 17]. The same holds true for limited microbial exposure or perturbation of intestinal microbiota (e. g. as a consequence of antibiotics), dietary habits, maternal obesity or low vitamin D levels during pregnancy [17–20].

Caesarean section: higher risk

The 3-fold higher risk of food allergy in infants born through Caesarean section (CS) in the first 3 years of life has been associated with the altered abundance and distribution of bacterial taxa over time, especially in the first year of life [17, 21]. The season of birth may play a role with children born in spring having the least risk or neonatal jaundice. Based on these situations, the definition of 'at risk for allergy' newborn should be extended.

Allergy protection through human milk

Human milk is the perfect mother-made infant nutrition. Breastfeeding confers unique nutritional and

Does breastfeeding contribute to allergy prevention?
Main reasons for the high heterogeneity of meta-analyses' results

- Variation in breastfeeding habits (duration, exclusive or mixed feeding)
- Breast milk immune composition (nutritional, immunomodulatory, bioactive composition)
- individual variation in infant´s response to human milk constituents including gut microbiota shaping
- Maternal exposures during lactation (diet, allergens …)
- Maternal microbiota
- Epigenetic mechanisms
- Methodological problems (missing factors, varying definitions, confounders, ...)

non-nutritional benefits to infant and mother. A plethora of studies could show the protective effect of breastfeeding to prevent pathologies like e.g. respiratory tract infections, obesity, type 1 and type 2 diabetes, necrotizing enterocolitis, gastroenteritis, and sudden infant death syndrome [22, 23]. According to Professor Isabella Annesi-Maesano (Paris/France), the health benefits of breastfeeding are unrivalled [23].

Although breastfeeding provides optimal nutrition for infants, studies on breastfeeding as allergy prevention strategy have failed so far to provide consistent results [24–30]. Especially the heterogeneity of studies hampers the chance to fully elucidate the protective potential of breastfeeding in allergy prevention.

Conflicting study results

The influence of breastfeeding on the development of allergic diseases has been investigated in many mainly cross-sectional or cohort studies, reported Annesi-Maesano. These studies, however, did provide inconsistent results [24–30]. For example, in 6–7 years old children no consistent association was observed between breastfeeding and eczema or rhinoconjunctivitis [24]. However, breastfeeding was associated with a reduced risk of severe eczema and severe rhinoconjunctivitis. In a meta-analysis Lodge et al. found evidence that exclusive breastfeeding for 3–4 months reduces the risk of eczema in children ≤2 years [25]. In children >2 years no significant association was found.

As Annesi-Maesano pointed out, "major weaknesses of the data are related to long retrospective recall periods and the lack of adjustment for potential confounding factors". Several authors reported a reduction in risk of food allergy, others surprisingly even an increase in risk after breastfeeding [26–29]. According to Greer et al. the advantages of breastfeeding are even less clear for infants of the general population. When mothers are able to choose on their own if they want to exclusively breastfeed or partially breastfeed (in combination with either hydrolysed or intact protein formula), no difference can be found in the infants' incidence for atopic dermatitis. This lack of effect might originate in "reverse causation" [31]: Parents who know about their increased familiar allergy risk, might decide to expand breastfeeding duration, or choose hydrolysed formula instead of intact protein formula in case of supplementation [31]. Thus, scientists have to include the possibility of this confounding factor.

Furthermore, in many studies the gold standard (i.e. double-blind oral food challenge) for confirming the diagnosis of food allergy has not been applied. Annesi-Maesano pointed out, that in these studies, the definition of food allergy was heterogeneous. The two most important studies, the LEAP (Learning Early About Peanut Allergy) Study and the EAT Study, showed that early introduction of peanuts or egg protein (before the age of 6 months) reduces the risk of allergy to these foods [2, 30].

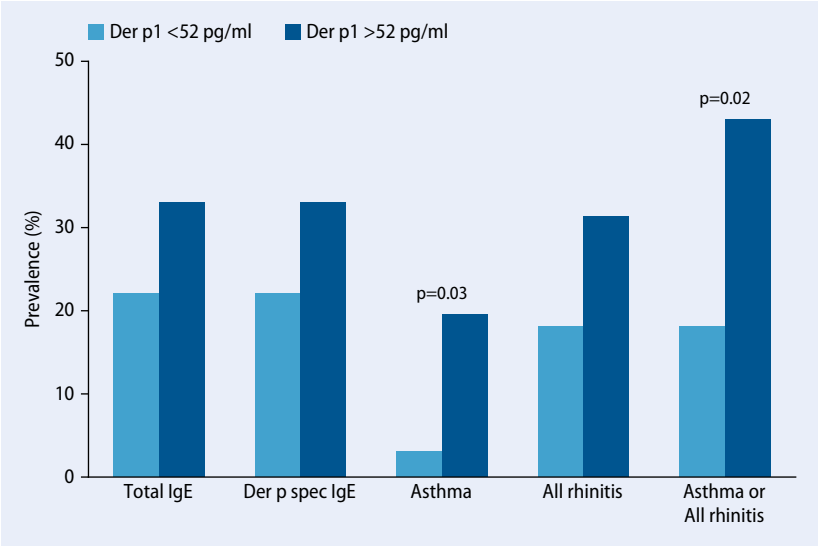

Fig. 2 ▲ Prevalence of respiratory diseases and allergic sensitization in children fed with human milk containing increased Der p1 levels (modified after [42])

Asthma prevention

"The probably most consistent data in this field establishs a relation between breastfeeding and asthma", said An-

nesi-Maesano. Two meta-analyses and one systematical review of cohort studies demonstrated the protective effect of breastfeeding on the development of asthma [25, 32, 33]. "But still we have to be cautious", commented Annesi-Maesano, because of the significant heterogeneity in study design, definition of outcome or breastfeeding (exclusive or not, duration), or asthma diagnosis (allergic vs. non-allergic asthma).

Many factors may explain the heterogeneity of the results, for example differences in human milk composition, maternal exposures during lactation, maternal microbiota, and infant's response to human milk constituents (box page 4).

How breastfeeding may protect against allergies

Duration and exclusivity of breastfeeding may influence the protective effect of human milk, said Annesi-Maesano. More importantly, human milk composition may affect oral tolerance induction and gut microbiome shaping, thereby contributing to the maturation of the immune system.

Furthermore, maternal dietary interventions (for example probiotics administration to pregnant and lactating women or a high fish intake) can alter the composition of bio- or immunoactive human milk components [34–37].

Human milk contains fats, carbohydrates, vitamins, minerals, and a multitude of bioactive peptides and proteins (including immunoglobulins, enzymes, hormones, antigens, or cytokines). Many of these components are able to modulate the immune system. For instance, specific cytokines and polyunsaturated fatty acids (PUFA) may be involved in inducing or protecting against food allergies (e. g. IL-4/-5/-13, C22:5n-6 fatty acids and e. g. TGF-ß, α-linoleic acid, n-3-PUFAs, respectively) [38]. The content of breast milk constituents varies with time after birth. For instance, colostrum (birth to day 4) is high in protein, fat-soluble vitamins, minerals, and immunoglobulins. In contrast, transitional milk (day 2 to 2 weeks) is characterized by high levels of fat, glucose, water-soluble vitamins, and a higher content of calories [39].

Early tolerance induction

Researchers found out that allergens present in breast milk may impact the priming of the immune system and long-term susceptibility to allergy.

By using murine models of allergy development, it could be shown that airborne antigens can be found in breastmilk. Ovalbumin antigens were effectively transferred through breast milk from mothers to neonates [40]. The antigen transfer induced oral tolerance (through a TGF-ß dependent mechanism) that protected the neonates against allergic airway disease.

In contrast, early exposure to house dust mite allergen through breast milk increased allergic sensitization and airway inflammation in newborn mice [41].

Transfer of allergens with human milk

In a study using general population data (where Annesi-Maesano participated), an association between the levels of Der p1 (Dermatophagoides pteronyssinus 1, one of the main house dust mite allergens) in human breast milk and the respiratory allergy risk in the

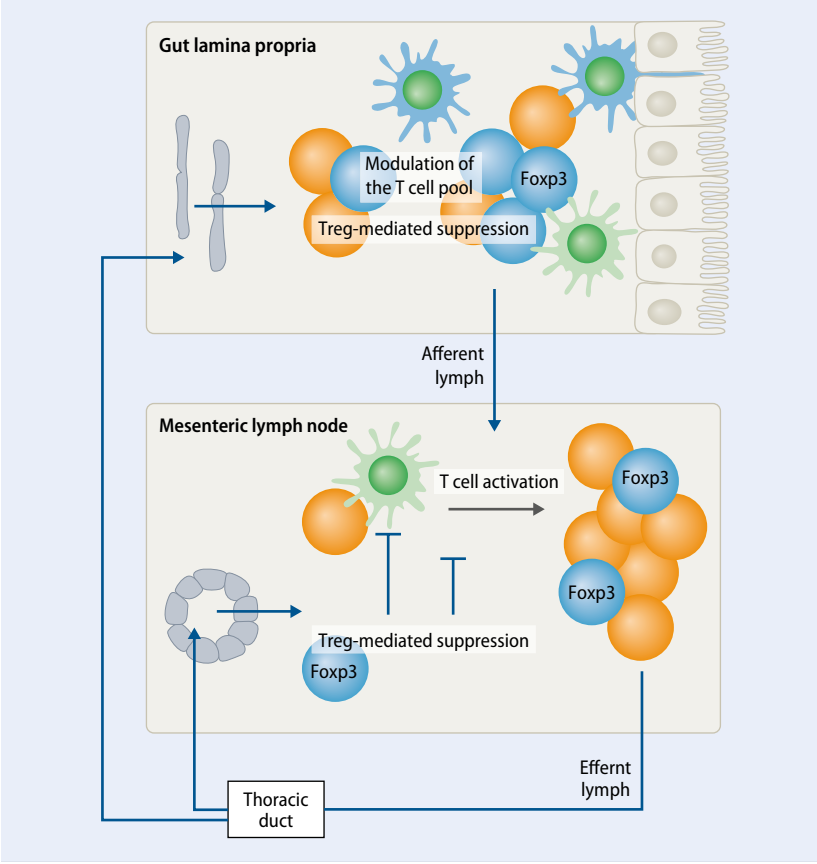

Fig. 3 ▲ Induction of oral tolerance includes priming and generation of Foxp3 Treg cells in the mesenteric lymph nodes and homing of the FoxP3 Treg cells to the gut lamina propria. After local expansion FoxP3 Treg cells mediate modulation of the T cell pool (modified after [50]) (green=dendritic cells; brown=naïve T cells; blue=Foxp3-cells)

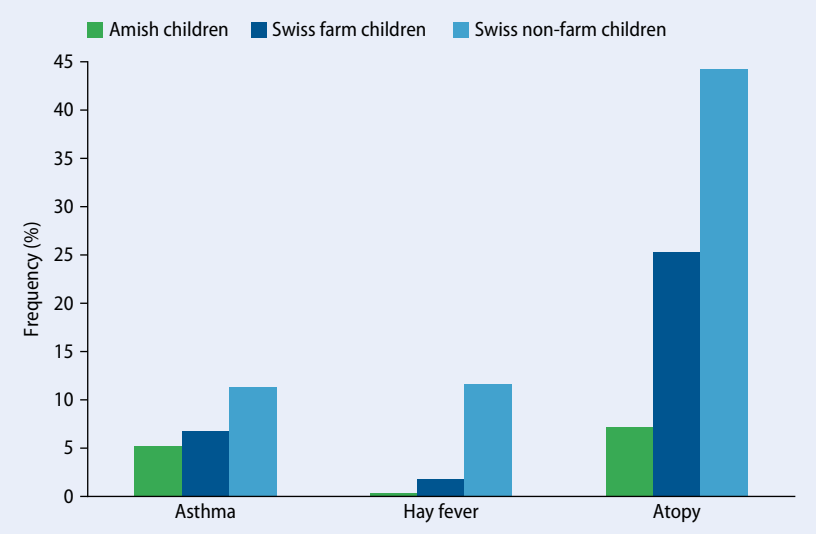

Fig. 4 ▲ Frequency (%) of allergic diseases in 6–12 years old Amish children, Swiss farm children and Swiss non-farm children (modified after [52])

offspring was identified: In children breastfed by allergic mothers who had increased Der p1 levels in milk, a significant higher risk of allergic sensitization or respiratory allergic diseases within the first 5 years of life was observed, as compared to children of allergic mothers who had lower Der p1 levels (**fig. 2**) [42].

Hygiene hypothesis

In the neonatal period, exposure of the gut mucosal barrier with luminal microorganisms and nutrients plays a pivotal role in the development of tolerance and the maturation of the immune system. The significant decrease in infections and the concomitant increase in autoimmune and allergic diseases led to the proposal of a causal relationship (hygiene hypothesis) between microbial components and allergy development. In addition, it became clear that the increasing prevalence of autoimmune and allergic diseases might be the result of early changes in the gut microbial exposure. For instance, higher abundance of lipopolysaccharide (LPS) producing Bacteroides spp. in the gut microbiome of infants in Estonia and Finland could explain the higher prevalence of early-onset allergies and autoimmune diseases as compared to Russia [43]. The observation that early-life antibiotic exposure increases the risk of developing allergic symptoms in later life points to the same direction [44].

Biodiversity hypothesis

The biodiversity hypothesis of health and disease englobes the hygiene hypothesis and has additionally societal impact [45]. It postulates that population growth, urbanization and global warming leads to loss of biodiversity (macro- and microbiota). Since the human microbiota (gut, skin, airways) is colonized from the environmental microbiota, this loss results in a poor human microbiota, immune dysfunction and finally clinical disease. Thus biodiverse natural environments provide immunoprotective factors, promote immune balance and protect from allergy [45–47].

The neonatal window of opportunity

According to the current hypothesis of the neonatal period as a 'window of opportunity', this period is non-redundant and therefore extremely important period, in which the immune system and potentially metabolic systems are primed. In this phase environmental factors, food or infections could alter the microbiome and therefore influence the maturation of the immune system and the susceptibility to diseases in later life [45], reported Professor Mathias Hornef (Aachen/Germany). In adults, host-microbial homeostasis is the result of a dynamic interplay between the microbiota in the gut lumen, the epithelium and the cells of the immune system. As shown in murine experiments, the neonatal and the adult gut differ in many respects.

Neonatal and adult gut

Main differences between the neonatal and adult gut concern the gut microbiota: the postnatal intestinal bacterial communities in both humans and animals are characterized by a much lower diversity and richness of bacterial species and an unstable composition, reported Hornef. This results in a lack of colonization resistance for new, potentially pathogenic bacteria and an increased susceptibility to perturbations (e. g. administration of antibiotics) in the neonatal host [48]. In mice, these postnatal changes in the microbiota are accompanied by major structural and functional alterations of the intestinal epithelial barrier that may help to define the window of opportunity. These alterations are less pronounced in human infants who are much more mature at birth, said Hornef. "Nevertheless, mice could be a model that gives us ideas".

Humans and mice exhibit a different gut epithelial structure with different epithelial cell types at birth. Nevertheless, both of them need antimicrobial peptides for defense. In humans, this is implemented by alpha-defensins (produced by Paneth cells) [49]. In mice, to bridge the time until alpha-defensin production offers protection, antimi-

crobial peptides like CRAMP (cathelin-related antimicrobial peptide) sustain the neonatal defense. These differences raise the idea that the neonatal intestine may not be considered "immature" but rather specifically adapted to the requirements during postnatal life, i.e. to foster and shape establishment of the enteric microbiota and fight specific types of enteric pathogens.

Mechanisms of tolerance induction in the neonate

In the gut, a single layer of epithelial cells separates the luminal content from the underlying lamina propria and a vast number of immune cells. Thus, intestinal immune cells are constantly exposed to foreign material that breaches the epithelial barrier, e.g. through small lesions. In this setting, regulation of immune responses is of outmost importance, said Professor Oliver Pabst (Aachen/Germany). One such mechanism of regulation is known as oral tolerance. Oral tolerance regulates immune responses to antigens encountered through the oral route and confers immune unresponsiveness to food antigens.

The mechanisms of oral tolerance induction have been determined in mouse models [50]. The immunological reaction to food antigens in its basic set up resembles the response to pathogens. However, unlike to pathogen-directed immune responses, a specialized immune cell population differentiates from T lymphocytes, the regulatory T cells (Treg cells). Tregs are important regulators of the immune system, supporting a balance between tolerance and sensitization. When mice are fed albumin, the antigen will be taken up in the gut lamina propria by dendritic cells which will migrate via afferent lymphatics towards the draining mesenteric lymph nodes (MLN) [50], reported Pabst. In MLN, the antigen is presented to naive T cells resulting in their activation and differentiation into FoxP3 Treg cells. After expansion, FoxP3 Treg cells home into the gut lamina propria where they induce expansion of the local T cell population in order to sustain systemic tolerance (**fig. 3**).

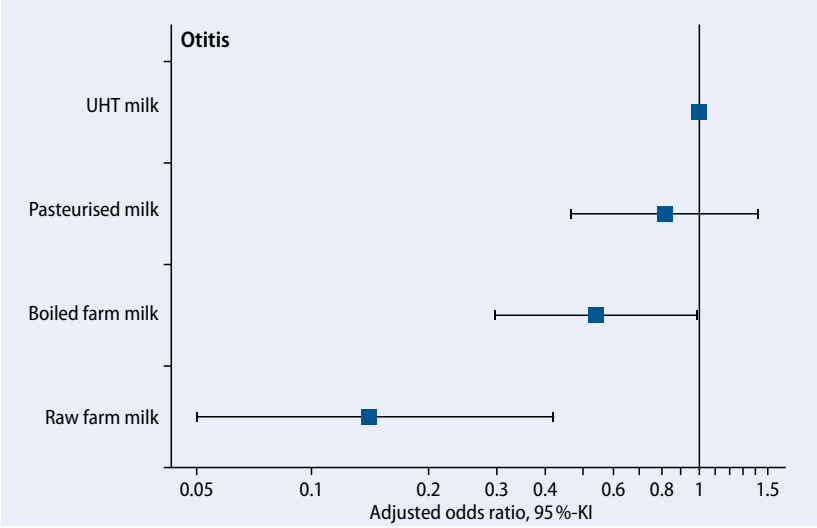

Fig. 5 ▲ Influence of early consumption of raw or boiled farm milk, pasteurized milk or UHT milk on the risk of otitis in the first year of life (modified after [54])

Farm children have a lower allergy risk

Strong evidence is provided by epidemiologic studies showing that farming exposure protects from childhood asthma, atopy and other allergic diseases. The relevant exposures seem to be animal sheds and consumption of raw (unprocessed) cow's milk [51–54] (whose routine consumption is not recommended by authorities). The relationship between farming exposure and allergy prevention has been investigated mainly in multicenter studies coordinated by Professor Erika von Mutius' group (Munich/Germany). Meanwhile, the results were reproduced in over 40 studies worldwide.

In one of the studies (GABRIELA Study) von Mutius and coworkers compared 6–12 years old children living in rural areas and grown up on a farm or in an urban environment. The prevalence of asthma, atopy, or hay fever was much lower in the group of farm children [51]. In another study, the group demonstrated an even lower prevalence of atopic diseases in 6–12 years old children of an Amish population (having a very traditional, dairy farming lifestyle without electricity or machines) as compared to a Swiss farm children population of the GABRIELA Study (**fig. 4**) [52].

In the ALEX Study similar results have been shown by exposure to animal sheds (mostly cowsheds) and unprocessed farm´s own cow's milk in the first year of life [53]. To confirm the results, the PASTURE (Protection Against Allergy Study in Rural Environments) Birth Cohort Study with 1144 children born to farm and non-farm mothers in Austria, Germany, Finland, France or Switzerland was initiated [54]. The children were closely followed up by weekly diaries (e.g. with respect to introduction of complementary food, stay in cowsheds, consumption of different kinds of cow's milk, atopic symptoms) up to the age of 1 year and subsequently with yearly questionnaires up to age 6 years.

Putative effects of raw milk

Early consumption of raw cow's milk reduced the risk of rhinitis (by 29 %) and otitis (by 86 %) in the first year of life as

compared to consumption of ultra high temperature (UHT) milk (**fig. 5**) [54]. Farm´s own raw milk was also clearly more effective in preventing rhinitis or otitis as compared to boiled farm milk or pasteurized milk. "After heating or boiling the milk, the protective effect is reduced or gone", said von Mutius. "So, there is something about heat labile compounds in the whey fraction of the milk that matter, but I would guess that also the homogenization may play a role". It should be pointed out, however, that routine consumption or raw milk is not recommended by authorities.

Currently, a randomized study with children aged ≥6 months is performed to investigate the opportunity to prevent asthma and other allergic diseases through the intake of minimally processed (mildly pasteurized) full cream milk as compared to semi-skimmed UHT milk in the MARTHA Trial (Milk Against Respiratory Tract Infections and Asthma).

Summary

According to current evidence, allergy is an increasingly frequent problem often initiated during childhood. Many environmental factors have been associated with an increased allergy risk, potentially due to early changes in the intestinal microbiota which are thought to play a pivotal role for tolerance induction and the maturation of the immune system. Though breastfeeding has been shown to protect against various pathologies, studies have failed so far to consistently demonstrate a protective effect of human milk in the development of allergic diseases. Many factors have already been identified that may explain the heterogeneity of study results. There is strong epidemiologic evidence, however, that farming exposure during childhood protects against childhood allergic diseases.

The contributions reported here reflect the opinions of the respective speakers. These do not necessarily correspond to the opinion held by HiPP.

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