Nutritional Interventions to Prevent the Development of Atopic Diseases: A Focus on Cow's Milk Allergy

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Abstract

In the western world the prevalence of atopic diseases such as food allergies is increasing highly significantly. One of the earliest and most prevalent food allergies occurring in the first year of life is cow's milk allergy. No treatment is available and only avoidance of the cow's milk allergens prevents the occurrence of an allergic reaction. Since cow's milk allergic children have an increased risk of developing other allergies later in life, investigating nutritional strategies to prevent the development of cow's milk allergy by developing oral tolerance is of high interest. Nutritional components such as prebiotics, probiotics, synbiotics and long-chain polyunsaturated fatty acids possess potential to support the maturation of the immune system early in life that might prevent the development of cow's milk allergy. The available research, so far, shows promising results particularly on the development of eczema. However, the preventive effects of the nutritional interventions on the development of food allergy are inconclusive. Future research may benefit from the combination of various dietary components. To clarify the preventive effects of the nutritional components in food allergy more randomized clinical trials are needed.

Keywords

Atopic disease · Cow's milk allergy · Food allergy · Long-chain polyunsaturated fatty acids · Nutritional prevention · Oral tolerance · Prebiotics · Probiotics · Synbiotics

1 Introduction

In the western world the prevalence of atopic diseases is increasing – with the first manifestations occurring early in childhood. Atopic diseases develop in a characteristic sequential pattern, starting early in life with atopic dermatitis, followed by food allergy, allergic rhinitis, and allergic asthma. This sequential process is known as the allergic march, which is also supported by the discovery that these atopic diseases are linked as infants diagnosed with one atopic disease are more predisposed to develop other allergies later in life (Czarnowicki et al. 2017).

Being the second manifestation of the allergic march, food allergies are potential disorders, which may clearly benefit (and have a need) for therapeutic interventions. One of the earliest and most prevalent food allergies occurring in the first year of life is cow's milk allergy (CMA) affecting around 2–5% of infants in some countries (Schoemaker et al. 2015; Fiocchi et al. 2010). Symptoms of CMA include skin rash, gastro-intestinal discomfort like diarrhoea, vomiting, respiratory problems and in severe circumstances anaphylactic shock. Although CMA is spontaneously remitted at the age of 3 in 79–90% of diagnosed children (Host and Halken 1990; Skripak et al. 2007), currently, no treatment is available and only avoidance of the cow's milk allergens prevents the occurrence of an allergic reaction. Since cow's milk allergic children have an increased risk of developing other allergies later in life,

investigating nutritional strategies to prevent the development of cow's milk allergy is of high interest. Here we review the preventive capacities of nutritional components in the development of allergic diseases with a focus on cow's milk allergy.

2 Development of Oral Tolerance Towards Food Allergens

At birth the baby's immune system is skewed towards a T helper 2 cell (Th2)-mediated response to prevent fatal immunological reactions between mother and child during pregnancy. If this Th2-skewed immune response is not adequately counterbalanced in a timely manner, Th2-mediated immunological disorders such as food allergy may arise. Environmental factors progressively educate the immune system towards a more balanced immune system, reflecting in appropriate regulatory T cell (Treg), T helper 17, T helper 1 (Th1) and Th2 responses, thereby preventing the development of diseases like autoimmunity and allergies (Gollwitzer and Marsland 2015).

An important environmental factor is exposure to food antigens, which is essential for the maturation of the immune system and the development of oral tolerance towards food allergens. The exact mechanism of immunological oral tolerance induction is unknown, but the differentiation into Tregs plays an important role. The differentiation into Tregs, involved in oral tolerance, takes place in the periphery, and more specifically in the gut-associated lymphoid tissue (GALT). Dendritic cells (DCs) sample antigens in the gut from where they migrate to the GALT. In the GALT the DCs instruct naïve T cells to differentiate into antigen-specific Tregs under the influence of anti-inflammatory and regulatory factors, like transforming growth factor-β (TGF-β) and interleukin (IL)-10 (Pabst and Mowat 2012).

Next to the exposure to food antigens, the development of the immune system is also dependent on the composition of the intestinal microbiota. It has been suggested that the microbiota plays a role in the development of mucosal immunological tolerance (Pabst and Mowat 2012). Indeed, the composition of the intestinal microbiota between atopic and healthy children is different, and reduced bacterial diversity and dysbiosis is associated with development of atopic diseases (Wopereis et al. 2014, 2018). A dysbiosis in allergic infants is characterized by low levels of genera Bifidobacteria and Lactobacilli compared to healthy infants (Cukrowska et al. 2020). Furthermore, it has been demonstrated that certain commensal intestinal bacteria, such as *Bacteroides fragilis* and several clostridial species through their ligands and metabolites, can stimulate macrophages and DCs to produce high amounts of TGF-beta and IL-10, thereby promoting the increase of Tregs (Hill and Artis 2010; Lehmann et al. 2015; Round and Mazmanian 2010; Smith et al. 2013). In addition, early life antibiotic exposure that has a major effect on the intestinal microbes increases the risk of developing allergic problems later in life (Ahmadizar et al. 2017a, 2018). Therefore, a dysbiosis in the intestinal microbiota might lead to an inadequately developed immune system associated with reduced

number of Tregs, reduced oral tolerance and possibly to the development of food allergy.

The development of the intestinal microbiota can be influenced by several factors during infancy. Some of these factors include the delivery mode (vaginal vs caesarean section), antibiotics usage during early life and most importantly early life diet (breast milk vs formula milk) will have a major impact on the intestinal microbiota. In conclusion, early life food allergies, such as cow's milk allergy, may be the result of intestinal dysbiosis and related derailed mucosal immune system not handling cow's milk proteins in a proper way.

3 Dietary Interventions for the Prevention of Cow's Milk Allergy

During the first years of life, diet affects the composition of the intestinal microbiota and has a major influence on the development of the immune system. We here review the allergy-preventive effects of several nutritional components that modulate the intestinal microbiota and/or the immune system early in life.

3.1 Human Milk

Breast milk is the recommended dietary source from the day of birth. It contains dietary nutrients important for the growth and development of the new-born as well as growth factors, antigens and immunomodulatory components like immunoglobulins, long-chain polyunsaturated fatty acids (LCPUFAs), bacteria, non-digestible oligosaccharides and vitamins, all derived from the maternal diet or maternal immune system. These components are essential for shaping the intestinal microbiota composition and for the maturation of the immune system, i.e. to develop oral tolerance in the new-born (van den Elsen et al. 2019; Verhasselt 2010). The 2011 guideline from the WHO recommends exclusively breast milk as nutrition for infants during the first 6 months of life (Exclusive breastfeeding for 6 months best for babies everywhere, https://www.who.int/mediacentre/news/statements/2011/breastfeeding_20110115/en/). Already after 3-4 months of consumption of breast milk the risk of wheeze, asthma and eczema development is decreased; however, the evidence is insufficient to form a conclusion regarding food allergy (Greer et al. 2019; Gungor et al. 2019; Ahmadizar et al. 2017b).

However, breastfeeding is not always possible and the best available alternative for infants is infant milk formula. To ensure optimal development of the intestinal microbiota and (mucosal) immune system, it is of great importance to identify all beneficial components in breast milk to enable full deployment of their potential when added to infant formula. Therefore, more information on the composition of breast milk and the function of the breast milk components might lead to new strategies to prevent allergy development.

3.2 Human Milk Oligosaccharides: Prebiotics

Human milk oligosaccharides (HMOs) are one of the major components of breast milk (Xiao et al. 2017). They stimulate the development of the immune system either directly via modulation of immune cells or indirectly by influencing the gut microbiota as a substrate for fermentation (Triantis et al. 2018). Indicative for the importance of HMOs is the finding that the profiles of HMOs in breast milk are associated with food sensitization early in life (Miliku et al. 2018; Ayechu-Muruzabal et al. 2018). Since the alternative for breast milk, infant formula, is based on cow's milk, the composition of oligosaccharides in infant formula is very different (low abundance) compared to human milk (Boehm and Stahl 2007). Therefore, to mimic the composition of human milk, it is favourable to supplement infant formulas with non-digestible oligosaccharides, which show beneficial (prebiotic) properties. The definition of a prebiotic according to the International Scientific Association for Probiotics and Prebiotics (ISAPP) is 'a substrate that is selectively utilized by host micro-organisms conferring a health benefit' (Gibson et al. 2017). Prebiotics stimulate the growth and activity of beneficial commensal intestinal bacteria (Gibson and Roberfroid 1995). Studies have shown that prebiotic supplementation of infant formula with a specific mixture of short-chain galacto-oligosaccharide (scGOS) and long-chain fructo-oligosaccharide (lcFOS) results in an intestinal microbiota composition similar to breastfed infants (Wopereis et al. 2018; Oozeer et al. 2013) indicating that supplementation of infant formula with certain prebiotics will beneficially affect the intestinal microbiota development. In a randomized double-blind placebo-controlled study with formula fed infants at risk of developing atopic manifestations it was shown that scGOS/lcFOS supplementation for 6 months reduced the development of atopic manifestations and infections during the first 6 months of life compared to the control group (Moro et al. 2006). This protective effect was still observed 2 and 5 years after the prebiotic intervention indicating that next to beneficial effects on microbiota composition and the shown health benefits, immune programming by prebiotics in early life can have a long-term protective effect (Arslanoglu et al. 2008, 2012).

The mechanisms by which these prebiotics exert their effects are diverse and not completely clear. Prebiotics stimulate the growth and activity of beneficial commensal intestinal bacteria like Bifidobacteria and Lactobacilli (Gibson and Roberfroid 1995). Increase in number and activity of the beneficial bacteria has antimicrobial effects since they compete with pathogenic bacteria to bind on intestinal epithelium (Ayechu-Muruzabal et al. 2018). In addition, it is known that HMOs and scGOS/lcFOS are able to cross the intestinal epithelial barrier either through receptor-mediated transcytosis or through paracellular transfer (Eiwegger et al. 2010; Gnoth et al. 2001). This indicates that these compounds may also have a systemic effect. This is in line with the fact that at least 1% of HMOs is detected systemically (Goehring et al. 2014). In addition to the microbial modulatory capacities of prebiotics, scGOS/lcFOS have been shown to have direct immunomodulatory effects on the immune system. In vitro assays showed that scGOS/lcFOS promotes IL-10 release by DC and these DC can upregulate the number of functional

suppressive Foxp3 positive T cells (Lehmann et al. 2015). In co-culture assays with intestinal epithelial cells and activated peripheral blood mononuclear cells (PBMCs), it is demonstrated that scGOS/lcFOS induces an epithelial cell-dependent development of tolerogenic Treg and Th1 responses (de Kivit et al. 2013; Hayen et al. 2018). Using a murine model of CMA it is demonstrated that the acute allergic response was significantly decreased in mice receiving scGOS/lcFOS during sensitization (Schouten et al. 2009). Moreover, the mixture of scGOS/lcFOS enhanced mucosal IL-10 and TGF-β transcription and induced Tregs response which were essential in allergy prevention since neutralizing TGF-β or IL-10 in vivo abrogated the protective effects (Schouten et al. 2010; Kerperien et al. 2014, 2018).

Despite the documented promising health benefit of prebiotics in several preclinical and clinical studies, some clinical studies show no differences (Ranucci et al. 2018; Boyle et al. 2016). One of these studies, a double-blind, randomized controlled trial comparing prebiotic containing formula with standard formula and breastfeeding, shows no differences in the incidence of allergic manifestations. The lack of difference may be due to the prebiotic mixture used in this trial, as this consisted of GOS and polydextrose (PDX) (Ranucci et al. 2018). These results indicate that a careful consideration of which type of prebiotic to use is important. So far, evidence from randomized trials that prebiotics (FOS, GOS and PDX) have a preventive effect on development of allergies is limited (Cuello-Garcia et al. 2017). More clinical studies are essential to learn more about the possible preventive effects on allergies of specific prebiotics, including HMOs. However, prebiotics are safe to use and the World Allergy Organization (WAO) guideline panel suggests prebiotic supplementation in not-exclusively breastfed infants, both at high and at low risk for developing allergy (conditional recommendation, very low certainty of evidence) (Cuello-Garcia et al. 2016).

3.3 Live Micro-Organisms: Probiotics

The intestinal microbiota play an essential role in the development of the (mucosal) immune system and also in the process of oral tolerance development. Modulation of the microbiota composition via nutrition is an appealing strategy. As discussed in the preceding paragraph, prebiotics are one strategy. Another strategy is to directly supplement diets with live micro-organisms. As live micro-organisms have been isolated from human milk (Martin et al. 2009; Jeurink et al. 2013), addition of selective bacterial strains to infant formula might further potentiate the beneficial healthy effects of infant formula. The category currently used to refer to these live micro-organisms is probiotics. The definition of a probiotic according to ISAPP is ‘live microorganism that, when administered in adequate amounts, confer a health benefit on the host’ (Hill et al. 2014).

There have been multiple clinical studies in which potential health benefits of probiotics were investigated. In a recently published double-blind placebo-controlled study, children receiving a daily mixture of *Lactobacillus rhamnosus* and *Bifidobacterium animalis* subsp. *lactis* for 6 months (at the age of 8–14 months)

developed less eczema compared to the control group. The number of sensitized children was not significantly different between the 2 groups (Schmidt et al. 2019). In another randomized placebo-controlled trial, a positive effect on eczema prevalence was only demonstrated for *Lactobacillus rhamnosus* and not for *Bifidobacteria animalis* subsp. *lactis*. The supplementation was given daily to mothers from gestational week 35 until 6 months after birth (if they were lactating) and to the infants from birth up to 2 years of age. At 6 years of age the incidence of sensitization in *L. Rhamnosus* group was reduced (Wickens et al. 2013); however, this reduction in sensitization was not further specified into the tested allergens, either food (egg, cow's milk and peanut) or aeroallergens (cat, grass pollen or house dust mite). At 11 years of age a significant lower prevalence of eczema was observed in the group receiving *L. Rhamnosus* whereas supplementation of the *Bifidobacteria* had no effects (Wickens et al. 2018). These data are in line with the meta-analyses (Cuello-Garcia et al. 2015; Zuccotti et al. 2015) which conclude that probiotic supplementation is beneficial in the prevention of eczema and that there is no proven effect on development of other allergies. It is important to realize that the preventive effect of probiotic supplementation is optimal when supplemented during both the pre- and postnatal period (Cuello-Garcia et al. 2015). This suggests that a combined strategy (pre- and postnatal) is most effective in prevention of eczema, and also to reduce sensitization. However, timing and duration of the intervention need more investigation and also food challenges are needed as an outcome in clinical trials to achieve more solid evidence of the preventive probiotic effects in food allergies (West et al. 2016; Zhang et al. 2016). Furthermore, a combination of probiotic strains seemed to lead to a more pronounced effect in the prevention of eczema compared with the use of single strains (Zuccotti et al. 2015). However, strain-specific differences should be taken into account. The WAO states the following: although the recommendations are supported by weak evidence, there can be a beneficial effect of probiotics in certain cases, i.e. pregnant women having a child at high risk, women who breastfeed children at high risk for developing allergies and infants at high risk for developing allergies (Fiocchi et al. 2015).

3.4 Synbiotics

As probiotics and prebiotics show some promising effects in allergy management, it is tempting to speculate that a combination of the so-called synbiotics might lead to synergistic effects. Synergy may be achieved by an optimal combination of prebiotics with probiotics, in which the prebiotics selectively promote the growth and activity of the probiotics. A few (pre)clinical studies have evaluated the synbiotic strategy on the development of (food) allergies.

In a mouse model of CMA, a synbiotic diet comprised of a mixture of prebiotics (scGOS/lcFOS, 9:1) in combination with the probiotic strain, *Bifidobacterium breve M-16 V*, significantly reduced the allergic response, and was shown to be more effective in symptom resolution than either the pre- or probiotics singularly (Schouten et al. 2009). Interestingly, next to alleviation of the allergic response, a

synbiotic diet (comprised of scFOS/lcFOS and *B. breve M16V*) was shown to increase tolerance development in a murine CMA preventive model. (Kostadinova et al. 2017). The beneficial effects of the synbiotics in these allergy models can be partly explained by their effects on the intestinal epithelial cells.

The synbiotic intervention increases epithelial-cell-derived galectin-9 (gal-9) levels in the intestine and mesenteric lymph nodes of mice in the CMA model. Moreover, it is demonstrated that in human PBMC assays gal-9 can induce the development of Th1 and Treg responses, which will contribute to amelioration of the allergic (Th2) response (de Kivit et al. 2012). Gal-9 is a soluble-type lectin and possesses sugar-binding motifs by which they bind to adaptive immune cells. Gal-9 also binds to IgE, which might prevent IgE cross-linking and consequently prevent degranulation of mast cells and/or basophils (Niki et al. 2009). In line with these results, the serum level of gal-9 in atopic dermatitis patients and in CMA mice was significantly increased after a synbiotic intervention and associated with amelioration of symptoms (de Kivit et al. 2012).

To the best of our knowledge, the preventive effects of a synbiotic strategy on the development of food allergies in clinical studies have not been evaluated. However, several studies investigated the synbiotic effect on the prevention of eczema and they all report significant improvements (Kukkonen et al. 2007; Roze et al. 2012; van der Aa et al. 2010). In one of the studies, infants diagnosed with atopic dermatitis (age < 7 months) received a synbiotic supplemented infant formula or a formula without synbiotic for 12 weeks. The synbiotic supplement significantly reduced the severity of eczema, in the infants with IgE-associated eczema (van der Aa et al. 2010). After 1 year, asthma-like symptoms and medication use were less in the infants who had received the synbiotic formula (van der Aa et al. 2011). In line with the preclinical data, systemic gal-9 levels in children with eczema were increased in the group receiving synbiotic supplementation (de Kivit et al. 2012).

In conclusion, limited studies have evaluated the synbiotic intervention as treatment of atopic diseases and the knowledge about the preventive capacities of synbiotics is still limited. Promising results from preclinical studies suggest synbiotics to be of considerable interest in the prevention of allergies.

3.5 Long-Chain Polyunsaturated Fatty Acids

Dietary long-chain polyunsaturated fatty acids (LCPUFAs) are important as they are incorporated in the cell membrane and facilitate a favourable environment for immune development and maturation. LCPUFAs can be divided into omega-3 (ω-3 PUFAs) and omega-6 (ω-6 PUFAs) fatty acids. The ω-6 PUFAs arachidonic acid (AA), also found in meat, can be converted into the pro-inflammatory eicosanoids 2 and 4 series like prostaglandin E_2. In contrast, the ω-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are incorporated in the cell membrane on the expense of AA, which leads to less available AA and therefore less conversion into pro-inflammatory prostaglandins and leukotrienes (Calder et al. 1994). DHA and EPA also compete with AA as substrates for

cyclooxygenase and lipoxygenase by which EPA and DHA can be metabolized into the less pro-inflammatory prostaglandin and thromboxanes 3 and 5 series (van den Elsen et al. 2012). In addition, cyclooxygenase can also convert DHA and EPA into resolvins, which are suggested to be anti-inflammatory through activation of the resolvins E1 receptor (Miles and Calder 2017).

The skewing towards a high consumption of ω-6 PUFAs in the western world has been associated with an increasing prevalence of allergies (Blumer and Renz 2007). This was also indicated in a preclinical model of CMA, where CMA mice exposed to ω-6 PUFAs containing diet demonstrated more severe allergic symptoms (van den Elsen et al. 2015; Thang et al. 2013). In contrast, a ω-3 PUFAs diet prevented the development of the acute allergic response as well as the IgE response and concomitantly increased the number of intestinal Tregs (van den Elsen et al. 2013, 2014). In a rat model of food allergy, it was shown that during two critical periods of immune development (pregnancy and weaning) extra supplementation with ω-3 PUFAs was able to steer the immune system towards oral tolerance. Perinatal supplementation (during pregnancy & lactation) of ω-3 PUFAs stimulated the maturation of the immune system of the offspring towards a Th1 (IFNγ) and Treg (IL-10) response (Richard et al. 2016). The data from these preclinical studies suggest a promising role for ω-3 PUFAs in the prevention of allergies.

Several clinical trials investigated the effect of fish oil, EPA and/or DHA supplementation during pregnancy and/or lactation on atopic disease development (Lumia et al. 2011; Furuhjelm et al. 2009, 2011; Bisgaard et al. 2016; Palmer et al. 2012; Best et al. 2016). However, there are differences between studies; which atopic diseases they evaluate, the timing of the intervention and the age of the children at the time of reporting the data. Some report beneficial effects on the development of food allergies and sensitization to allergens (e.g. sensitization to egg) whilst others report no effects on these atopic diseases (Furuhjelm et al. 2009; Palmer et al. 2012; Best et al. 2016, 2018; Noakes et al. 2012). According to a meta-analysis of maternal fish oil supplementation during pregnancy, the infants were at lower risk of developing eczema and a significant reduction in sensitization to egg was demonstrated in the first 12 months. This meta-analysis suggests maternal ω-3 PUFAs to have positive effects regarding the prevention of infant allergy development; however, the authors conclude that the link between maternal intake of ω-3 PUFAs and allergic disease development in the infants can be neither rejected nor confirmed due to inconsistency in results from the consulted studies (Best et al. 2016). Based on current studies there is no clear evidence whether maternal consumption of ω-3 PUFAs and/or fish oil prevents development of allergies in offspring, more adequate-designed randomized clinical trials are needed to establish adequate evidence.

The evidence that supplementation of ω-3 PUFAs after birth and/or during infancy influences allergy development is limited. In infants receiving fish oil or ω-3 PUFAs after birth a lower incidence of diagnosed food sensitization was reported and also a delayed time to first allergic illness (Clausen et al. 2018; Foiles et al. 2016; D'Vaz et al. 2012a). Mechanistic insights showed that immune cells from infants receiving fish oil displayed a decreased IL-13 production and increased

IFNγ and tumour necrosis factor α (TNFα) production indicating a favourable shift towards Th1 in the Th1/Th2 balance (D'Vaz et al. 2012a). In contrast, in another study no effect was observed on allergic outcomes in infants receiving ω-3 PUFAs supplementation after birth (D'Vaz et al. 2012b). A meta-analysis from 2016 concluded that LCPUFAs supplementation during infancy has no effect on the development of food allergy, asthma and eczema (Schindler et al. 2016).

4 Avoidance or Early Life Introduction of Cow's Milk Proteins

Historically, allergen avoidance during pregnancy and lactation has been the recommendation to mothers with children at high risk for allergic diseases. Avoidance of food allergens such as cow's milk, fish, and egg from the maternal diet was hypothesized to prevent and reduce the risk of food allergic reactions in the infants (American Academy of Pediatrics 2000). As the ingested allergens have been shown to pass through the placenta and are present in breast milk, this may lead to sensitization of the baby. However, the evidence that avoidance decreases the risk of food allergy is insufficient (Agostoni et al. 2008). Moreover, it has been demonstrated that early introduction of peanut could actually prevent peanut allergy in infants at risk (Du Toit et al. 2015, 2016, 2018; Perkin et al. 2016). The increased risk for allergy in infants avoiding allergens, can be explained by the lack of allergen-specific oral tolerance induction due to the absence of the allergen and/or by sensitization towards the allergen via other routes (like the skin or airways) (Nowak-Wegrzyn and Chatchatee 2017; Fox et al. 2009).

For infants at risk of developing cow's milk allergy, consumption of infant formulas exposes these infants to the major cow's milk allergens, casein and whey, which may lead to sensitization. To reduce the sensitizing potential of infant formulas, the allergenic load of the formula can be reduced by processes such as hydrolysation, heat-treatment and/or ultra-filtration (Hays and Wood 2005). This leads to reduction in the molecular weight of the cow's milk protein and is expected to reduce sensitization capacities of casein and whey (von Berg 2009). Hydrolysates exist as partial and extensive hydrolysates. Partial hydrolysates are used in the prevention of CMA in high risk infants and extensive hydrolysates are used for infants already diagnosed with CMA (Fiocchi et al. 2010). The preventive property of the hydrolysates is mainly tested in children at risk, only a few studies were conducted in healthy infants. According to a systematic review, hydrolysates have no effect on the prevention of allergic diseases in non-allergic infants; however, the quality of evidence was very low (Osborn et al. 2017). In infants at risk only limited studies have been performed with contradictory results. A recently published systematic review concluded that the use of partial hydrolysates in high risk infants reduces the risk of development of any allergic disease and in particular of eczema (Szajewska and Horvath 2017). The effect of hydrolysed cow's milk formula on allergy prevention has been shown in a cohort of infants at risk of atopic diseases (von Berg et al. 2003). The preventive effect of hydrolysates was particularly shown to reduce the risk of developing atopic dermatitis, which even persisted after 10 years

(von Berg et al. 2013). Further investigation into the exact composition of hydrolysates might further contribute to identifying specific tolerizing capacity of the various hydrolysates. It has recently been demonstrated that certain peptides within whey-based hydrolysates can contribute to the development of oral tolerance to whey (Gouw et al. 2018). Moreover, it is tempting to speculate that less processed milk, which is proven to be less allergenic, may have tolerance-promoting capacities (Abbring et al. 2019a, b). Further research is necessary to investigate the role of processing of milk in cow's milk allergy-preventive strategies.

5 Conclusion

The incidence of food allergies is increasing and there is a need for preventive strategies. Several nutritional components with intestinal microbiota and immune modulatory properties are suggested to have a potential role in the prevention of development of allergies. Next to the components reviewed in this chapter other important nutritional components like vitamins, postbiotics, ferments, short-chain fatty acids are also known to have potential beneficial effects but could not all be discussed in this overview. The available research, so far, shows promising results particularly on the development of eczema. However, the preventive effects of the nutritional interventions on the development of food allergy are not conclusive. A reason for this can be inconsistency (e.g. differences in prebiotic mixtures, differences in probiotic strains, differences in timing of intervention) in the used dietary components and the timing of intervention. Future research may benefit from the combination of various dietary components. To clarify the preventive effects of the nutritional components in food allergy more randomized clinical trials are needed.

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