Review

Cow's Milk Allergy: A Complex Disorder

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Cow's milk allergy (CMA) is a complex disorder. Numerous milk proteins have been implicated in allergic responses and most of these have been shown to contain multiple allergenic epitopes. There is considerable heterogeneity amongst allergic individuals for the particular proteins and epitopes to which they react, and to further complicate matters, allergic reactions to cow's milk are driven by more than one immunological mechanism. Finally, the incidence and dominant allergic mechanisms change with age, with IgE-mediated reactions common in infancy and non-IgE-mediated reactions dominating in adults. The complexity of CMA has lead to many public misconceptions about this disorder, including confusion with lactose intolerance and frequent self-misdiagnosis. Indeed, the prevalence of self-diagnosed CMA in the community is 10-fold higher than the clinically proven incidence, suggesting a sizable population is unnecessarily eschewing dairy products. Avoidance of dairy foods, whether for true or perceived CMA, carries with it nutritional consequences and the provision of appropriate nutritional advice is important. In this review, the epidemiology and natural course of CMA is discussed along with our current understanding of its triggers and immunological mechanisms. We examine current strategies for the primary and secondary prevention of allergic sensitization and the ongoing search for effective therapies to ultimately cure CMA.

Key teaching points

- Cow's milk allergy is an inflammatory response to milk proteins and is distinct from lactose intolerance.
- CMA is more prevalent in infants (2–6%) than in adults (0.1–0.5%), and the dominant immunological mechanisms driving allergic reactions change with age.
- The prevalence of self-diagnosed CMA in the community is substantially higher than the incidence reported in blinded and controlled challenge trials, suggesting that a proportion of the population is unnecessarily eschewing dairy products
- Breast-feeding is the best preventative strategy, although it cannot eliminate the risk of allergic sensitization in infants.
- Management of CMA involves avoidance of dairy during the duration of the disease, and the provision of appropriate nutritional advice is important to prevent nutritional deficiencies, particularly for parents of young children who have dairy withdrawn from their diet due to either diagnosed or perceived CMA.

INTRODUCTION

Epidemiology and Natural History of CMA

Cow's milk allergy (CMA) is a complex and often misunderstood disorder. A frequent misconception among the general public is confusion between CMA and cow's milk intolerance, which is mainly intolerance to lactose (Fig. 1). While consumers often use these terms synonymously and interchangeably they are distinct disorders driven by different aetiological mechanisms. Hence, they require separate methods of diagnosis and distinct strategies for management and treatment (Table 1). It is the involvement of the immune system in the adverse reaction that defines food allergies. In CMA, the immune system is incorrectly programmed to react to innocuous milk proteins. Allergy symptoms result from the collateral damage to tissues caused by the immune system's aberrant inflammatory response. Some individuals are exquisitely allergic to cow's milk proteins and the reactivity threshold can be as little as 0.1 mL of milk [1].

Abbreviations: CMA = cow's milk allergy, CMI = cow's milk intolerance, DBPCFC = double-blind, placebo-controlled food challenge, eHF = extensively-hydrolyzed formulas, GALT = gut-associated lymphoid tissue, IgE = immunoglobulin E, IL-10 = interleukin-10, pHF = partially-hydrolyzed formulas, RAST = radioallergosorbant test, SPT = skin prick test, TGF-β = transforming growth factor-beta, Th1 = T helper cell-type1, Th2 = T helper cell-type 2, T reg = regulatory T cell.

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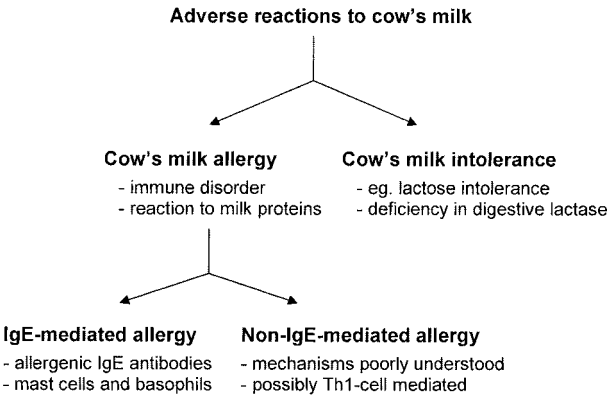

Fig. 1. Cow's milk allergy is distinct from cow's milk intolerances such as lactose intolerance and is caused by an aberrant inflammatory immune response to milk proteins. CMA is also not a single disease, but possibly involves a spectrum of immunological mechanisms. It is generally classified into IgE-mediated allergy and non-IgE-mediated allergy.

Cow's milk is a member of the so-called "Big-8" food allergens, ranking alongside egg, soy, wheat, peanuts, tree nuts, fish and shellfish in terms of prevalence [2–5]. The incidence of CMA varies with age. Cow's milk is the most frequently encountered dietary allergen in infancy when the immune system is relatively immature and susceptible to sensitization from environmental antigens. Hence, CMA is the dominant food allergy in babies [6]. The reported prevalence of CMA in infants and adults varies between studies, in part due to the difficulties in accurate diagnosis, differences in the age of study populations, and the clinical assessment criteria used. However, it is clear that CMA is most prevalent in early childhood, with figures generally reported between 2 and 6% [7–9], and decreases into adulthood to an incidence of 0.1–0.5% [10–11]. The long-term prognosis for the majority of affected infants is good, with 80–90% naturally acquiring tolerance to cow's milk by the age of 5 years [6, 12]. However, there remains a strong trend in infants who recover from CMA to develop atopic symptoms such as asthma, hay fever, or dermatitis to inhalant allergens later in life: the so-called "atopic career" or "atopic march" [12–13]. CMA appears to be an early indicator of atopy.

Perception versus Reality

Of concern is that the prevalence of self-diagnosed CMA in the community is significantly higher than the incidence supported by evidence from randomised, controlled, food challenge trials. Woods et al. [10] demonstrated that the self-diagnosed incidence of CMA in an Australian population was 10-fold higher than the clinically diagnosed prevalence. A similar pattern has been observed with other food allergies in other Western populations [14]. The reasons underlying this large discrepancy between the incidences of perceived and clinically proven milk allergy remain to be explored. Either dairy intolerance and/or allergy extends beyond the current diagnostic criteria, or more likely, many people misdiagnose

Table 1. Differences among the Most Prevalent Adverse Reactions to Cow's Milk

	Lactose intolerance	IgE-mediated cows' milk allergy	non-IgE-mediated cows' milk allergy
Prevalence	high	low	low
Racial variation	high	low	unknown
Common age	adolescence/adulthood	infancy	infancy and adulthood
Offender	lactose	milk proteins	milk proteins other components?
Mechanism	metabolic disorder - intestinal lactase deficiency	immunologic - IgE	immunologic - cell-mediated - immune complex - others?
Symptoms	gastrointestinal (GI)	one or more of GI, skin, respiratory, anaphylaxis	mainly GI and/or respiratory
Time of onset post ingestion	0.5–2 hours	<1 hour	>1 hour to days
Diagnostics	lactose tolerance test; breath test; stool acidity test; intestinal biopsy	skin-prick test; RAST	no simple diagnostic tests; DBPCFC
Prevention			
-primary	—	Breast-feeding. Milk protein avoidance in infancy (0–6 months)	unknown
-secondary	Avoid lactose	Avoid intact milk proteins	Avoid intact milk proteins
Processing options	Lactose hydrolysis or chromatographic lactose removal	Remove allergenic epitopes. Milk protein hydrolysis	Remove allergenic epitopes. No suitable products available

themselves without clinical evaluation and unnecessarily eschew dairy products. This carries with it nutritional implications, particularly for adequate vitamin and calcium intake and bone health [15–17]. Misdiagnosis of CMA by parents and restriction of dairy intake in young children without adequate dietetic supervision can lead to poor nutritional outcomes for growth, bone density and, where unorthodox alternative diets are implemented, inadequate protein and energy intake [15–19].

Understanding the Mechanisms of CMA

Perhaps contributing to the prevalent public perception of allergy is the lack of simple and reliable diagnostic tests for many individuals with CMA. In addressing why this is the case it is important to dispel another common misconception about CMA. That is, while it is often thought of as a single disease, CMA is in fact driven by at least two, and possibly more, distinct immune pathologies. Allergies to milk are often broadly classified into immunoglobulin E (IgE)-mediated allergy and non-IgE-mediated allergy (Fig. 1) [7, 20]. The immunopathological mechanisms of non-IgE-mediated allergy in particular remain poorly understood, and this has hindered the development of simple and reliable diagnostics. Recognising that understanding mechanisms is critical to the development of diagnostics and effective management, treatment and therapeutic strategies, numerous research groups are now focusing on acquiring an understanding of the molecular and cellular mechanisms of CMA. The following sections outline what we currently know about the triggers and immunology of CMA and how this knowledge is being applied in disease management, prevention and treatment.

BACKGROUND

Milk Protein Allergens

While some similarities exist between the protein composition of bovine and human milk (Table 2), there are substantial differences in the types of proteins and their homologies that provide ample scope for cow's milk proteins to be recognized as foreign by the human immune system [21–22]. In most people the immune system is able to recognise the milk proteins as harmless and tolerate them. However, in allergic individuals the immune system becomes sensitized to the milk proteins and mounts a damaging inflammatory response. The reasons why an unfortunate few develop CMA are not well understood. There appears to be a hereditary predisposition, but the phenotypic expression of allergy depends on a complex interaction between genetic and environmental factors [23] and the fundamental mechanisms of sensitization remain unclear.

Table 2. Typical Compositions of the Major Proteins in Human and Cow's Milk.

Protein	Human (mg/mL)	Cow (mg/mL)
α-lactalbumin	2.2	1.2
α-s1-casein	0	11.6
α-s2-casein	0	3.0
β-casein	2.2	9.6
κ-casein	0.4	3.6
γ-casein	0	1.6
immunoglobulins	0.8	0.6
lactoferrin	1.4	0.3
β-lactoglobulin	0	3.0
lysozyme	0.5	trace
serum albumin	0.4	0.4
other	0.8	0.6

In contrast, our understanding of the number and nature of allergenic determinants in milk is rapidly improving. It is known that both the allergy triggers in milk and the immune responses to those triggers in allergic individuals are multifarious. For example, most major cow's milk proteins (more than 30 so far) have been implicated in allergic responses, including both casein and whey proteins [21]. Epitope mapping of a number of milk proteins has revealed multiple allergenic epitopes within each protein, both for B cells that produce antibodies, and for T cells that direct both antibody and cell-mediated immune responses [22, 25–30]. Additionally, there is considerable heterogeneity amongst allergic individuals for the particular proteins and epitopes to which they react [21]. While there is scope for further epitope mapping of milk proteins, the complexity of antigenic determinants in milk is already apparent, as is the scale of the challenge to selectively eliminate them.

Immunological Mechanisms in CMA

Since different mechanisms are involved in driving CMA, different approaches are required for diagnosis and eventual treatments. A basic appreciation of the immunology of CMA is helpful in understanding the basis of strategies for prevention and therapies currently under investigation.

IgE-Mediated CMA (Immediate Hypersensitivity). IgE-mediated allergy is the best-understood allergy mechanism and, in comparison to non-IgE-mediated reactions, is relatively easily diagnosed. Since the onset of symptoms is rapid, occurring within minutes to an hour after allergen exposure, IgE-mediated allergy is often referred to as "immediate hypersensitivity" [31]. In healthy immune systems, this type of inflammatory response has evolved to target multicellular parasites such as worms [31]. Allergic responses occur when benign environmental antigens, such as food proteins, are incorrectly targeted.

The development of IgE-mediated CMA occurs in two stages. The first, "sensitization", occurs when the immune system is aberrantly programmed to produce IgE antibodies to milk proteins. These antibodies attach to the surface of mast cells and basophils, arming them with an allergen-specific trigger. Subsequent exposure to milk proteins leads to "activation" when the cell-associated IgE binds the allergenic epitopes on the milk proteins and triggers the rapid release of powerful inflammatory mediators leading to allergy symptoms (Fig. 2).

The symptoms associated with IgE-mediated CMA include one or more of cutaneous (eczema; urticaria; angioderma), gastrointestinal (oral allergy syndrome; nausea; vomiting; diarrhoea) or respiratory manifestations (rhinoconjunctivitis; asthma) [7]. Life-threatening anaphylactic reactions to cow's milk may also occur, but are fortunately rare [32]. Since reactions to cow's milk proteins can occur on contact with the mouth or lips, strategies to reduce allergenicity by improving protein digestibility in the gut are unlikely to be effective for all allergic individuals.

Simple diagnostic procedures, such as skin-prick tests (SPT) and RAST (radioallegosorbant test), can be used to identify individuals with IgE-mediated CMA, although both of these tests produce false-positive results in some individuals [33]. Food elimination and challenge testing are sometimes required to confirm milk allergy, and double-blind, placebo-controlled, food challenge (DBPCFC) testing remains the gold standard diagnostic. IgE-mediated reactions account for an estimated half of the CMA cases in young children [7, 34], but are rare in adults. Woods et al. [10] reported an incidence of 0.1% challenge-confirmed IgE-mediated CMA in a randomised population of more than 3000 Australian adults, a finding that was recently supported in a study of German adults [5].

Non-IgE-Mediated CMA (Delayed Hypersensitivity). A significant proportion of infants and the majority of adults with CMA do not have circulating milk protein-specific IgE and show negative results in skin prick tests and RAST [7, 35, 36]. These non-IgE-mediated reactions tend to be delayed, with the onset of symptoms occurring from 1 hour to several days after ingestion of milk. Hence, they are often referred to as "delayed hypersensitivity" [37]. As with IgE-mediated reactions, a range of symptoms can occur, but are most commonly gastrointestinal and/or respiratory in nature [7]. The gastrointestinal symptoms, such as nausea, bloating, intestinal discomfort and diarrhoea, mirror many of those that are symptomatic of lactose intolerance, complicating self-diagnosis. Anaphylaxis is not a feature of non-IgE mediated mechanisms [37]. IgE and non-IgE mediated reactions are not mutually exclusive and reactions to milk can involve a mixture of immunological mechanisms [37]. Adults with non-IgE-mediated allergy to milk tend to suffer ongoing allergy without the development of milk tolerance.

The precise immunopathological mechanisms of non-IgE-mediated CMA remain unclear. A number of mechanisms have been implicated, including type-1 T helper cell (Th1) mediated reactions (Fig. 2) [38–44], the formation of immune complexes leading to the activation of Complement [45], or T-cell/mast cell/neuron interactions inducing functional changes in smooth muscle action and intestinal motility [46–48].

There appears to be a discrepancy between reportedly higher rates of natural recovery during childhood from non-IgE-mediated CMA (compared to IgE-mediated CMA) [6, 12, 49], and the predominance of non-IgE-mediated CMA in adult populations [10, 35–36]. This suggests that a non-IgE-mediated CMA population emerges later in life. In a study of different

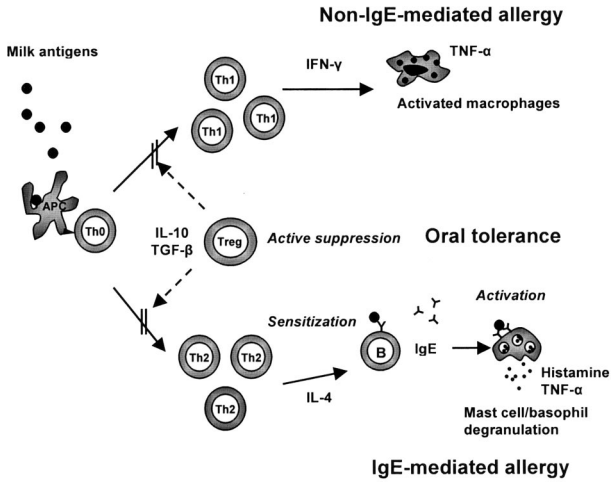

Fig. 2. Mechanisms of allergic reactions to milk proteins. Milk proteins are pinocytosed by antigen presenting cells (APC) and peptide epitopes are presented to T cells. Dendritic cells are an important class of APCs with a strong ability to program naive T cells. In IgE-mediated allergy, Th2 effector T cells signal B cells via interleukin-4 (IL-4) to class switch antibody production to allergenic milk protein-specific IgE, which then binds to, and arms, mast cells (sensitization). Milk proteins cross-linking the IgE on armed mast cells cause cell degranulation and rapid release of powerful inflammatory mediators (activation). Non-IgE-mediated mechanisms are poorly understood, but may involve activation of inflammatory cells via interferon-gamma (IFN-γ). Oral tolerance is achieved by T cell anergy, or by the action of regulatory T cells (T reg) that suppress the action of effector T cells (Th1 and Th2) via interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), or cell-to-cell contact.

age groups in Germany, Zuberbier et al. [5] reported an increase in the incidence of non-IgE-mediated food allergies with increasing age. However, the emergence of a new CMA population in adults remains to be conclusively demonstrated. Good epidemiological data for non-IgE-mediated CMA in both adults and children remains scarce because tedious DBPCFC trials remain the only truly conclusive diagnostic tests to confirm this form of allergy [50]. In many cases, gastrointestinal food allergy remains undiagnosed or is classified as irritable bowel syndrome.

Dysfunctional Tolerance. Even in the midst of a discussion on allergy it should be remembered that the majority of infants and adults are not allergic to cow's milk proteins. Understanding how this tolerance is mediated is central to developing strategies to prevent or treat allergy. Food antigens contact the immune system throughout the intestinal tract via the gut associated lymphoid system (GALT), where interactions between antigen presenting cells and T cells direct the type of immune response mounted (Fig. 2). Unresponsiveness of the immune system to dietary antigens is termed "oral tolerance" and is believed to involve the deletion or switching off (anergy) of reactive antigen-specific T cells and the production of regulatory T cells (T reg) that quell inflammatory responses to benign antigens [51–53].

CMA is believed to result from the failure to develop these tolerogenic processes or from their later breakdown. In the case of IgE-mediated CMA, a deficiency in regulation and a polarisation of milk-specific effector T cells towards type-2 T helper cells (Th2) lead to signalling of B-cells to produce milk protein-specific IgE [24, 40] (Fig. 2). Non-IgE-mediated reactions may be due to Th1 mediated inflammation [7]. Dysfunctional T reg cell activity has been identified as a factor in both allergy mechanisms [54–55]. Additionally, the induction of tolerance in children who have outgrown their CMA has been shown to be associated with the development of T reg cells [56–57]. Much research is currently focused on manipulating the activity of dendritic cells (specialised antigen presenting cells important in programming immune responses) to induce T reg cells and/or to redress Th1/Th2 imbalances in order to promote tolerance to allergenic foods.

DESCRIPTION OF SUBJECT

Management and Treatment of CMA

There is currently no cure for CMA and the only effective management strategy is avoidance of intact cow's milk proteins throughout the duration of the disease. The homologies between various mammalian milk proteins means that milks from other species (for example, goats and sheep) share many allergenic epitopes with cow's milk proteins and are often not reliable hypoallergenic cow's milk substitutes [58–60]. Individuals with CMA are also often allergic to a number of foods including soy, which is one of the "Big-8" allergens [61]. Hence, soymilk is often not a suitable alternative, and is especially not recommended for young infants (< 6 months) who are more susceptible to allergic sensitization [62]. Hypoallergenic infant formulas are available for CMA infants who cannot be breast-fed, while for adults with CMA the inclusion of milk proteins in an ever-expanding array of processed foods provides an increasing challenge to the management of their conditions.

Intervention strategies in CMA have been targeted at three levels; 1) primary prevention of initial sensitization; 2) secondary prevention of the triggering of allergic reactions; and 3) induction of tolerance in already sensitized individuals (specific immunotherapy, SIT). While there is general scientific agreement on how to manage the triggering of allergic reactions, debate on the most effective strategies to avoid initial sensitization remains intense, and more fundamental research into allergy and tolerance mechanisms is required to allow targeted strategies to induce tolerance.

Primary Prevention of Sensitization

CMA has a strong hereditary prevalence and currently familial history of atopy is the best predictive test for identifying children at risk of developing CMA. The precise point at which infants become sensitized to milk proteins is still controversial, which contributes to the sometimes fierce debate as to the best methods to prevent sensitization. There is emerging evidence from studies of cord bloods that both sensitization and the acquisition of tolerance can begin *in utero* [8, 63]. The window of main danger for sensitization to food proteins extends prenatally, remaining most critical during early infancy when the immune system and intestinal tract are still maturing.

Breastfeeding Is the Best Preventative for CMA. Although sensitization may perhaps begin *in utero,* there is no conclusive evidence to support the restriction of dairy intake in the maternal diet *during pregnancy* in order to prevent CMA. It is generally not recommended since the drawbacks in terms of loss of nutrition out-weigh the benefits [64–65]. Breastfeeding during the first 4–6 months is the most protective strategy known against the development of CMA [66]. Traces of cow's milk proteins ingested by the mother can be transferred to the sucking infant through breast milk [8], and exclusive breastfeeding does not completely eliminate the risk [67]. For at-risk infants, there are indications that maternal avoidance of dairy proteins during lactation can further minimize the risk of infant sensitization [65]. However, further randomised, controlled trials are required to examine if dietary exclusion by lactating mothers can truly minimize risk to a significant degree and if any reduction in risk is out-weighed by deleterious impacts on maternal nutrition.

For a variety of reasons, some babies cannot be breast-fed and require infant milk formulas. Evidence from a number of prospective studies indicates that the use of hydrolyzed formulas in early infancy provides better protection than the use of formulas with intact cow's milk proteins, especially in at-risk infants (having at least one atopic parent) [8, 66, 68–69]. It remains to be seen if these hydrolyzed formulas provide any protection against the later development of atopic disease [70]. A Cochrane analysis of studies comparing soy to hydrolyzed cow's milk formula found a significant increase in infant and childhood allergy cumulative incidence and infant eczema in infants fed soy formula [71]. The authors concluded that soy formula should not be recommended for the prevention of allergy or food intolerance in infants at high risk of allergy or food intolerance.

Partially Hydrolyzed Formulas (pHF). The proteins in hypoallergenic cow's milk infant formulas are extensively hydrolyzed in order to destroy allergenic epitopes. While these extensively hydrolyzed formulas (eHF) remove allergenicity, the loss of immunogenicity also prevents the immune system from developing tolerance to milk proteins. Partially hydrolyzed cow's milk formulas (pHF) have been developed with the aim of minimizing the number of sensitizing epitopes within milk proteins, while at the same time retaining peptides with sufficient size and immunogenicity to stimulate the induction of oral tolerance. Since they contain larger peptides than eHF, pHF trigger activation of symptoms in a relatively large percentage of already sensitized infants [72] and are therefore not

recommended where there is a risk of severe CMA symptoms [64]. Human intervention studies in at-risk infants have shown that pHF reduce the incidence of atopic dermatitis in the first 2 years compared to intact cow's milk protein formulas [8, 73–74]. However, despite animal studies indicating that pHF have an increased capacity to induce tolerance [75–77], there remains no clear evidence from human studies that they are better than eHF in preventing CMA [23, 70]. Further prospective human feeding studies are required to establish if they can play a useful role in preventing CMA.

Probiotics. Epidemiological evidence shows that allergy is more common in industrialized countries than in developing nations and more frequent in urban compared to rural communities [78]. This has lead to the development of the "hygiene hypothesis", which speculates that a decline in Th1-inducing exposure to pathogens and parasites contributes to the Th2-skewed immunity seen in IgE-mediated allergies [79–80]. Providing a microbial challenge in the form of dietary probiotic bacteria (live *Lactobacillus* and *Bifidobacterium* cultures used in fermented dairy products) has redressed Th1/Th2 imbalances and induced regulatory T cell activity in animal studies [70, 81–82]. Interestingly, controlled feeding studies using probiotics in human infants have produced clinically significant ameliorations of atopic dermatitis [83–84] that have been maintained up to the age of 4 years [85]. Probiotics are now included in some infant formulas, together with oligosaccharides (prebiotics), which can induce the development of a *Bifidobacterium*-dominated intestinal microbiota, replicating the effect of human breast milk. Although still in its infancy, the use of probiotics, prebiotics and components of intestinal parasites in the prevention of allergy [86] is an exciting and burgeoning area of research.

Immune Factors in Milk. Regulatory cytokines in human milk, such as transforming growth factor-beta (TGF-β), play an important role in promoting appropriate responses to food antigens during early infancy when the gut immune system is still developing [87]. However, cow's milk-based infant formulas are generally deficient in regulatory cytokines [88]. Using a rodent model, Penttila et al. [89] reported that supplementing infant formulas with cow's milk fractions rich in immunoregulatory factors enhanced the development of oral tolerance to food antigens. In the future, replicating the immunoregulatory capacity of human breast-milk may prove a valuable strategy to promote the tolerogenicity of cow's milk formulas.

Secondary Prevention: Making Cow's Milk Proteins Less Allergenic

For individuals who are already sensitized to cow's milk, CMA is managed by the avoidance of intact cow's milk proteins. The sheer number of allergenic epitopes and their conformational and sequence-based nature preclude the use of genetic selection or protein denaturation processes such as heating to remove allergenicity. Manufacturers of hypoallergenic infant milk formulas have approached the problem by destroying allergenic epitopes through extensive hydrolysis of milk proteins to peptides typically smaller than 1500 Da [66, 90]. These extensively hydrolyzed formulas (eHF) successfully prevent the triggering of allergy symptoms in the majority of allergic infants [90] and are evidently effective for both IgE-mediated and non-IgE-mediated reactions. In a small percentage of cases, even eHF trigger symptoms in highly sensitive infants and amino acid-based formulas are required [90]. While extensive hydrolysis eliminates allergenicity, it also destroys the physical and biological functionalities of milk proteins, and the search for alternative methods to produce hypoallergenic milks continues [91–96].

Curing Allergy: Immunotherapy

Specific immunotherapy (SIT) aims to induce immune regulation in sensitized individuals through controlled exposure to the allergen, which is often modified to prevent the triggering of adverse reactions. To date, trials of SIT for CMA have been limited largely to experimental animal models. Systemic immunizations using milk proteins, or recombinant milk protein fragments with appropriate adjuvants, have induced tolerogenic responses in Th2 skewed rodent [97–98] and dog models of CMA [99]. Similarly, the use of a DNA vaccine using a bacterial plasmid encoding the milk protein β-lactoglobulin has also been effective in inducing tolerance in a mouse model [100]. Recombinant bacteria expressing milk proteins and peptides have also been developed for oral vaccinations [97, 101], although they have not yet been effective in inducing tolerance to cow's milk proteins.

A recent report has detailed a protocol for oral desensitization in older children with severe IgE-mediated CMA [102]. The experiment showed that gradually increasing the daily oral dose of milk protein over a period of months improved tolerance to cow's milk in the majority of patients (15 of 21). This preliminary result requires confirmation in larger, double-blind, placebo-controlled studies. However, it shows that SIT has the potential to benefit food allergy sufferers in a similar way to its current effective use for desensitizing people against aeroallergens.

CONCLUSION

Recent years have seen major advances in our understanding of the immunological processes involved in the development of CMA and importantly, oral tolerance to food antigens. They have revealed the complexity of CMA in terms of the number of allergenic epitopes, the heterogeneity of allergic responses, and the potential diversity in immunological pathways leading to allergy symptoms. The epidemiology of CMA requires further investigation, but it is clear that it is more

frequent in young children (2–6%) and then decreases in prevalence among adults (0.1–0.5%). Importantly, the prevalence of self-diagnosed CMA in the community far exceeds the clinically proven incidence leading to unnecessary avoidance of dairy foods with nutritional consequences in terms of inadequate calcium and vitamin intake. While the mechanisms of IgE-mediated allergy are fairly well understood, the immunology and variety of non-IgE mediated reactions remains largely unknown. A better understanding of these allergy mechanisms is a prerequisite to the development of improved diagnostics, which in turn will facilitate an improved understanding of the epidemiology of CMA, particularly for non-IgE-mediated reactions. It will also aid the development of hypoallergenic dairy products, especially for adults with CMA for whom there is currently a dearth of suitable low-allergenic dairy products.

Some of the risk factors for the development of CMA have been identified, with a familiar history of atopy one of the main determinants. However, the mechanisms of allergic sensitization and the precise interactions between genetics and various environmental factors leading to CMA remain to be elucidated. The first few months of life, during which the immune system is still maturing, appears to be a critical risk period for the allergic sensitization. For at-risk infants with at least one atopic parent, breast-feeding during this period is currently the best identified preventative strategy, with the use of hydrolyzed formulas recommended for babies who cannot be breast-fed. The use of immunomodulatory dietary adjuvants such as probiotics is an emerging approach with considerable promise for primary prevention.

For CMA sufferers, avoidance of dietary milk proteins remains the only effective management strategy, but carries with it nutritional implications, particularly for adequate vitamin and calcium intake, and protein and energy intake where unorthodox alternative diets are implemented. A growing understanding of the molecular and cellular mechanisms of oral tolerance is underpinning advances in potential therapies for food allergies and is pivotal to eventually curing allergy in sensitized individuals. Unravelling the links between innate and adaptive immunity and the roles of dendritic cells and T cells in directing immune responses and homeostasis to environmental antigens are likely to remain a focus of fundamental food allergy research in coming years.

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