Allergy Prevention via Co-Administration of Intact Food Allergen and Its Epitope Soup?

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Cow's milk is the first foreign protein consumed in large quantities by the infant. Most infants develop oral tolerance to milk protein, i.e. inability to mount systemic immune responses after oral administration of a protein. However, cow's milk allergy (CMA) develops in approximately 2–3% of young children. Early introduction of milk formula during the first 3 days of life has been associated with an increase in CMA [1], whereas hydrolyzed formulas have been recommended for the prevention of CMA in high-risk individuals [2]. Caseins are the major allergens responsible for CMA comprising about 80% of the total protein content in cow's milk, but the whey fraction also includes allergenic proteins such as α -lactalbumin and β -lactoglobulin (BLG). It is currently not fully appreciated what makes some dietary proteins allergens, although resistance against heat-denaturing and gastric fluid treatment may play an important role. Its absence in breast milk may be a crucial component of the allergenicity of BLG, although the presence of caseins in human milk does not exclude them as major allergens.

In the paper by Lindholm Bøgh et al. [3], the sensitizing potential of BLG and its gastroduodenal digests was assessed by measuring humoral responses in a food allergy-prone Brown Norway rat model. The authors show that while BLG is virtually completely resistant to pep-

sinolysis, digestion by trypsin and chymotrypsin results in partial digestion of BLG containing approximately 15% of intact BLG. After dissociation of the intact BLG, the remaining peptide fragments that included proteins with $M_r < 5,000$ in size completely lost sensitizing capacity measured by the development of specific IgE responses after intraperitoneal sensitization. This differs from what is known about peanut and cashew digests [4–6] that retain their sensitization potential even after gastric or gastroduodenal digestion that results in virtually complete digestion of the proteins both in vitro and in vivo using animal models. Unfortunately, in the paper by Lindholm Bøgh et al. [3], the sensitizing potential was only assessed based on the development of specific IgE responses and not on the response to an oral feeding test.

Even more interestingly, co-administration of intact BLG together with BLG digests resulted in reduced immunogenicity (measured by the development of humoral responses) when compared to the administration of intact BLG alone, although the preparations contained the same amount of intact BLG. As the authors speculate this could be through epitope masking by peptide fragments in the intact protein aggregate, which the authors, however, demonstrated not to occur. Alternatively, BLG peptide fragments could result in the development of tolero-

genic immune responses, which remain to be fully demonstrated. Whether this is relevant to clinical disease and development of oral tolerance in humans can be speculated. Animal studies have shown partially hydrolyzed formulas efficacious in the prevention of cow's milk sensitization, whereas extensively hydrolyzed formulas were not [7–9]. This is based on the notion that partially as opposed to extensively hydrolyzed formulas contain peptides big enough for the induction of oral tolerance [10]. However, human studies suggest that although partially hydrolyzed formulas also have some preventive effect on atopic disease and cow's milk protein sensitivity, it is less so than with extensively hydrolyzed formulas, as reviewed by Muraro et al. [11] in 2004. Furthermore, exposure to cow's milk proteins typically occurs via the gastrointestinal tract, and, therefore, it is likely that an infant's immune system is naturally exposed to varying degrees of BLG digests unless sensitization occurs via other routes (inhalation/cutaneous route), or clinical conditions or treatments such as anti-acid medications prevent effective digestion of dietary proteins.

Before extrapolating the results to humans, particular limitations of the study setup need to be considered. Unfortunately, the authors used only the intraperitoneal sensitization procedure for BLG and its digests to avoid *in vivo* digestion of antigens to assess the sensitizing potential of protein digests in principle. However, a comparison to the oral sensitization would have seemed interesting to see the outcome of exposure to different degrees of BLG digests via the more physiologic oral route. Furthermore, until the mechanism of reduction in sensitization occurring with co-administration of intact BLG with protein digests is fully elucidated, it remains only tempting to speculate that administration of mixes of intact and digested food allergens might turn out to be advantageous in the induction of neonatal oral tolerance over completely hydrolyzed or intact forms. Such knowledge may ultimately contribute to our understanding of the optimal form and timing of introduction of breast milk substitutes and complementary foods in order to prevent food allergies.

References

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