

WIDENING SENSITIZATION SPECTRUM THROUGH CARBOHYDRATE PANEPITOPES - A HYPOTHESIS

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SUMMARY: Cross-reactive carbohydrate determinants (CCD) differ from classical peptide epitopes because their cross-reactivity is not restricted to a protein family or domain. They can be considered as panepitopes. Antigen presenting cells (APC) express membrane receptors for IgE. APC-bound IgE are able to widen the patient's sensitization spectrum through cross-binding of allergens belonging to the same protein family or domain. In the case of carbohydrate panepitopes the same mechanism could induce a much larger array of new sensitizations than peptide epitopes can do.

Key-words: Cross-reactive Carbohydrate Determinants - CCD - Panepitopes, cross-reactivity - IgE - Sensitization process

Carbohydrate chains borne by glycoproteins are a potent source of IgE synthesis (1). The nature of the sugars, and their sequences, greatly vary among these glycans (2). But some of them share common features and are able to bind to the same anti-carbohydrate IgE molecules. These cross-reactive structures are now well studied among allergenic products, such as pollens, and are referred to as CCD or Cross-reactive Carbohydrate Determinants (3).

Cross-reactivity is a general property of IgE antibodies. Unspecific binding of IgE is possible as long as cross-reactive epitopes share a minimum level of homology (4). In the case of peptide epitopes, cross-reactivity is restricted to members of a same protein family: for example, birch pollen and apple contain allergens belonging to the PR-10 protein family (ie. Bet v 1 and Mal d 1, respectively) (5). Sometimes, the homology is more concentrated and it applies only to a protein domain: for example, Pers a 1, a chitinase from avocado pear, cross-reacts with Hev b 6.01, a barwin-like protein found in hevea latex, through the hevein domain they have in common although these allergens do not belong to the same protein family (6).

CCD can give rise to a wider cross-reactivity than peptide epitopes because the spectrum of cross-reactive glycans is neither restricted to a defined protein/domain

family, nor to close organisms. For example, the carbohydrate chain found on bromelain, a plant cysteine protease from pineapple, can cross-react with Api m 1, an insect phospholipase from honeybee venom (7).

Why a protein is an allergen is greatly unknown. Even the mechanisms the antigen presenting cells (APC) use to catch some proteins in order to signal them as allergens to T lymphocytes have been poorly studied (8). A role for specialized membrane receptors located onto APC could be suspected because such sensors constitute the first defense line in many organisms like plants and insects. For example, Toll-like receptors have been shown to play a major role in innate immunity mechanisms (9). But these molecules sense danger with a rather low specificity: they have affinity for a molecular pattern, a signature less defined than an IgE epitope.

Recently, the presence of cell receptors for IgE onto APC was demonstrated (10). Although these receptors slightly differ from those found on mastocytes or basophils, their affinity for IgE is high and APC do bear IgE linked to these receptors as soon as the priming phase of an immune response results in IgE synthesis.

Binding of IgE onto APC has a significant consequence: APC are now able to recognize more efficiently the allergen than innate immunity probably can. And this APC's function gain turns to an amplification of the immune response dedicated to this allergen (11).

But IgE binding onto APC generates another important immune consequence : because IgE are not strictly

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specific for a given epitope (a given allergen), other epitopes (or allergens) with a sufficient level of homology can also bind to the same IgE. This cross-binding can then lead to a facilitated presentation to T cells of otherwise poorly immunogenic allergens. For example, a patient allergic to birch pollen has APC bearing anti-Bet v 1 IgE: these APC can efficiently bind an homolog allergen, like Mal d 1 from apple, and can prime an immune response to this apple allergen. This situation, called pollen-food related allergy, clearly shows that sensitization to birch facilitates the priming of another immune responses (12): so IgE binding onto APC can widen the patient's sensitization spectrum.

The more homologous the allergens the patient comes in contact to, the greater the chance that this mechanism operates. Some protein families are known to give rise to such multi-sensitizations and their members have been called "panallergens": profilins, tropomyosins, lipid-transfer proteins, etc. (13).

As explained above, CCD are even wider cross-reactive structures than peptide epitopes of panallergens: they clearly correspond to "panepitopes".

Anti-CCD IgE do not differ from anti-peptide IgE : they both bind to APC IgE receptors. And they both are

able to expand the immune response to the allergens they are dedicated to. But a major difference can be inferred from the larger cross-reactivity of anti-CCD IgE in comparison to that of anti-peptide IgE: anti-CCD IgE have the potential to cross-bind many more diverse allergens than classical anti-peptide IgE. Such sensitization widening could thus encompass glycoprotein allergens which do not belong to the same protein/domain family and which come from very distant organisms.

The following hypothesis is thus suggested: cross-binding of carbohydrate panepitopes to IgE on APC is a powerful means to widen the sensitization spectrum farther than the classical protein/domain family limits. figure 1 depicts how it could work.

Demonstrating this mechanism could explain why so many patients show in vitro positive results to very different allergenic products (14). It could also reconcile the discrepancy between these frequent positive data and the apparent absence of clinical impact of CCD: allergens sensed through CCD cross-binding by APC could give rise to new anti-CCD IgE rather than to new anti-peptide IgE, a situation leading to a limited diversity of IgE on mastocytes and to a poor in vivo reactivity.

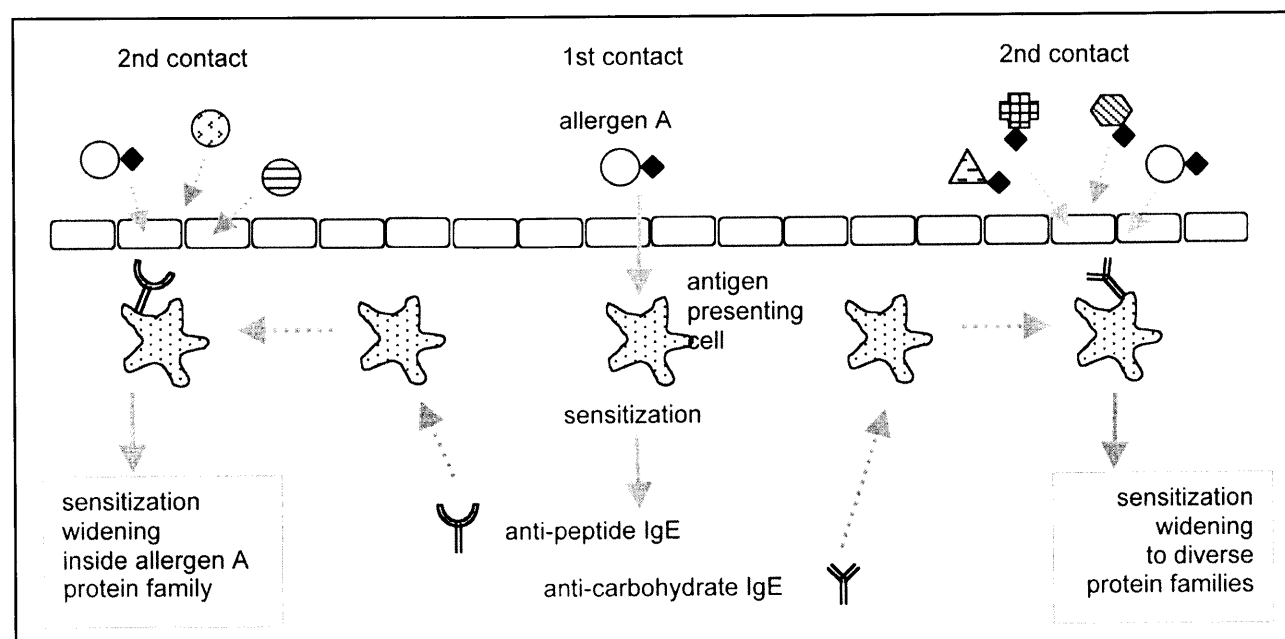


Figure 1: Carbohydrate panepitopes and widening of sensitization spectrum.

Sensitization to allergen A induces the synthesis of IgE which ultimately bind onto antigen presenting cells (APC). This binding leads to an amplification of the immune response next time allergen A comes into contact with these IgE-loaded APC. The same mechanism offers a means for widening the patient's sensitization spectrum if another allergen is able to cross-bind to the same IgE than allergen A on APC (2nd contact on the left side of the figure).

Cross-binding of a carbohydrate panepitope leads to a possibly more widened spectrum of new sensitizations than in the above situation : sensitization widening is not restricted to the molecular family which allergen A belongs to (2nd contact on the right side of the figure).

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PRESS RELEASE

Could you have asthma?

MILWAUKEE - The ongoing cough you can't get rid of could be a signal that you have asthma, according to the American Academy of Allergy, Asthma & Immunology (AAAAI). Asthma is a chronic lung disease that affects 20.3 million people in the United States. It accounts for approximately 14.5 million missed work days for adults and 14 million missed school days for children annually.

For people who have asthma, the air flowing in and out of their lungs may be blocked by muscle swelling and squeezing. Symptoms of asthma include cough, chest tightness, shortness of breath and wheezing.

Ask yourself these questions:

For you:

- Is there a family history of asthma or allergies?
- Are you constantly short of breath and wheezing?
- When do you notice your symptoms - when you have a cold, when you are exercising or around allergens, such as pollen, mold and animal dander?
- Are you missing work because of symptoms?
- Is coughing and wheezing keeping you up at night?

For your child:

- Does your child cough, wheeze (a rattling sound when they breathe), have chest tightness or shortness of breath?
- Does your child cough or wheeze with play, exercise, laughter or during temper tantrums?
- Is your child missing school because of symptoms?
- Is coughing and wheezing keeping your child up at night?
- Is there a family history of asthma or allergies?

If you are experiencing symptoms and they are keeping you from work, school or normal activities, you should consider talking to a doctor to see if you have asthma.

"Every person has their own triggers," said Jonathan Corren, MD, member of the AAAAI's Quality of Care for Asthma Committee. "If you have asthma, you can minimize your symptoms by avoiding the factors that trigger your symptoms and by working with your allergist/immunologist".

An allergist/immunologist is a physician specially trained to manage and treat allergies and asthma. To help prevent symptoms, he or she will work with you to figure out your asthma triggers and develop an appropriate management plan, including developing environmental controls and prescribing medication if needed. To find an allergist/immunologist in your area or to learn more about asthma, call the AAAAI Physician Referral and Information Line at 1-800-822-2762 or visit the AAAAI Web site at www.aaaai.org. The American Academy of Allergy, Asthma & Immunology is the largest professional medical specialty organization in the United States, representing allergists, asthma specialists, clinical immunologists, allied health professionals, and others with a special interest in the research and treatment of allergic disease. Established in 1943, the AAAAI has nearly 6,000 members in the United States, Canada and 60 other countries.