

Highlights of the 8th Drug Hypersensitivity Meeting: Amsterdam, April 19–21, 2018

Drug hypersensitivity is a worldwide health problem that has gained importance in the last years due to the increased number of patients labeled as drug allergic, especially to antibiotics, and to the onset of allergy to new drugs such as biologicals and chemotherapy. The 8th Drug Hypersensitivity Meeting (DHM), organized by the European Academy of Allergy and Clinical Immunology (EAACI), took place in Amsterdam in 2018. DHM8 brought together international experts from different disciplines, including allergists, dermatologists, pharmacologists, immunologists, biologists, chemists, and toxicologists, for exchanging their valuable knowledge. The aim of the meeting was to progress in the understanding of the underlying mechanisms and to improve the diagnosis and management of drug hypersensitivity. The attendees of this meeting updated the state of the art of the old challenges in drug hypersensitivity and agreed on the best way to address the new ones, as well as on to discuss all controversial aspects.

Inspiring discussion arose about the mechanisms involved in IgE-mediated reaction and T cell-mediated drug hypersensitivity reaction (DHR). For T cell-mediated reactions, the interest focused on the

understanding of drug interactions with the immune system, hapten processing, and presentation, according to the different hypotheses (hapten theory, pharmacological interaction [p-i] concept, altered peptide repertoire, and danger signal) (Figure 1). Each of these mechanisms displays their own strengths and limitations in explaining the mechanisms of DHR. Although some of these mechanisms seem to be linked to specific drugs, such as altered peptide repertoire and abacavir, they are not necessarily mutually exclusive, and they can even work synergistically. Actually, some drugs can stimulate T cells through hapten-protein conjugates, inducing mainly mild exanthemas, but also through noncovalent interaction with specific human leukocyte antigen (HLA) molecules causing liver damage, such as betalactams and sulfamethoxazole.¹

The way drugs are presented, and the influence of HLA molecules was also highlighted. Using HLA-B*57:01-mediated hypersensitivity to abacavir as a model system, it was suggested that the T-cell polyclonal response to abacavir involves multiple subsets, including T cells that recognize self-peptide/HLA-B*57:01 complexes and cross-react with viral peptide/HLA-B*57:01 complexes

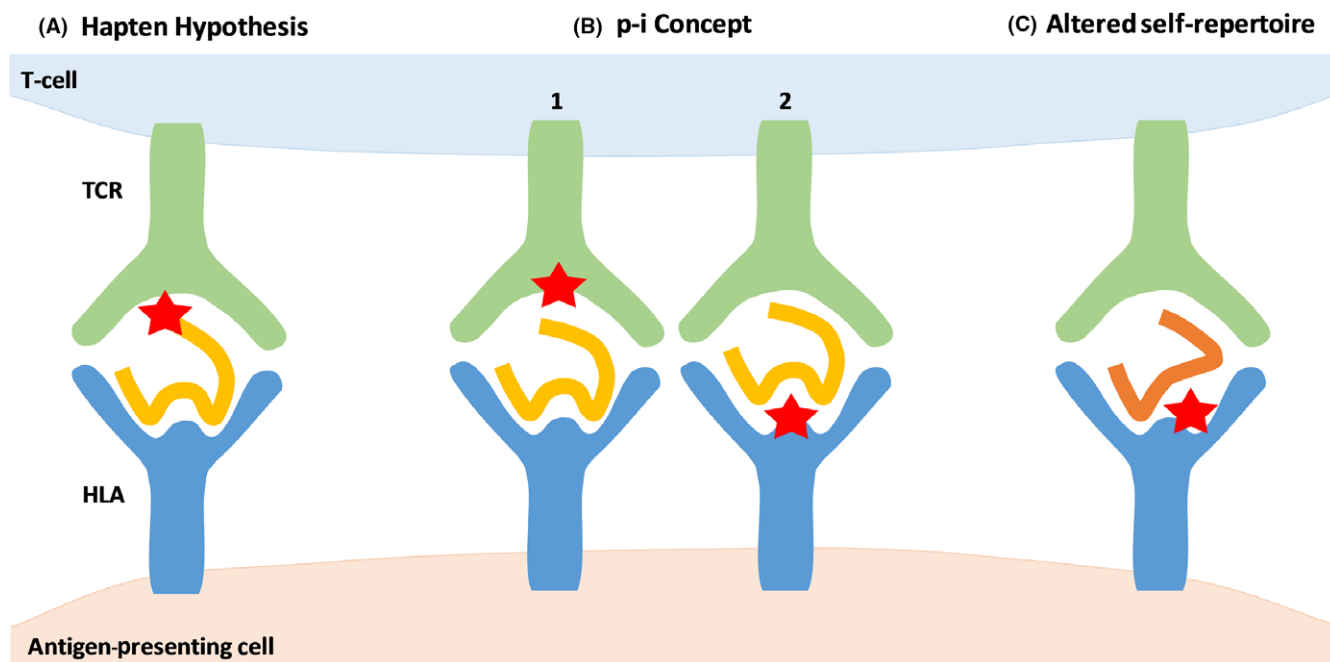


FIGURE 1 Scheme representing the mechanisms of drug presentation to T cells. A: The hapten is covalently bound to a peptide and presented according to the hapten hypothesis. B: Pharmacological interaction (p-i) concept: (1) The T-cell receptor (TCR) molecule itself is modified in the site of human leukocyte antigen (HLA) interaction or (2) the HLA molecule itself is modified in a region exposed to the TCR. C: The drug binds to the peptide binding groove of empty HLA in endoplasmic reticulum altering the specificity of the molecule, resulting in presentation of novel peptides, as in the altered self-repertoire hypothesis [Colour figure can be viewed at wileyonlinelibrary.com]

due to similarity in T-cell receptor (TCR) contact residues. Other important aspects in the onset or enhancement of DHR are risk factors related to TCR repertoires.² It was discussed that an individual may be predisposed to develop DHR by the availability of specific TCR repertoires, the dysregulation of co-inhibitory mechanisms controlling naïve and memory T-cell responses, and the lack of resident Tregs effectively controlling the hypersensitivity response. The analysis of other risk factors will be required to fully define individual predisposition to DHR. The genetic polymorphisms and epigenetic factors involved in these reactions were also widely discussed. Each year, new HLA associations with severe DHR are identified, and to date, there is no general rule for predicting susceptibility.³

One of the new challenges presented in this meeting was the role of exosome-mediated antigen presentation during antibiotic treatment. During the therapy to eradicate *Helicobacter pylori*, a significant number of degraded bacteria is absorbed by the small intestine and processed by antigen-presenting cells. These bacterial components can be found in serum exosomes and have the ability to induce a specific cell-mediated immune response with skin manifestations, leading to confusion with DHR.⁴ Finally, new techniques such as live imaging were presented as new potential tools to study cell kinetics of cutaneous immune cells. In an animal model of contact dermatitis, the intravital cell movement analysis in real time

provided evidence of how cutaneous immune cells interact *in vivo*. In future, this technique might facilitate the *in vivo* observation of the deep layers of the human dermis.⁵

Regarding the mechanisms involved in IgE-mediated reactions, the meeting mainly focused on anaphylaxis (Figure 2). The covalent binding of the hapten to proteins is not sufficient to induce the cross-linking of IgE, as the distance between epitopes and the density of IgE in the surface of mast cells and basophils is crucial in this process. On the other hand, several investigations identified a new receptor, MRGPRX2, that can induce IgE-independent degranulation of mast cells. This mechanism could explain some types of anaphylaxis.⁶

From a clinical point of view, the concept of precision medicine was extensively discussed, although we are far from reaching a consensus. Importantly, there is no agreement on a unique classification for DHR able to include all identified phenotypes and endotypes. Regarding immune-mediated DHR, it is difficult to establish a cutoff time for differentiating immediate (IgE-mediated) and nonimmediate (T cell-mediated) reactions, which have important implications in diagnosis. The situation is even more confusing in non-immune-mediated DHR, as those induced by nonsteroidal anti-inflammatory drugs (NSAIDs) where frequent phenotypes such as “blended reactions” and NEFA (NSAID-exacerbated food allergy) are not included in classical classifications.

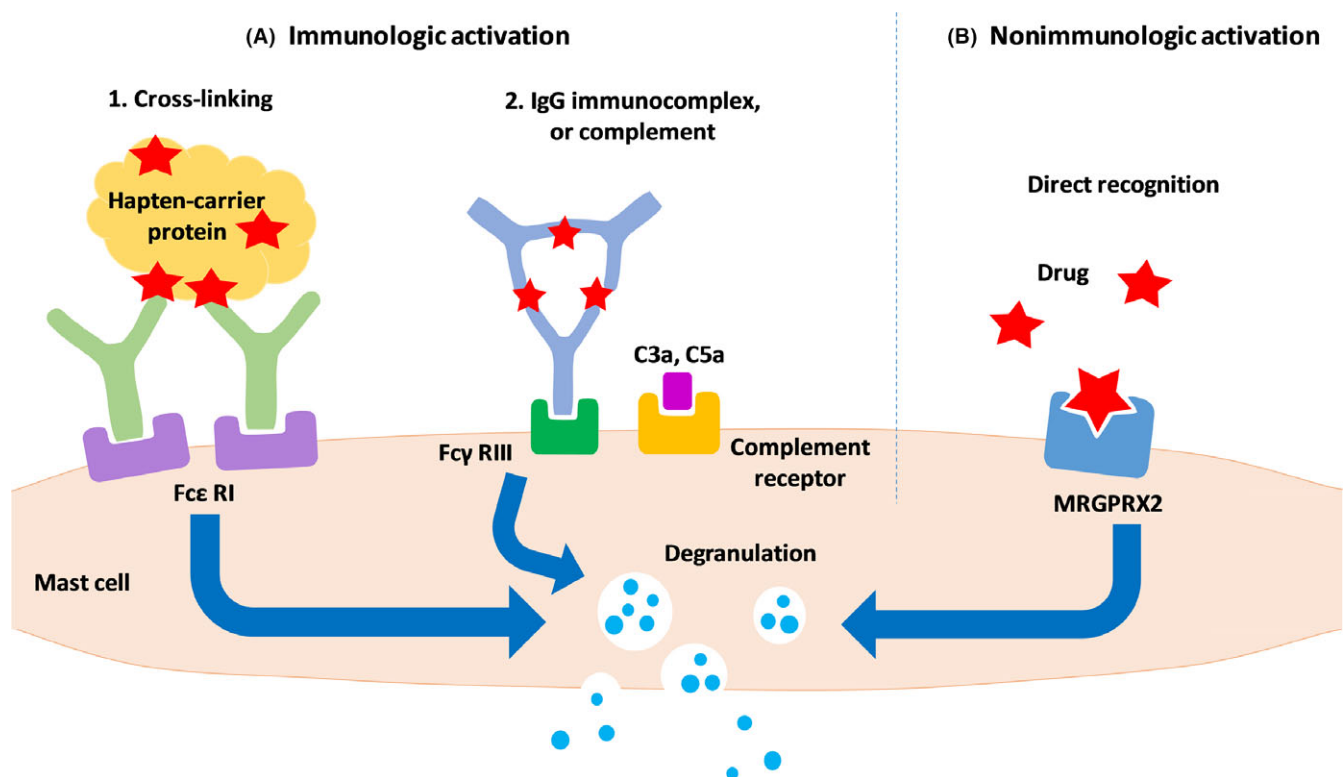


FIGURE 2 Mechanisms of mast cell activation by drugs. A: Immunologic activation: (1) degranulation process by IgE-mediated activation is induced by the recognition of the covalent drug-carrier protein adduct by two adjacent molecules of specific IgE simultaneously (cross-linking process). (2) Degranulation can be also induced by the formation of IgG immunocomplex or by specific recognition of complement molecules. B: Nonimmunologic activation: Degranulation process is activated by the recognition of some drugs by the mast cell surface receptor MRGPRX2 [Colour figure can be viewed at wileyonlinelibrary.com]

The role of *in vitro* diagnostic tests was discussed in detail, especially basophil activation test (BAT). Although BAT seems a promising tool for diagnosing immediate reactions, further technical and clinical validation is needed for its implementation in the routine practice. Moreover, it was discussed the need for developing *in vitro* tools to predict the immunogenicity of drugs before commercialization. In this regard, preliminary studies examined T-cell priming with drugs associated with HLA risk alleles, showing that the priming of T cells with certain drugs is skewed toward donors expressing specific HLA alleles.⁷

Regarding *in vivo* diagnosis, it was highlighted the need to incorporate allergy testing into antimicrobial stewardship and its impact on antibiotic prescription. Currently, to perform an accurate delabeling of betalactam allergy constitutes a challenge for physicians. It was discussed the need for a risk stratification to decide the safest diagnostic approach and the best alternative medications.⁸

Finally, there were different presentations that analyzed the best approaches to manage patients with DHR. It was discussed that “treating through” might be an option for patients with mild exanthemas, potentially induced by viruses. Conversely, drug desensitization is an established method in patients with chemotherapy or biological hypersensitivity. However, a drug provocation test prior to the desensitization process in patients without severe reactions might help to exclude DHR, and to avoid unnecessary procedures.⁹

This meeting demonstrated the great interest of the scientific and clinical community in DHR, and the high degree of uncertainty faced by physicians in the management of these patients. The DHM 2018 paved the way for understanding the underlying mechanisms of DHR, with the aim to develop quicker and safer diagnostic and therapeutic methods for the patients.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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