

LETTER OPEN ACCESS

The Complex Nomenclature of Allergic Diseases and Hypersensitivity Reactions: An Addendum to the EAACI Position Paper

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To the Editor,

We read with great appreciation the EAACI position paper, in which Jutel et al. [1] included T-cell subpopulations (type IVa, b and c reactions), the role of barrier damage (type V), the importance of metabolic alterations (type VI) and direct effects of various chemicals (type VII) in the novel nomenclature for hypersensitivity reactions. While we fully agree with their proposed new classification based largely on effector mechanisms, we recommend extending the model with initial and central phases and a more detailed description of the p-i (pharmacological interaction with immune receptors) mechanism (Figure 1).

Even in their initial phases, some hypersensitivity reactions can be distinguished by the characteristic adjuvant signals that trigger dendritic cell (DC) activation (Figure 2). An encounter with the antigen is often associated with concurrent infections and damage to self-cells, so pattern recognition receptor signalling in DCs can be involved in the development of most hypersensitivity reactions. Recent discoveries have highlighted that barrier damage contributes to immune activation (type V) [2], but in many cases, it is the allergen exposure itself that induces

barrier disruption and alarmin release leading to DC activation and consequent T2 immune responses [3]. Therefore, the early events of type V, type I and type IVb reactions can overlap. Tissue resident innate lymphoid cells (ILCs) serve as sensors of epithelial-derived alarm signals and key determinants of the cytokine microenvironment. In metabolism-induced immune dysregulation, the activation of DCs is a complex and not fully explored process. Immune modifying metabolites, mediators from stressed and hypoxic adipose tissue, as well as from impaired gut microbiota may also be engaged in promoting dominantly T3 immune responses (Figure 2).

In the central phase of the response, differently stimulated DCs activate naïve T cells in secondary lymphoid tissues/organs. Depending on both peripheral and central tissue-derived factors, T-cell receptor signal strength, and costimulatory receptor signalling, follicular helper T cells (Tfh) or conventional helper T cells (Th) differentiate at the expense of each other [4]. Following this separation, the dominantly activated T-cell type determines the polarisation of the effector response, causing either Tfh-regulated antibody production and thus type I–III reactions or Th-cell-mediated effector T-cell-dependent type IV

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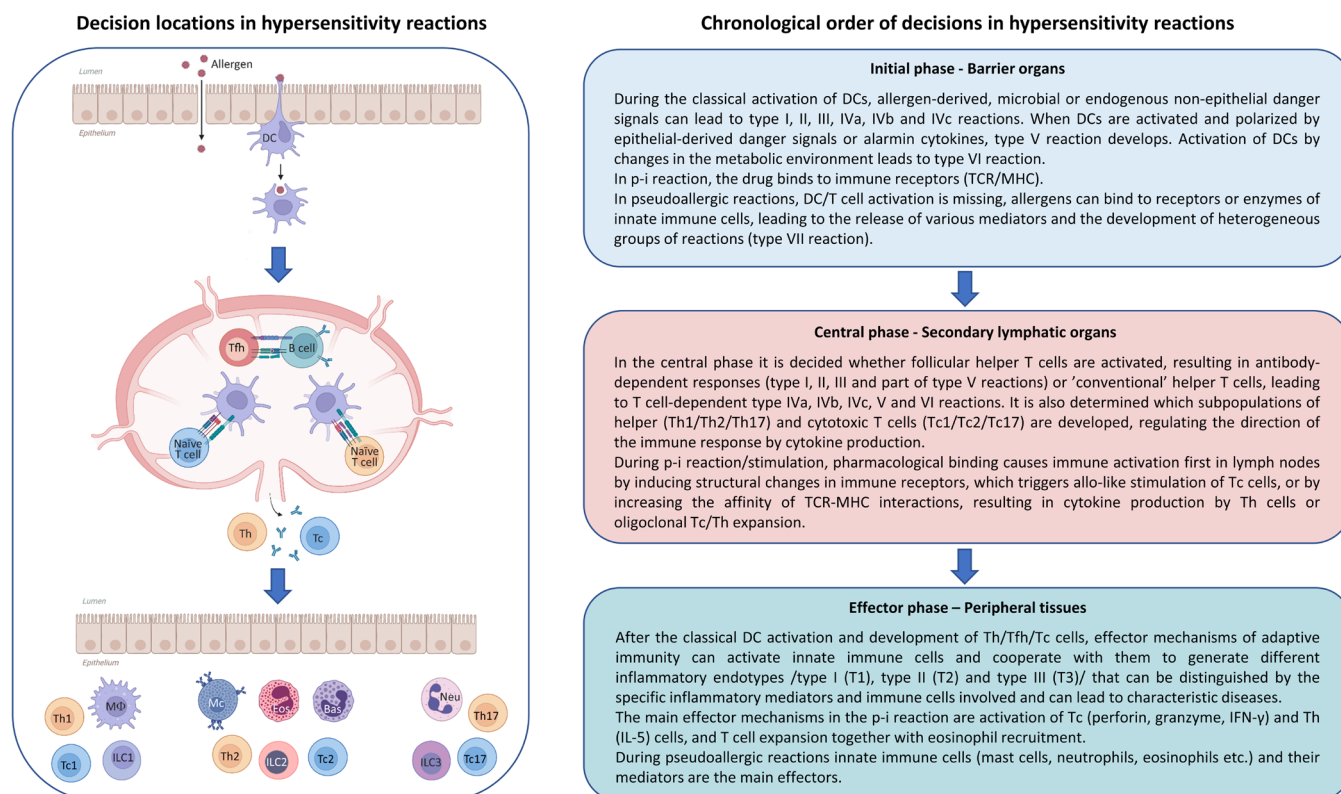


FIGURE 1 | Novelty of the complex nomenclature of hypersensitivity reactions. The classification of the complex development of hypersensitivity reactions, that is, not only the effector mechanisms but also the initial and central phases, allows the identification of the location and chronological order of decisions during the immune response. The new proposal emphasises the fundamental influence of the tissue environment on the activation and immune response-polarising capacity of DCs in the initiation phase and also demonstrates how the lymph node environment in the central phase regulates the decision on the development of humoral or cellular responses and the direction of immune responses (T1/T2/T3 inflammatory endotypes). The complex nomenclature also introduces the main steps of the p-i reaction in the tissues and lymph nodes. The graphical part mostly focuses on classical DC activation-type reactions.

reactions [5]. At the same time, the properties of the adjuvant-like substances and the cytokine environment determine the further polarisation towards the Th1/Th2/Th17 subtypes or the corresponding Tfh subpopulations into groups 1/2/3. Similar to helper T-cell subtypes, after the intracellular appearance of allergens, subpopulations of cytotoxic T cells, Tc1/Tc2/Tc17 are also activated depending on the conditions of DC-mediated presentation and the cytokine milieu (Figure 2). However, due to the parallel reactions occurring in multiple follicles and the subsequent tissue damage induced by effector functions, antibody- and cell-mediated symptoms may coexist.

In addition to the previously mentioned classical activation of DCs and T cells, the p-i mechanism is an unconventional T-cell stimulation that was discovered in the context of drug hypersensitivity. The drug stimulates MHC and/or TCR by non-covalent direct binding, resulting in structural or affinity changes in the receptor. These can lead to allo-like activation of cytotoxic T cells, cytokine release, and oligoclonal T cell expansion. A unique feature of the p-i mechanism is that no sensitisation phase is required and it can be predicted by determining the structure of the immune receptors. The p-i concept, alongside the classical hapten concept, has contributed greatly to the understanding of drug hypersensitivity reactions and is now proposed to be considered as a separate entity similar to the pseudoallergic reaction (Figure 2) [6, 7].

In conclusion, we believe that the integration of the afferent and central immune mechanisms, as well as the p-i reaction into the nomenclature of hypersensitivity reactions allows for the differentiation of hypersensitivity responses according to spatiotemporal characteristics, emphasises the fundamental role of peripheral tissues not only in the initiation but also in the determination of hypersensitivity reactions, and demonstrates our knowledge of immunological decision-making points. This way we can appreciate the overlapping, promiscuous and sometimes redundant nature of the various mechanisms of hypersensitivity reactions in their complexity and that several of them may be involved simultaneously in different disease endotypes.

Author Contributions

Conceptualisation, writing – original draft preparation, visualisation: Andrea Szegedi, Zsolt I. Komlósi, Gábor Koncz, Attila Bácsi. Review and editing: all the authors. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

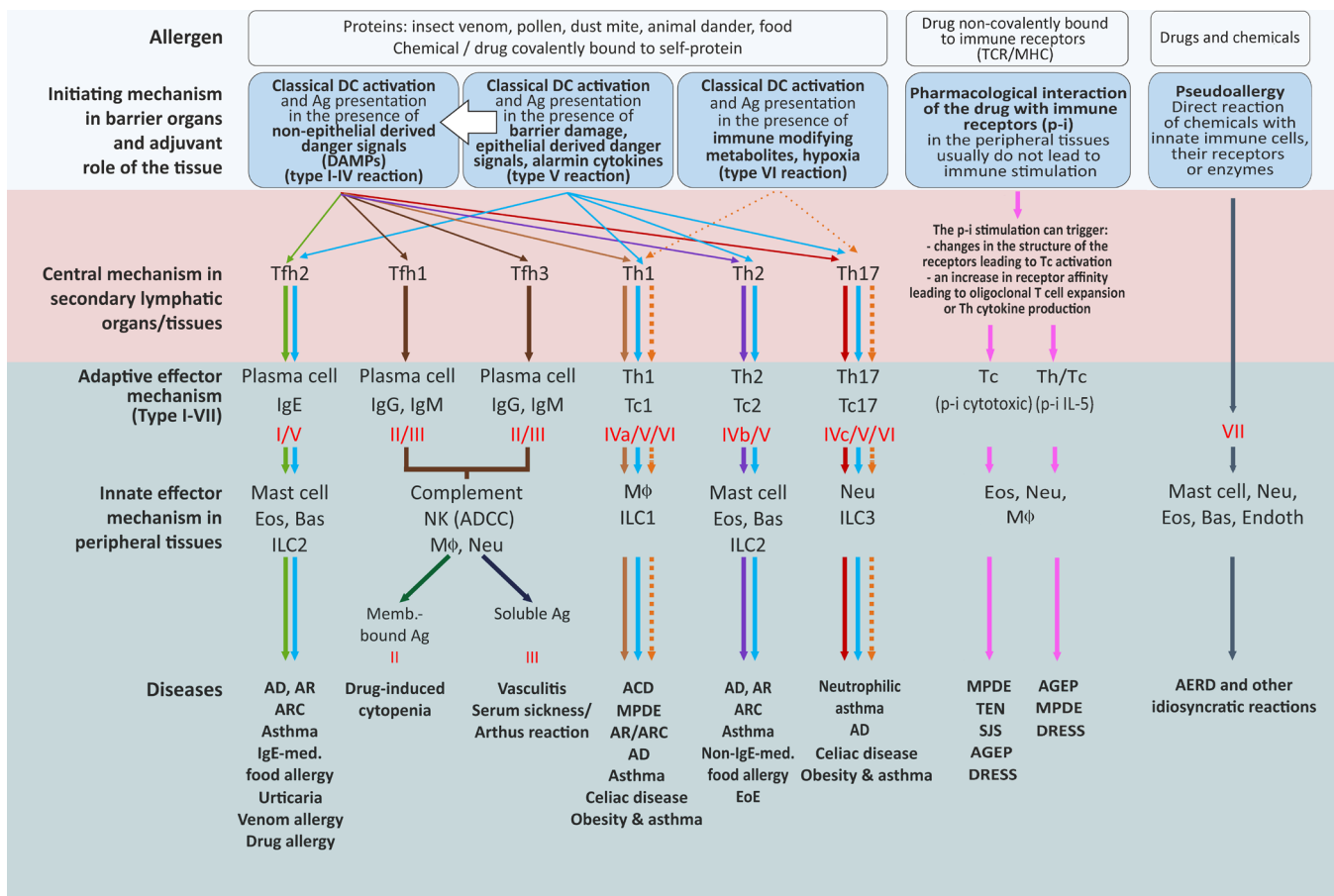


FIGURE 2 | The proposed complex nomenclature of hypersensitivity reactions. Integration of the afferent and central immune mechanisms and the p-i reaction into the nomenclature of hypersensitivity reactions may have several advantages, such as (1), emphasising the fundamental role of peripheral tissues not only in the initiation but also in the determination of hypersensitivity reactions, (2) demonstrating our knowledge of immunological decision-making points that influence whether the response is dominated by cellular or humoral effector mechanisms and the balance between them, (3) demonstrating that different hypersensitivity reactions behind disease endotypes may have common roots/phases, and (4) reflecting the currently sparse knowledge of metabolic, p-i and pseudoallergic reactions compared to classical DC activation mechanisms. For the detailed explanation of this figure, please see the supplementary text of the letter. ACD, allergic contact dermatitis; AD, atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; AERD, aspirin exacerbated respiratory disease; AG, antigen; AGEF, acute generalised exanthematous pustulosis; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; Bas, basophil; DAMP, damage-associated molecular pattern; DC, dendritic cell; DRESS, drug reaction with eosinophilia and systemic symptoms; Endoth, endothelial cell; EoE, eosinophilic oesophagitis; Eos, eosinophil; Ig (E,G,M), immunoglobulin (type E,G,M); ILC1/2/3, innate lymphoid cells type 1/2/3; MPDE, maculopapular drug eruptions; Mφ, macrophage; Neu, neutrophils; NK, natural killer cell; P-i, pharmacological interaction with immune receptors; SJS, Stevens–Johnson syndrome; Tc1/2/17, T cytotoxic lymphocyte type 1/2/17; TEN, toxic epidermal necrolysis; Tfh1/2/17, T follicular helper lymphocyte; Th1/2/17, T helper lymphocyte type 1/2/17. Type I reaction, antibody-mediated immediate reaction; Type II reaction, antibody-mediated cytotoxic reaction; Type III reaction, antibody-mediated immune complex reaction; Type IVa reaction, cell-mediated T1 reaction; Type IVb reaction, cell-mediated T2 reaction; Type IVc reaction, cell-mediated T3 reaction; Type V reaction, tissue-driven mechanism epithelial reaction; Type VI reaction, tissue-driven mechanism metabolic reaction; Type VII reaction, direct response to chemicals reaction.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.