The new nomenclature by the EAACI – was drug hypersensitivity (p-i) forgotten?

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The EAACI position paper on nomenclature by M Julel(1) is coauthored by 40 (!) scientists and addresses many old and new concepts in connection with allergic and hypersensitivity diseases with the aim to better define and categorize them. Such an undertaking must rest on solid facts and should not omit crucial findings.

Immune stimulation by antigen or not? The authors are focusing on classical, antigen (protein) driven reactions, which are developing based on an interplay of dendritic cells, lymphocytes and other cells to handle an antigen and to react to it (1). Although the authors claim to include drug hypersensitivity (DH), they completely omit the fact that drugs can stimulate the immune system in an alternative, unorthodox way ("p harmacological interaction with i mmune receptors", p-i concept)(2-4). Thereby an initial off target activity of a drug with certain structures of TCR or HLA is followed by complex immune activations, which can result in inflammatory reactions manifested as exanthems, DRESS, SJS/TEN, AGEP (2-4). Various types of p-i can occur together (3, 5).

Problem of cytotoxicity : the cytotoxic functions of T cells as an own category (formerly G&C Type IVc) is omitted and handled as part of a type IVa/T1 reaction: This is problematic:

1. Cytotoxicity plays a role in *all* T cell mediated DH (exanthema, DRESS, AGEP, SJS/TEN) (2, 3) and is often associated with massive eosinophilia (e.g. DRESS). Why is this so? The reason is that both, cytotoxicity and eosinophilia, do NOT arise from a classical antigen driven mechanism (3, 5). E.g., the eosinophilia in DH is not due to the development of a classical Th2/IVb reaction, but is due to a certain type of p-i, which results in massive IL-5 production (5).
2. The unusual induction of cytotoxicity in DH includes also CD4 cells, which are the predominant *cytotoxic* cells in drug induced exanthema (2). Thus, cytotoxicity in DH is not restricted to CD8 and NK cells, as stated (1).
3. Analysis of drug specific T cell clones has revealed that many are cytotoxic, but do not secrete IFNg, or vice versa, many IFNg producing T cells are not cytotoxic.

New classification: The 1967 nomenclature by G&C promoted an unknown area (immunology) into the clinic; the revised version (G&C I-IV a, b, c, d; (2)) connected T cell reactions with activation of inflammatory cells and different clinical pictures and thus helped to better understand different forms of DH. The proposed new nomenclature (1) tries to combine quite different topics like immune reactivity (I-IV), disposition (V, VI) and pharmacological/toxic actions (VII). Actually, types I-IVabcd(2) were only slightly changed (- I-IVa,b,c) in(1). Thereby the use of the same label (e.g. IVc) for different manifestations (IVc for cytotoxic reactions in(2), but neutrophilic in (1)) programs for misunderstandings.

The main problem of (1) is that unorthodox immunity (p-i) was omitted, and thus DH cannot be explained or classified. As discussed (6), DH like ACD can rely on classical immunity like formation of drug/hapten protein complexes (= a new antigen) and such reactions follow G&C I-IV; But the majority of DH are due

to unorthodox immune reactions (different forms of p-i[3-5]), which do NOT follow G&C! They are labelled separately [4-6], and these unorthodox immune reactions are actually the main reason why G&C needs to be revised[5, 6].

In summary, although DH may not be the main interest of many allergologists, the omittance of unorthodox immune stimulations (p-i) in an official EAACI nomenclature paper, claiming to cover allergy and hypersensitivity, is not understandable. It should be clearly stated that this position paper [1] addresses only antigen reactions but not unorthodox ways of immune stimulations (DH). Surely, unorthodox immune stimulations by drugs, known since > 20 years [2], are still a difficult topic and needs education – but just ignoring these findings is no solution.

Hoping that this critic is considered helpful;

Best regards

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P.S:

The references (e.g. nr 74) do not correspond to the text; this needs to be corrected;

Legend fig 5/line7: ....in a process called \southarmonization haptenation

Word count: 641

References:

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