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REVIEW ARTICLE

Advances and highlights in T and B cell responses to drug antigens

Ruben Fernandez-Santamaria[1] | Adriana Ariza[1] | Tahia D. Fernandez[1,2] | José A Cespedes[1] | Marina Labella[1,3] | Cristobalina Mayorga[1,3,4] | María J Torres[1,3,4,5]

[1]Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA-ARADyAL, Málaga, Spain

[2]Departamento de Biología Celular, Genética y Fisiología, Universidad de Málaga, Málaga, Spain

[3]Allergy Unit, Hospital Regional Universitario de Málaga-ARADyAL, Málaga, Spain

[4]Andalusian Center for Nanomedicine and Biotechnology-BIONAND, Málaga, Spain

[5]Departamento de Medicina, Universidad de Málaga, Málaga, Spain

Correspondence
Cristobalina Mayorga, Research Laboratory-Allergy Unit, Pavilion 5, Basement, Regional University Hospital of Malaga, Plaza del Hospital Civil, 29009 Malaga, Spain.
Email: lina.mayorga@ibima.eu

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Abstract

The immunological mechanisms involved in drug hypersensitivity reactions (DHRs) are complex, and despite important advances, multiple aspects remain poorly understood. These not fully known aspects are mainly related to the factors that drive towards either a tolerant or a hypersensitivity response and specifically regarding the role of B and T cells. In this review, we focus on recent findings on this knowledge area within the last 2 years. We highlight new evidences of covalent and non-covalent interactions of drug antigen with proteins, as well as the very first characterization of naturally processed flucloxacillin-haptenated human leukocyte antigen (HLA) ligands. Moreover, we have analysed new insights into the identification of risk factors associated with the development of DHRs, such as the role of oxidative metabolism of drugs in the activation of the immune system and the discovery of new associations between DHRs and HLA variants. Finally, evidence of IgG-mediated anaphylaxis in humans and the involvement of specific subpopulations of effector cells associated with different clinical entities are also topics explored in this review. All these recent findings are relevant for the underlying pathology mechanisms and advance the field towards a more precise diagnosis, management and treatment approach for DHRs.

KEYWORDS
B cell, basic immunology, drug allergy, T cell

Abbreviations: AGEP, acute generalized exanthematous pustulosis; AX, amoxicillin; APC, antigen presenting cell; BCR, B cell receptor; BL, betalactam; BP, benzylpenicillin; Breg, B-regulatory; CBZ, carbamazepine; CLA, cutaneous lymphocyte antigen; COX-1, cyclooxygenase-1; CTL, cytotoxic T cells; DHR, Drug hypersensitivity reaction; DRESS, drug rash with eosinophilia and systemic symptoms; FasL, Fas ligand; FcεRI, high affinity IgE receptors; FcγR, Fcγ receptor; FDR, fixed drug reactions; HLA, human leukocyte antigen; Gal-9, galectin-9; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSA, human serum albumin; IDHR, immediate drug hypersensitivity reactions; IL, interleukin; MRGPRX2, Mas-related G-protein receptor; IFN, interferon; MDH, multiple drug hypersensitivity syndrome; MPE, maculopapular exanthema; NIDHR, non-immediate drug hypersensitivity reactions; NK, natural killer; NMBA, neuromuscular blocking agents; NSAID, non-steroidal anti-inflammatory drugs; p-i, pharmacological interaction; PAF, platelet-activating factor; sIgE, specific IgE; sIgG, specific IgG; SJS, Stevens-Johnson syndrome; TCR, T cell receptor; TEN, toxic epidermal necrolysis; Tfr, follicular regulatory T; Tfh, follicular T helper; TFG, transforming growth factor; Th, T helper; Tim-3, T cell Ig- and mucin domain-containing molecule; T_{RM}, resident memory T cells; TNF, tumour necrosis factor; Treg, T-regulatory cell.

Ruben Fernandez-Santamaria, Adriana Ariza, Cristobalina Mayorga and M.J. Torres equal contribution.

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1 | INTRODUCTION

Drug hypersensitivity reactions (DHRs) are the third most common cause of allergy. Their prevalence reaches 8% in the general population[1] and is increasing in both adults and children, according to studies in populations from Europe and the United States.[2-4] Their classification is complex, controversial and challenging due to the heterogeneity regarding drugs involved, clinical symptoms and underlying mechanisms, which are not fully understood.[5-8] DHRs are classically classified according to clinical and mechanistic aspects, and more recently based on drug interaction with the immune system. Clinically, DHRs are divided into immediate (<1–6 h) and non-immediate reactions (>1 h) depending on the time interval between drug exposure and onset of symptoms. Although this classification is useful in clinical routine, some controversies exist mainly due to temporal overlap between immediate and non-immediate reaction periods.[9] Based on the mechanism involved, DHRs can be allergic or non-allergic.[10] Allergic reactions are mediated by a specific immunological mechanism and traditionally classified into type I-IV reactions,[11] being types I (IgE-mediated, produced by B cells) and IV (T cell-mediated) the most frequently involved in immediate drug hypersensitivity reactions (IDHRs) and in non-immediate drug hypersensitivity reactions (NIDHRs), respectively.[9,12] Non-allergic or pseudo-allergic reactions include other IDHRs without a demonstrated immune mechanism.[13] Frequently, they are clinically indistinguishable from IgE-mediated ones, as they are produced after drug interaction with inflammatory cells such as mast cells, basophils and neutrophils. The mechanisms involved in non-allergic reactions are based on the over-inhibition of specific enzymes such as the cyclooxygenase-1 (COX-1) (pharmacological effect) in non-steroidal anti-inflammatory drugs (NSAIDs) reactions,[14,15] or on the off-target occupation of receptors such as the Mas-related G-protein receptor (MRGPRX2) on mast cells[16] by neuromuscular blocking agents (NMBAs),[17,18] fluoroquinolones[19] or clozapine.[20] These mechanisms may be determined by how drugs interact with the immune system,[13,14] which could explain differences in drug sensitization, uncommon clinical manifestations, dose-dependent, predictability and cross-reactivity.[13,14] According to this, DHRs are developed through immune/allergic stimulation (hapten hypothesis), pharmacological interaction (p-i) with immune receptors (p-i concept) and non-immunologically mediated pathways (pseudo-allergy, described above). In this review, we focus on DHRs involving the stimulation of B cells and/or T cells.

2 | DRUG INTERACTION WITH THE IMMUNE SYSTEM

2.1 | Hapten hypothesis

This hypothesis proposes that covalent binding of drugs or drug metabolites to endogenous proteins is required to elicit a DHR.[21] Some drugs reported to bind covalently to proteins are betalactam (BL) antibiotics,[22,23] carbamazepine (CBZ),[24] sulfanilamides[25] or pyrazolones.[26] Identifying the exact determinant recognized by the immune system is crucial to understand the mechanism involved and to improve diagnostic methods. A recent study[27] identified an antigenic determinant of clavulanic acid that is responsible for IgE-mediated reactions and able to bind covalently to human serum albumin (HSA) and to activate allergic patients' basophils. Another interesting study has characterized for the first time naturally processed flucloxacillin-haptenated human leukocyte antigen (HLA) ligands presented on the surface of antigen-presenting cells (APCs) that may drive drug-specific T cell responses.[28] Although covalent drug-protein adducts are required to induce sensitization, non-covalent drug-protein adducts have been suggested to induce the effector response in previously sensitized patients.[29]

2.2 | p-i concept

The p-i concept states that drugs or drug metabolites may bind directly, reversibly and non-covalently to immune receptors through different pathways involved in NIDHRs.[13,30] Drugs can directly bind on T cell receptors (TCRs), promoting the activation of T cells without the need for peptide and HLA recognition.[13] Despite the fact that the number of studies that address this topic is limited, those dealing with the potential of the sulphamethoxazole model are the most validated ones.[31] A more recent study found to predominate and public αβTCR clonotype able to directly bind to CBZ and its analogues in NIDHRs.[32]

Other drugs can directly interact with the binding groove of HLA or with the peptide presented in the binding groove, which alters the conformation of peptide-HLA complexes and promotes the expansion and activation of T cells.[33] Drugs such as CBZ[34] and oxypurinol[35] are the most studied ones in this model. Moreover, a recent study detected atabecestat metabolite-responsive T cell clones activated via non-covalent pharmacological binding interaction with HLA, with no requirement for protein processing.[36] Moreover, direct interaction of drug with HLA can alter the regular repertoire of peptides presented by HLA and lead to T cell proliferation.[37,38] This has been confirmed for abacavir, which binds to HLA-B*57:01 and triggers the hypersensitivity reaction.[37] More recently, the metabolite CBZ-10,11-epoxide, but not CBZ, has been shown to induce the alteration of peptides presented by HLA-B *15:02.[39]

Despite these advances and new findings, more studies are needed to fully understand how pathways of drug interaction with the immune system could influence the elicitation of different clinical entities, cross-reactivity, dose-dependence, desensitization responses, and prediction of DHRs.

3 | IMMUNOLOGICAL MECHANISMS IN DHRs

The development of both B cell and T cell responses includes a previous phase of sensitization without clinical symptoms and a later phase of effector response.

3.1 | Sensitization phase

During first exposure, drugs or drug metabolites are presented by APCs through class I or II HLA to TCRs from naïve T cells, which are primed, activated and clonally expanded (Figure 1). In IDHRs, naïve T cells differentiate into T helper (Th) cells with Th2 cytokine pattern (interleukin (IL)-4, IL-5, IL-9 and IL-13). Then, close contact occurs between activated B cells after antigen encounter through B cell receptor (BCR) and activated Th2 cells. This contact via CD40-CD40 ligand causes a cognate activation of B cells that, together with IL-4, induces B cell proliferation, B cell differentiation into antibody-secreting cells, IgE isotype class-switching and release of drug-specific IgE (sIgE) to the bloodstream. These drug-sIgE binds to high-affinity IgE receptors (FcεRI) on basophils and mast cells, leading to IgE sensitization.[40] Beyond IgE-mediated mast cell and basophil sensitization, evidence supports the influence of other mechanisms. In this sense, different studies have shown human mast cell and human neutrophil activation mediated by IgG bound on FcγR,[41,42] which would require a previous IgG sensitization.

In NIDHRs, drug presentation promotes the expansion of Th cells with Th1 cytokine pattern (mostly interferon (IFN)-γ, tumour necrosis factor (TNF)-α, and IL-2). Nevertheless, it has been proven that different Th cells are involved, depending on the clinical entity, such as Th2 cells in maculopapular exanthema (MPE)[43] and drug rash with eosinophilia and systemic symptoms (DRESS)[44,45] or Th17 in acute generalized exanthematous pustulosis (AGEP).[45] The immune system requires at least 7 days in order to prime a new T cell-mediated reaction (usually 2–8 weeks).[46] During the effector response, the time will depend on the clinical entity, with symptoms in MPE taking between 7 and 12 days to appear, and a longer period of time in severe allergic reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or DRESS. These differences could be explained by the drug interaction with the immune system, hapten hypothesis or p-i concept.[13,14,47]

3.2 | Risk factors for hypersensitivity vs. tolerance

Although studies aimed to identify risk factors associated with DHRs have provided relevant information, there is still a lack of knowledge about the factors involved in the critical sensitization phase that leads to a hypersensitivity or tolerance response and that drives towards IDHR or NIDHR[48] (Figure 1). These factors could be related to the generated drug-protein adducts, the drug presentation through

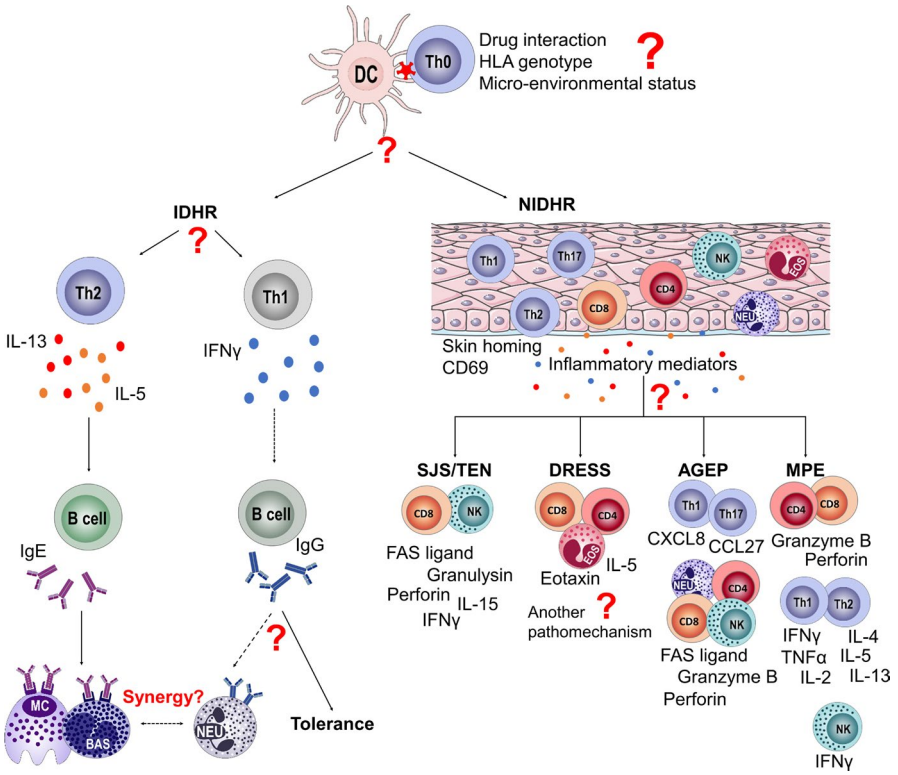

FIGURE 1 Scheme representing the different key points and unsolved questions in the development of drug hypersensitivity reactions (DHRs). Several factors must affect the first interaction of the drug with dendritic cells and its presentation to T cells. There are unsolved questions regarding the factors that first drive towards tolerant or allergic responses and secondly, within the latter, towards immediate (IDHR) or non-immediate (NIDHR) drug hypersensitivity reactions. Once the 'decision' of an IDHR is taken, the second unmet key point is the development of a Th2 response that induces the production of IgE, which binds to effector cells, or the development of a Th1 response. Moreover, unknown factors can lead to the production of IgG, which can bind to neutrophils surface and induce a reaction alone or in synergy with an IgE response. On the contrary, once the 'decision' of a NIDHR is taken, undetermined factors lead to the development of a particular clinical manifestation with specific immunological characteristics

specific HLA molecules, the induction of specific T cells, the IgE isotype class-switching, the role of T-regulatory (Treg) and B-regulatory (Breg) cells, or the existence of some inhibitory check point receptors.[47,49] Independently of the mechanism involved, there is clear evidence that the immune system can efficiently recognize drugs, a process that is followed by a tolerance response in most cases.[50] Regarding this, T $CD4^+$ and T $CD8^+$ cells from healthy donors can efficiently recognize benzylpenicillin (BP)-HSA adducts[51] and BP,[52] respectively. Similarly, amoxicillin (AX)- and clavulanic acid-specific T cells clones have been generated, and identical drug-protein adducts have been detected from both allergic and tolerant subjects.[53]

Moreover, the redox status, a concomitant factor in numerous pathological situations that requires drug administration, can affect drug protein-adduct formation. In this regard, the drug oxidative metabolism could result in chemical modification of endogenous macromolecules, which may activate the immune system.[54] Besides, oxidative stress could affect the formation of large amounts of AX-protein adducts involved in AX adverse reactions.[55]

Although the key cellular and molecular requirements for a B cell to undergo IgE class-switching are known, the reason why some patients develop a Th2 pattern response that induces IgE class-switching, and others do not, remains unclear. Recently, a rare population of IL-13-producing follicular T helper (Tfh) cells that are also the major producers of IL-4, referred to as Tfh13 cells, have been reported. These cells seem to be required for producing high-affinity IgE by B cells.[56] Moreover, an additional study in house-dust-mite allergy has shown that follicular regulatory T (Tfr) cells control Tfh13 cell-induced IgE. The loss of Tfr cells, in addition to causing an increase in sIgE, impairs sIgE affinity.[57] Interestingly, Tfr cells and IL-10 have been recently shown to contribute to the generation of IgE[58]; therefore, the role of Tfr cells seems somewhat controversial. Moreover, these findings have not been demonstrated in DHRs yet. Many efforts have been made for years to understand and establish-specific associations between HLA alleles and DHRs.[43] Despite the fact that a wide variety of studies have reported strong associations between HLA alleles and DHRs, most patients do not have a strong genetic predisposition, which suggests that other factors should be considered. Moreover, contradictory data exist mainly due to the low number of samples in each study, and specific allele frequencies differences between ethnic groups, as recently summarized.[59] Moreover, new studies in European populations have found associations between HLA-B*15:02 and HLA-A*31:01 with severe and mild-moderate DHRs to CBZ respectively,[60] HLA-A*32:01 and DRESS induced by vancomycin.[61] Other studies have suggested an association between HLA-B*13:01 and dapsone and dapsone metabolites hypersensitivity,[62] as well as between HLA-B*58:01 and DHRs to allopurinol in Asian populations, but not in others such as Europeans or Africans.[63,64]

On the other hand, a recent high-density genome-wide genotyping study has shown *GNAI2* as a significant predictor of NSAIDs- induced hypersensitivity in a Spanish population. This association may reflect its influence on the recruitment of immune cells involved in the pathological mechanisms of NSAID hypersensitivity.[65]

3.3 | Effector phase

3.3.1 | Role of B cells in drug allergic reactions

The current knowledge about the involvement of B cells in the effector phase of IDHR is limited to the production of specific antibodies. The mechanisms involved in the production of IgE by B cells are still not well known, and most of the knowledge comes from studies in animal models. In general, professional APCs, such as follicular B cells in lymphoid follicles bearing compatible B cell receptor (BCR), activate after having internalized and processed the drug. After activation, they can migrate to the T cell zone and, through the necessary costimulatory signals, induce naïve Th cell differentiation towards a Th2 phenotype. The contact of these activated Th2 cells bearing appropriate TCRs with activated drug-presenting B cells induces subsequent activation of transcription factors, B cell proliferation, somatic mutation, and production of drug-specific antibodies.[66] In IgE-mediated reactions, as described above, a large proportion of drug-sIgE binds reversibly on FcεRI on mast cells and basophils during sensitization.[67] While IgE is reversibly bound to FcεRI, the K_D is low and, IgE can remain bound to this receptor for extended periods of time in the absence of circulating IgE.[68,69] During re-exposure, drug-carrier adducts interact with at least two adjacent cell-surface bound sIgE (cross-linking) and lead to the activation and degranulation of mast cells and basophils, with inflammatory mediator release[70] leading to urticaria or anaphylaxis.[66] Recent human studies have found evidence that mature B cells that produce allergen-specific IgG (sIgG) would be the previous step to allergen-sIgE B cells.[71,72] In spite of the extreme rarity of IgE memory B cells,[73] non-secreting IgE memory B cells have been found in the blood of allergic subjects,[74] as well as non-circulating IgE-secreting plasma cells in their bone marrow.[75]

On the other hand, evidence of IgG-mediated activation has been demonstrated in different studies as an alternative pathway to the classical IgE-mediated one. IgG-mediated reactions are characterized by the formation of drug-sIgG complexes that, depending on their nature, involve different effector cells (macrophages/monocytes, basophils, mast cells, and neutrophils)[76] able to activate endothelial cells and to induce Fcγ receptor (FcγR)-dependent complement activation.[66] The existence of IgG-mediated anaphylaxis has been demonstrated in mouse models, where drug-sIgG bound to FcγRIII stimulate the release of platelet-activating factor (PAF) by basophils, macrophages, or neutrophils.[77-79] Interestingly, mice studies suggest dose-dependence of IgG-mediated anaphylaxis, unlike IgE-mediated anaphylaxis.[77] However, evidence of IgG-mediated anaphylaxis in drug allergy in humans are scarce. Some studies could demonstrate the presence of IgG anti-IgA in patients with immunodeficiency that developed anaphylaxis after immunoglobulin infusion.[80] Biological agents have been shown to induce anaphylaxis in the absence of sIgE but with high levels of sIgG in patients infused with relatively high doses of the culprit.[81] Finally, a relevant study[42] found a correlation between levels of anti-NMBA IgG, IgG receptors on neutrophils, and neutrophil activation with anaphylaxis severity.

These findings suggest the existence of an IgG-neutrophil pathway in human NMBA-induced anaphylaxis, which may aggravate anaphylaxis in combination with the IgE pathway or underlie anaphylaxis in the absence of sIgE.

3.3.2 | Role of T cells in drug allergic reactions

As part of the adaptive immune system, T cells play a crucial role in the elicitation of DHRs, with important differences depending on the type of reaction. Although T cells are not the main effector cells in IDHRs, their activation can modulate basophil, mast cell and B cell responses by releasing different cytokines and mediators. Regarding NIDHRs, T cells are the common effector cells involved in all these reactions despite the heterogeneous clinical entities, from mild-moderate reactions as MPE and fixed drug reactions (FDR) to the most severe ones as AGEP, DRESS, or SJS/TEN.[12,43,82] The common immunopathogenic mechanism for NIDHRs consists in the activation of $CD4^+$ drug-specific cytokine-secreting T cells and $CD8^+$ cytotoxic T cells (CTLs).[47] Moreover, skin is the most commonly affected organ, although liver, pancreas, lungs, or kidney can be also involved.[83]

Following drug exposure in sensitized patients, naïve T cells, besides drug-specific $CD4^+$ and $CD8^+$ T cells, are activated and, depending on their homing receptors, infiltrate the skin. In this regard, different studies have reported that activated T cells highly express the cutaneous lymphocyte antigen (CLA), related to the skin-homing process by behaving as ligand for E-selectin.[84] Moreover, infiltrating T cells also express a high amount of skin-homing markers such as CCR10, CCR6, and CXCR3.[43] After migrating to the skin, they release several mediators such as granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokines and cytokines, mainly IL-12, IFN-γ and TNF-α, but also IL-4, IL-5, IL-8 or IL-17; this promotes the recruitment of other cell populations, which include T cells, dendritic cells, macrophages, eosinophils or neutrophils, responsible for the skin inflammation.[43,45]

Allergic patients can respond several years after the initial hypersensitivity reaction and under drug avoidance, suggesting that drug-specific memory T cells persist for a long time.[85] Recent interesting findings on the nature of tissue-resident memory T (T_{RM}) cells reveal that, during the resolution phase in the skin, the majority of $CD4^+$ and $CD8^+$ T cells express CD69, which is responsible for retaining them into the tissue.[86] Interestingly, T_{RM} cells can downregulate CD69 and exit the skin, promoting the spread of T_{RM} cells, mainly of $CD4^+$ T cells, which is consistent with the more prolonged tissue residency of $CD8^+$ T cells.[84]

There is clear evidence that drug-specific CTLs are important effector cells in NIDRHs,[87] although with differences in the role of specific T cell subpopulations in each clinical entity. Regarding this, it has been proposed that $CD8^+$ T cells mediate bullous diseases as SJS-TEN or AGEP, whereas $CD4^+$ T cells are more related to skin inflammatory non-bullous diseases as MPE,[43] although controversy exists.[50] A recent article has shown a common contribution of T $CD4^+$, T $CD8^+$ and natural killer (NK) cells in all NIDHRs; however, specific cell subpopulations have been reported to be involved in different clinical entities.[44]

3.3.3 | Role of T cells in specific clinical entities

SJS/TEN

Drug-specific T $CD8^+$ and NK cells mediate keratinocyte apoptosis through the release of different cytotoxic molecules, such as perforin and granulysin and the expression of FAS ligand (FasL).[43,44,88] The release of cytokines such as IFN-γ and IL-15, related to the proliferation of NK cells, has been also associated with the severity of SJS/TEN.[89] The most frequent drugs involved in SJS/TEN are sulphonamides, anticonvulsants and allopurinol.[44,88,90]

DRESS

Clinical entity characterized by high levels of eotaxin and IL-5 in skin lesions (responsible for the recruitment of eosinophils), and by skin infiltration of $CD4^+$ and $CD8^+$ T cells.[90] A recently published work showed that if there is an exposure to antibiotics during the active phase of DRESS, it can trigger a sensitization to the administered drug; which is explained by the massive activation of reactive immune cells.[91] A later manuscript has shown that other drugs such as radiocontrast media, proton pumps inhibitors or analgesics could be also involved in DRESS relapses.[46] These relapses may be associated with unknown mechanisms, and, in most cases, patients tolerate the drug after the complete recovery. On the contrary, relapses with proven sensitization to secondary drugs may trigger a multiple drug hypersensitivity syndrome and therefore, culprit drugs cannot be readministered.[92]

AGEP

It is characterized by the activation and migration of a high number of $CD8^+$ and $CD4^+$ T cells to the skin, mainly with a Th1/Th17 cytokine pattern and high expression of HLA-DR. T cell activation promotes CXCL8, CCL27, and CCR6 secretion by keratinocytes, molecules involved in neutrophil recruitment.[43,88,90,93] Moreover, it has been reported that $CD4^+$Th1/Th2 and inflammatory/cytotoxic NK cells,[44] as well as a high expression of FasL and release of perforin and granzyme B by drug-specific CTLs, provoke keratinocyte apoptosis.[94]

MPE

It is characterized by the infiltration of $CD4^+$ T cells in the dermis, and of $CD4^+$ and $CD8^+$ T cells, with high expression of perforin and granzyme B, at the dermo-epidermal junction zone adjacent to basal keratinocytes.[43,87] New insights into cytokine detection, enzyme-linked immunospot and T cell clone phenotyping have revealed a more complex immunoprofile than previously thought, which is composed of a high amount of Th2 cytokines, a lesser extent of Th1 cytokines, and different regulators of eosinophil maturation and recruitment molecules.[43,50] Moreover, a recently published study

has shown a higher contribution of CD4+Th2 T cells and IFN-γ+ NK cells.[44]

3.4 | Role of Treg and Breg cells

Past and recent studies have demonstrated that different cell subsets of Treg cells play an important role in the immune regulation to tolerate antigens.[8] These cells, which constitute 5–10% of total peripheral CD4+ T cells, have the ability to regulate the response of effector cells, mainly, CD4+ but also CD8+ T cells and B cells, which limits the allergic inflammation.[95] It has been proposed that allergic reactions can be suppressed by different mechanisms through Treg cells, such as the release of inhibitory cytokines (IL-10, TGF-β, IL-35) or the induction of apoptosis and cytolysis (galectin-9 (Gal-9), granzymes A and B). These mechanisms induce metabolic disruption (CD25, cAMP, adenosine receptor 2, histamine receptor 2, CD39 and CD73) and expression of suppressive bound-membrane molecules (CTLA-4, PD-1).[96,97] Related to this, patients with human immunodeficiency virus (HIV) infection, who are characterized by the loss of CD4+ T cells and expansion of CD8+ T cells, present a higher risk of suffering DHRs.[47] This fact could be explained by the loss of Treg cells.[98]

Despite the few number of studies addressing the role of Treg cells in DHRs, it has been suggested that the inadequate function of Treg cells could impair their regulatory role in controlling severe diseases such as SJS/TEN or DRESS. Moreover, a significant reduction in IL-10 producing Treg cells was found in skin lesions during acute and recovery phases of MPE, compared with tolerant subjects.[97] Nevertheless, other molecules and mechanisms could be also involved in the control of number and function of effector cells. The interaction between Gal-9, secreted (among others) by Treg cells, and the T cell Ig- and mucin domain-containing molecule (Tim-3) on the surface of Th1 and Th17 cells induce the apoptosis of these effector cells. Based on this, a recent study has shown a lower number of Gal-9-producing Treg cells during the resolution phase of MPE, compared with tolerant subjects.[97] Altogether, these data suggest the importance of Treg cells for controlling MPE,[88] although more studies are needed in order to understand better the role of Treg cells in allergic diseases (Figure 2).

Breg cells are immunosuppressive B cells that have been described in both mice and humans and which have been receiving increasing attention during the last two decades.[99] Certain subpopulations of plasma cells have been recently included under the umbrella of Breg cells.[100,101] Three main cytokines produced by Breg cells have been reported to contribute significantly to suppressive properties: IL-10, transforming growth factor (TGF)-β, and IL-35.[102] IL-10 not only displays a very potent immunosuppressive capacity but also regulates positively B cell survival and class-switch recombination, as well as plasma cell differentiation.[103,104] Importantly, Breg cells promote the generation of functional Treg cells and suppress effector T cell activation. B cells switching to IL-10-producing B cells was demonstrated in humans in high-dose allergen exposure models and allergen immunotherapy.[104] Moreover, Breg cells also express surface-bound molecules that enable cellular interactions of immunosuppressive nature (eg PD-1, FASL, CD73, CD9, CD1d).[105] However, until now, no studies have demonstrated the role of Breg cells in DHRs (Figure 2).

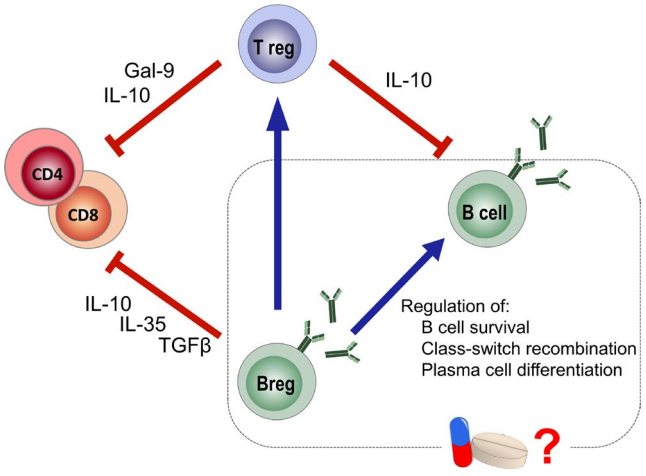

FIGURE 2 Role of T regulatory (Treg) and B regulatory (Breg) cells in drug hypersensitivity reactions (DHRs). Treg cells can modulate the allergic response by different ways: through the release of IL-10 and Gal-9 inhibiting the proliferation of CD4+ and CD8+ T cells and also of B cells. On the contrary, Breg cells have the ability to inhibit CD4+ and CD8+ proliferation through the production of IL-10, IL-35 and TGFβ. Moreover, they can induce the differentiation of Treg cells and regulate the B cell survival, class switch recombination and plasma cell differentiation

4 | CONCLUSIONS

The recent findings highlight the importance of improving our knowledge about drug interaction with immune system, with new evidences of antigenic determinants covalently bound on proteins including HLA ligands. Moreover, non-covalent interaction can be important in the immunological activation, as additional factors as oxidative metabolism of drugs have a crucial role in adduct induction. At the effector response, it has been reported new insights about the B and T cell subpopulations in the elicitation of the response in DHR, including the consequences of the inadequate function of Treg cells that impair the control of effector cells.

Despite these important advances, there are still multiple immunological aspects that remain poorly understood about the induction of either hypersensitivity or tolerance responses, and specifically about the role of B and T cells in these responses. In order to understand the underlying pathology mechanisms of DHRs, it is required to further advance the knowledge of the interaction of drugs with the immune system, the effector cells involved in different clinical entities and the identification of relevant risk factors. This would be essential to achieve in future a more precise diagnosis, management and treatment of DHRs.

Major milestones discoveries:

- New DHR classification based on the interaction between drugs and the immune system.
- New evidence of antigenic determinants covalently bound on proteins and the very first characterization of naturally processed flucloxacillin-haptenated HLA ligands.
- New evidence of non-covalent interaction of drugs with immune system involved in immunological activation: non-covalent pharmacological interaction of atabecestat metabolites with HLA and capacity of CBZ metabolites to induce alteration of peptides presented by HLA.
- New insights into the oxidative metabolism of drugs which can be an important factor in the activation of the immune system in DHRs.
- New associations between DHRs and HLA variants in European populations (HLA-B*15:02 and severe DHRs to CBZ; HLA-A*31:01 and mild-moderate DHRs to CBZ; HLA-A*32:01 and vancomycin DRESS), and in Asian populations (HLA-B*13:01 and DRHs to dapsone; HLA-B*58:01 and DHRs to allopurinol).
- Evidences of the existence of IgG-mediated anaphylaxis (IgG-neutrophil pathway) in humans.
- Involvement of different cell subpopulations in the elicitation of the effector phase in NIDHR, depending on the clinical entity.
- The inadequate function of Treg cells impairs the control of effector cells in NIDHRs by different mechanisms.

Future research perspectives:

- To identify the antigenic determinants (drug or drug metabolite) that are immunologically recognized and their mechanism of interaction with the immune system.
- To understand better the direct interaction between different drugs or drug metabolites with TCRs and HLAs.
- To get a deeper insight into the specific factors involved in drug sensitization, which can trigger a tolerance or a hypersensitivity response, as well as to determine the type of DHR elicited.
- To increase the current limited knowledge about the role of B cells, and especially Breg cells, in DHRs.
- To confirm genetic associations recently established between DHRs and HLA variants.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ORCID

Ruben Fernandez-Santamaria https://orcid.org/0000-0002-0255-4280
Adriana Ariza https://orcid.org/0000-0003-1524-9602
Tahia D. Fernandez https://orcid.org/0000-0003-0625-2156
Cristobalina Mayorga https://orcid.org/0000-0001-8852-8077
María J. Torres https://orcid.org/0000-0001-5228-471X

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