

Role of dendritic cells in drug allergy

Ana B. Blázquez^a, Javier Cuesta^b and Cristobalina Mayorga^a

^aResearch Laboratory for Allergic Diseases, Fundación IMABIS-Carlos Haya Hospital, Málaga and ^bAllergy Department, Fundación Jiménez Díaz, Madrid, Spain

Correspondence to Cristobalina Mayorga, Research Laboratory, Fundación IMABIS-Carlos Haya Hospital, Hospital Civil, Pabellón 5, Sótano, 29009 Málaga, Spain
Tel: +34 951290224; fax: +34 951290302;
e-mail: mayorga.lina@gmail.com

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Purpose of review

Immune reactions to drugs can cause a variety of diseases involving organs such as the skin, liver, kidney, and lung. Although the role of T cells in hypersensitivity reactions to drugs (HDRs) have been demonstrated by several studies, little is known about the role of the innate immune system, served mainly by dendritic cells, in the hypersensitivity response.

Recent findings

Our knowledge about the mechanisms of HDRs is very superficial, and the hypotheses for the involvement of reactive metabolites in many cases are circumstantial and with no evidence. It is not clear which group of HDRs is due to reactive metabolites, nor is it clear the mechanisms by which reactive metabolites can cause allergic reactions. Several studies support the hypothesis that drugs interact differently with dendritic cells from drug-allergic and nonallergic patients, modifying their maturation level. Dendritic cells are also able to metabolize drugs and to present their metabolites to T lymphocytes eliciting a hypersensitivity response. All these findings show that the innate immune system and mainly dendritic cells might play a critical role in drug allergy.

Summary

The interaction of drugs with dendritic cells is an emerging area of research which can bring new insights in order to have a better understanding about the physiopathology of HDRs.

Keywords

dendritic cells, drug allergy, immune mechanisms

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Introduction

Hypersensitivity reactions to drugs (HDRs) usually appear during their clinical use and constitute a serious health problem, as they are an important cause of patient morbidity and mortality [1]. Mechanisms of many HDRs remain poorly understood, and the heterogeneity of the clinical manifestations often discourage physicians from prescribing drugs which may be beneficial who then end up using less effective alternatives. HDRs can be classified as type A reactions that account for 80% of HDR, are predictable and due to the pharmacologic action of a drug; and type B reactions that may occur in a small percentage of patients (15%), are unpredictable, idiosyncratic, and immune-mediated side-effects [2]. HDRs are often considered immune-mediated [3,4] and may affect the skin [5], inducing toxic epidermal necrolysis (TEN) as the most severe reaction, as well as the liver producing hepatotoxicity including liver failure [6,7]. In non-immediate allergic reactions (NIRs) to drugs, mediated by specific immunological mechanisms, the skin is the most frequently involved target organ [8]. NIRs can appear hours, days, or even weeks after drug intake.

In HDRs, a spectrum of clinical entities may appear that includes mild reactions such as maculopapular exanthema (MPE) and urticaria, and other less common but more severe reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) or TEN [9].

Several mechanisms have been proposed: the hapten hypothesis, reactive metabolite hypothesis, and metabolic idiosyncrasy hypothesis. Since 40 years ago, the most commonly accepted is the hapten hypothesis [10] which showed that antigen-presenting cells (APCs) are able to present small molecules to T lymphocytes, after covalent binding to proteins. In-vitro [11] and in-vivo [12,13] studies have demonstrated that some drugs such as betalactams are able to react with proteins producing adducts that are recognized by IgE antibodies or T lymphocytes from betalactam-allergic patients. The innate immune system has received more attention recently, and it may play a critical role in influencing the adaptive immune response [10]; however, little is known about the initial steps involved during HDRs. In this review we examine the latest findings showing the role of dendritic cells in drug allergy.

Drug interaction with the immune system

As stated above, three major working hypotheses for the mechanism of drug interaction with the immune system have been proposed: the hapten hypothesis, the danger hypothesis, and the pharmacological interaction with immune receptors hypothesis.

The hapten hypothesis is based on earlier observations by Landsteiner and Jacobs [14], who reported that small molecules are not immunogenic unless they bind irreversibly to proteins. This small molecule that binds to protein is referred to as a hapten. A classical example of the hapten hypothesis is penicillin-induced allergic reactions [15]. Parker [15] found that the betalactam ring of penicillin reacts irreversibly with free amino and sulfhydryl groups on proteins and patients who are allergic to penicillin have IgE antibodies against the penicillin–protein adduct leading to a severe allergic reaction such as anaphylaxis. Our group has also reported by using in-vitro [11] and in-vivo [12,13] studies that betalactams are able to react with proteins producing adducts that are recognized by IgE antibodies or T lymphocytes from betalactam-allergic patients. In addition to that, with the production of monoclonal antibodies to betalactams, it has been demonstrated that specific recognition of different antigenic epitopes within the hapten-carrier structure [16,17] occurs.

The danger hypothesis, proposed by Matzinger [18], showed that the immune system responds to anything that causes damage to the organism. In this context, a reactive metabolite or the native drug itself can induce cell injury leading to a danger signal that causes dendritic cell activation and the development of HDRs.

The most recent concept, pharmacological interaction with immune receptors hypothesis, is based on the finding that some drugs are able to initiate an immune response through a reversible interaction with the major histocompatibility complex–T-cell receptor complex in the absence of reactive metabolite formation acting as a pharmacological agent [19].

Although it is believed that reactive metabolites rather than the native drug are responsible for many HDRs [20], in most of the cases the evidence is circumstantial. One important property of reactive metabolites is that they covalently bind to proteins or other macromolecules, but we do not know whether there is a direct correlation between the amount of covalent binding with the risk that a drug causes HDRs.

Drug metabolism

Once drugs are ingested, they are metabolized, and presumably this process acts as a self-defense mechanism

Key points

- Dendritic cells are able to metabolize drugs and present their metabolites to T lymphocytes.
- Several studies have shown that some haptens or their metabolites trigger dendritic cell maturation and increase the specific proliferative response.
- There is an important cross-talk between both the innate and the adaptive immune system and that is critical for the immunopathology of drug allergy.
- Virus infection might affect the phenotype of dendritic cells and the nature of the adaptive immune response.

in the human body. Many drugs or their metabolites can form drug–protein adducts which can be processed and presented by APCs to T lymphocytes. Drug metabolism is classically categorized into two major pathways: oxidation and reduction (bioactivation process), and conjugation reactions. The oxidative metabolism is catalyzed by peroxidases, amine oxidase, and flavin-containing mono-oxygenase among others, with the cytochrome P450 (CYP) playing a key role [21], leading to the formation of reactive electrophiles. These metabolites are capable of modifying covalently proteins or nucleic acids recognized by the immune system, and which eventually lead to organ toxicities.

Conjugation reactions include glucuronidation and sulfation, which are catalyzed by uridine 5'-diphosphate-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs), respectively. Acyl glucuronides are able to modify covalently proteins through transacylation, in which process the glucuronic acid moiety is displaced by free thiol, tyrosine or lysine residues [10]. Drug molecules are ultimately eliminated with or without structural changes via biliary or urinary excretion, a process that is facilitated in many cases by active transporters.

Capacity of dendritic cells to metabolize drugs

Dendritic cells exist in different functional states including resting and activated, also known as immature and mature, classically described as the morphological and functional changes associated with their activation by microbial stimuli via toll-like receptor (TLR) [22]. Under steady state, dendritic cells in the peripheral tissue are immature, a phenotype characterized by a low surface expression of costimulatory molecules and chemokine receptors that trigger migration (e.g. CCR7), and an inability to release T-cell-directed immunostimulatory cytokines [23]. Maturation of dendritic cells, as triggered by TLR agonists or a specific antigen, up-regulates the expression of costimulatory molecules and these mature

dendritic cells are able to migrate to draining lymph nodes to present antigen to naïve T cells [23]. It is believed that a danger signal is required to trigger a pathologic response in which the hapten carrier is recognized by the immune system and a humoral or adaptive immune response is generated.

Most haptens are chemically inert and require metabolic activation in order to bind to proteins. The human CYP isoenzymes are known to metabolize small molecular weight compounds to highly reactive species which are able to bind to proteins, which is considered as a prerequisite for the development of a hypersensitivity reaction [24]. Most of the drug biotransformation capability is located in the liver, although other organs, including the skin, also have this function [25^{••},26,27]. It has been recently reported that dendritic cells might metabolize drugs that could influence their outcome in the course of drug allergic events [28]. Sieben *et al.* [29] have shown that CYP isoenzymes are constitutively expressed in human blood monocytes and monocyte-derived dendritic cells. There is a recent study [25^{••}] in which the authors demonstrated that human epidermal keratinocytes express several active metabolic enzymes and transport-associated enzymes and are, therefore, capable of metabolizing and eliminating different xenobiotics.

In the case of hypersensitivity reactions, the drugs or their metabolites must be presented to T lymphocytes by mature dendritic cells or act as danger signals inducing dendritic cell activation [30]. A number of studies have shown the effect of different haptens, mainly present in contact sensitizers, on dendritic cell maturation [31,32]. Similar studies have been performed on drugs as betalactams or sulfamethoxazole, and more interestingly on their metabolites, for instance nitroso sulfamethoxazole [33,34^{••}] showing an induction of costimulatory signaling on dendritic cells [33]. Regarding betalactams, it has been shown that these drugs are a dendritic cells maturation stimulus that are presented to T cells developing a hypersensitivity response [34^{••}], which could be consistent with both the hapten and the danger hypothesis [18]. These findings showed that some drugs or their metabolites trigger dendritic cell maturation and that favors the initiation of a pathological adaptive immune response.

Drug interaction with the innate immune system

The role of T lymphocytes in NIRs has been demonstrated by several studies; and after the interaction with dendritic cells they act as effector cells inducing tissue damage and inflammation [35]. NIRs are mostly Th1 reactions producing IFN- γ , TNF- α , IL-2, [36,37], and the cytotoxic markers, perforin and granzyme B [37,38],

although the levels of these markers may vary depending on the clinical symptoms [36–39].

Over the past years, several authors have investigated the role of dendritic cells in T-cell-mediated responses to haptens [31,34^{••},40,41]. The best studied model is a delayed-type hypersensitivity reaction to nickel [31] demonstrating that this hapten is able to induce dendritic cell maturation leading to a specific T-cell response [31,40].

Recent studies hypothesize that drugs interact differently with dendritic cells in drug-allergic and nonallergic patients and most of them support the evidence that the immunologic mechanisms involved in the interaction between immature dendritic cells (imDCs) and the drug could modify the maturational level of these imDCs and eventually affect the adaptive immune response. Our group has demonstrated that different drugs such as amoxicillin and heparins can induce maturational changes on dendritic cells, leading to an increase in T-cell proliferation in allergic patients but not in tolerant controls [34^{••},41]. Antunez *et al.* [42] reported that iodixanol, a widely used contrast medium, induced maturation of monocyte-derived dendritic cell from patients with delayed reactions to this drug but not from tolerant patients, triggering an increase in T-cell proliferation and cytokine production. These results support the role of dendritic cells in the recognition and cell presentation of different drugs.

An unexplored area is the effect of drugs on different dendritic cell subsets. It has been hypothesized that plasmacytoid dendritic cells (pDCs) are specialized for viral recognition and antiviral responses and that activated pDCs are involved in psoriasiform and lichenoid drug reactions [8]. In addition to that, Sugita *et al.* [43] have recently reported the role of skin pDCs in drug-induced hypersensitivity syndrome (DIHS). They found that pDCs accumulate in the skin of DIHS patients, and the number of pDCs in circulation decreases significantly around the time point of viral reactivation. They speculate that the paucity of circulating pDCs could depress the antiviral activity in patients with DIHS. This hypothesis is supported by the observation that circulating IgG levels are low in DIHS, because pDCs induce B-cell maturation to produce IgG [44]. Since human herpesvirus (HHV)-6 transcripts were detected in the skin of patients with DIHS [35], pDCs may accumulate in this tissue to attack the herpesvirus. In addition, the causative drugs such as anticonvulsants might stimulate fibroblasts and/or endothelial cells to release skin homing chemoattractants for pDCs.

Natural killer (NK) cells are lymphocytes mainly involved in the innate immune system but they can also

participate in effector immune responses, as has been demonstrated in atopy, asthma, and autoimmunity [45,46] and also in NIR to drugs, especially in those with more severe clinical manifestations [2,47,48]. At the initial steps of the hypersensitivity response to drugs, when there is a tight interaction between the innate and the adaptive immune system, it might be critical to distinguish between tolerant and effector responses as well as the nature of the T-cell response. This link can be related to the NK–dendritic cell cross-talk [49,50]. Dendritic cells can activate NK cells by releasing cytokines (IL-2, IL-12, and IL-15) [51], and on the contrary, activated NK cells can induce dendritic cell maturation or imDC death through the production of either cytokines or cytotoxic factors [52,53]. In this way, NK cells regulate dendritic cell homeostasis and thereby the balance between tolerant and immunologic responses [49]. We have recently evaluated the role of NK and NK–dendritic cell interaction in the immunopathological mechanisms of NIR to betalactams showing that, in allergic patients, amoxicillin was able to induce NK activation and production of cytotoxic markers [54^{*}]. Moreover, we observed that activation, proliferation, and production of cytotoxic markers by AX-stimulated NK cells increased in the presence of dendritic cells. The increase of inflammatory NK subpopulation that produces IFN- γ was mainly observed in the presence of amoxicillin-matured dendritic cells. This study supports the hypothesis that the cross-talk between both the innate and the adaptive immune system is critical in the immunopathology of allergic reactions to drugs.

Virus and dendritic cell interaction

An association between drug allergic reactions and viruses has been reported. However, a better understanding of the link between virus–drug interactions and the immune system is needed. Several viruses have been associated with allergic reactions to drugs, including HHV-6, cytomegalovirus, Epstein–Barr virus (EBV), and more recently paramyxovirus. Viruses can interact with the immune system at different points: drug metabolism, drug presentation by dendritic cells to lymphocytes, and cytokine and chemokine production in the effector phase [55].

One of the most important points when evaluating drug-allergic reactions is to discriminate from viral infections since they produce similar clinical manifestations, although there are differences in the mechanisms involved [56]. A well known interaction between drug hypersensitivity and viral infection is the ampicillin-induced rash in patients with infectious mononucleosis when the intake of ampicillin increases the occurrence of rashes by 28.8–69% in adults and by up to 100% in children [57].

The best studied drug-allergy reaction associated with viral infection is DRESS/DIHS, in which the slow resolution has been related with HHV-6 reactivation [58] which is favored by hypogammaglobulinemia that can occur during treatment with certain drugs such as anticonvulsants [44]. Moreover, these drugs can activate monocytes and CD4⁺ T lymphocytes during the allergic reaction, leading to the reactivation of the HHV-6 from a latent infection, thus delaying resolution of DRESS/DIHS [44].

The relation between viruses and drugs in the induction of NIRs is unknown. We have demonstrated that amoxicillin induces a semimature state of dendritic cells and enhances T-cell proliferation [34^{**}]. The fact that in many cases a confirmed NIR shows a negative T-cell proliferation test to a specific drug might be due to the absence of concomitant viral stimulation which has been shown to induce dendritic cell maturation. Preliminary studies with drugs and TLR agonists have shown an increase in dendritic cell maturation and T-cell proliferation only in drug-induced MPE patients during an infectious state (data not published). These data suggest that both the drug and the virus might be necessary in order to mimic the in-vivo immunologic reaction.

Conclusion

There is strong evidence for the generation of reactive metabolites during the biotransformation of a wide variety of drugs, and the general hypothesis is that rather than the native drug, its metabolites are involved in HDRs. However, the mechanisms by which reactive metabolites can cause allergic reactions remain unknown. This suggests that further work is required to enhance our knowledge on the nature of the metabolites potentially involved in HDRs.

Several findings point to an important role of the innate immune system, mainly dendritic cells, in the pathophysiology of drug allergy. It has been reported that some drugs interact directly with dendritic cells affecting their maturational state and increasing the specific T-cell proliferative response. In addition to that, concomitant agents such as viruses may affect the phenotype of dendritic cells and eventually the nature of the adaptive immune response. All of these findings suggest that a better understanding of the dendritic cell activation mechanisms involved in HDRs is needed.

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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