

IMMUNE MECHANISMS OF DRUG ALLERGY

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The majority of adverse reactions to drugs do not involve specific immunologic sensitization (Table 1). Such nonimmunologic reactions include side effects, toxicity, and other pharmacologic effects, and will not be addressed here. Historically, immunologic drug reactions have been described in the context of the Gell and Coombs system (Table 2). This model continues to be useful clinically in certain situations. Indeed, demonstrating the presence of specific IgE to penicillin in the context of an appropriate clinical history has impressive predictive value. This approach, however, has limited use when applied to other drug reactions. For example, the well-known pseudoallergic reactions to nonsteroidal anti-inflammatory drugs (NSAIDs), radiocontrast media, and opiates all may present clinically with immediate urticaria, angioedema, bronchospasm, gastrointestinal distress, and cardiovascular collapse indistinguishable from IgE-mediated anaphylaxis, yet they do not require sensitization and do not appear to be allergenic as haptens or complete antigens.

Clinical serum sickness symptoms that have been generally attributed to the Gell and Coombs Type III (i.e., immune complex) mechanism also may be misleading. For example, cells from patients who have had classic serum sickness reactions (e.g., fever, arthralgia, or erythema multiforme) to the antibiotic cefaclor die *in vitro* when exposed to a metabolized form of the drug, whereas cells from patients without such a history do not die.²³ In addition, immune complexes associated with cefaclor-induced serum sickness have never been identified. This suggests that the serum sickness may be caused by a cytotoxic effect of the drug on cells rather than by an immunologic reaction to the drug. To improve our ability to address these clinical challenges in the future, we must extend our understanding of the mechanisms involved.

By definition, a true hypersensitivity response to a drug requires the development of an immune response to that agent. Such an immune response must

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Table 1. ADVERSE DRUG REACTIONS: CATEGORIES, EXAMPLES

Specific immunologic
Penicillin (anaphylaxis)
Neomycin (allergic contact dermatitis)
Pharmacologic activation of immune mechanisms
Radiocontrast media (anaphylactoid reaction)
Drug-induced autoimmune
Procainamide (lupus erythematosus)
α-methyldopa (hemolytic anemia)
Toxicity (common reaction with overdose)
Theophylline (seizures)
Side effect (common adverse reaction at therapeutic dose)
Pseudoephedrine (insomnia)
Intolerance (uncommon adverse reaction at therapeutic dose)
Antihistamine (headache)
Idiosyncratic
Corticosteroids (psychosis)

be similar to the immune response to any antigen. There are several unique aspects of drugs, however, which make their interaction with the immune system unusual. This article provides an overview of how immune responses develop to antigens and emphasizes the unique features pertinent to the development of drug hypersensitivity. The factors that potentially influence the development of drug allergy are summarized in Table 3.

Unfortunately, little is understood regarding the immune response to drugs; thus, much of this overview is speculative. This article emphasizes several unique aspects of the immune response to drugs, and most importantly, their function as incomplete antigens (i.e., haptens), which cannot trigger hypersensitivity reactions until they become covalently linked to an appropriate carrier molecule.^{13, 25, 35} Any theory regarding the mechanism of drug allergy must also explain the phenomenon that in contrast to the atopic diseases—allergic rhinitis, asthma, and atopic dermatitis—drug allergies develop with the same frequency in atopic and nonatopic individuals.^{2, 46} Although atopy is not a risk factor for

Table 2. IMMUNOLOGIC DRUG REACTIONS CLASSIFIED IN THE GELL AND COOMBS SYSTEM

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From Sullivan TJ: Drug allergy. In Middleton E, Reed CE, Ellis EF, et al (eds): Allergy: Principles and Practice, ed 4. St. Louis, Mosby, 1993, p 1730.

Table 3. POTENTIAL FACTORS INFLUENCING THE DEVELOPMENT OF DRUG ALLERGY

Reactivity as haptens
Ability to bind autologous protein
Variability in drug metabolism
Variability in antigen processing and presentation
Intracellular antigens
MHC I phenotype
LMP polymorphism
TAP polymorphism
Extracellular antigens
Dose and concentration of antigen
Pre-existing drug-specific immunoglobulin on antigen-presenting cell surface
Capacity to covalently bind MHC molecules or T-cell receptor
Variability in T-helper response
Variability in NT-cell response
Patterns of exposure
Concurrent infection

the development of drug allergy, surprisingly, there may be a familial predisposition.⁴ Any mechanism proposed for the development of hypersensitivity toward haptens must provide a mechanism for this genetic predisposition and the tendency to develop multiple drug sensitivities to what are often completely unrelated compounds.

HAPTENS AND ANTIGENS

The most unique aspect of drugs, and what contrasts them to most other allergens, is that with a few unusual exceptions (such as L-asparaginase, insulin, heteroantisera, and clotting factors), they are small (< 1000 d), nonproteinaceous substances. The immune system evolved to primarily and most efficiently recognize large proteins, which it then metabolizes into smaller peptides that ignite the immune response. Antigen specificity is derived from the immune system's recognition of unique antigenic epitopes that bind to receptors either on B lymphocytes (i.e., surface immunoglobulin) or T lymphocytes (T-cell receptors). In contrast, drugs are too small to directly interact with either immunoglobulin or T-cell receptors, and must covalently link to a larger carrier substance, usually a peptide, before they become immunogenic.^{13, 25, 35} Drugs are therefore not antigens by themselves, but rather are termed *haptens*. Most drugs have little or no ability to form covalent bonds with tissue components and therefore are not immunogenic.¹ Some drugs, such as the β -lactam antibiotics, are highly reactive and readily covalently bind to autologous proteins.⁷ Alternatively, other drugs are not intrinsically reactive with autologous proteins, but must be metabolized into a form that can link covalently to the carrier.^{12, 14, 34, 52} For example, the sulfonamides, phenytoin, carbamazepine, dapsone, and rifampin are metabolized by hepatic *N*-acetylation or by cytochrome P-450 *N*-oxidation into their immunogenically active forms. Variations in individual metabolic pathways, such as acetylation rates, may contribute to individual susceptibility toward the development of drug allergy and the familial clustering of drug allergy.^{12, 14, 36, 37} For example, inherited defects in the enzyme that metabolizes arylamines may be responsible for the phenytoin hypersensitivity syndrome.¹⁴ The influence of unique individual pathways in determining susceptibility towards the develop-

ment of drug allergy is somewhat analogous to what is observed with atopic allergy; the familial component involves a nonspecific predisposition toward the development of IgE reactivity to inhalants. Each individual, however, develops a unique pattern of specific IgE reactivity based on individual allergen exposures and immune response (i.e., major histocompatibility) genes. For hapten (i.e., drug) allergy, the familial component may involve genetically determined metabolic and antigen-processing pathways. This would explain the phenomenon of drug hypersensitivity reactions being familial, but specific individual patterns of drug allergy are not necessarily inherited, reflecting individual patterns of exposure, immune response genes, and a putative confounding role provided by the concurrent infection.^{4, 16, 40}

One of the challenges in studying drug allergy is our poor ability to study drugs' haptenized form. Although the contact point(s) between the complete antigenic form of the hapten and Ig or the T-cell receptor presumably includes the drug, these antigen-binding domains also include noncovalent interactions with the relevant carrier molecule. Several issues arise from this concept. First, it becomes impossible to study adequately the immunology of drug allergy without having available the actual immunogenic form of the drug. Although it would be important to know which class of T lymphocytes are responding to the hapten (e.g., $\gamma\delta$ T cells, CD4 lymphocytes, CD8 lymphocytes, or natural killer cells), the phenotype and cytokine repertoire of the responding cells (e.g., type I or II T-helper lymphocytes or cytotoxic cells), and the tissue locations of the responding T cell, it is not feasible without the knowledge of which protein(s) or other carrier the drug is binding to, the tissue source for this carrier, and the structure of the metabolized and haptenized form of the drug. Theoretically, there is nothing to limit a therapeutic's ability to link covalently to one or even a limited number of self-derived carrier proteins. There is the potential for hundreds or thousands of forms of haptenized drug-derived antigens to develop in presumably every tissue of the body, each having different possible immune sequelae. There are additional consequences to this concept that immune responses to drug or hapten actually represent an interaction between the immune system and drugs covalently bound to an autologous protein carrier. Although this concept permits the development of specific, possibly IgE-mediated immunity to the drug itself, this process also may contribute to many of the systemic inflammatory aspects of drug allergy. A specific cytotoxic, cellular, or humoral immune response to a drug that is covalently bound to a tissue substrate clearly has the potential for producing innocent bystander damage to that tissue.^{7, 32} For example, immune responses to drug covalently bound to cutaneous tissue or erythrocytes can lead to drug-induced cutaneous eruptions or hemolytic anemias, respectively. Alternatively, because the self-protein becomes a component of the immunogenic form of the complete drug or hapten antigenic complex, the immune response may develop against the carrier protein, bypassing the usual mechanisms of tolerance toward self and leading to the development of autoimmune disease. This may be relevant to the ability of α -methyl dopa to induce autoimmune (i.e., anti-Rh) hemolytic anemia or to the ability of numerous drugs (e.g., procainamide, isoniazid, hydralazine, penicillamine, and quinidine) to induce antihistone antibodies and the development of drug-induced systemic lupus erythematosus.

ANTIGEN PROCESSING AND PRESENTATION

No matter what form the functional antigenic structure of the haptenized drug may take, the subsequent process leading to the development of a hyper-

sensitivity response must involve established antigen processing and presentation pathways.^{27, 50} Two dominant pathways exist. The first involves the processing of internally generated antigens, their presentation by major histocompatibility complex (MHC) class I molecules, and the activation of CD8+ cytotoxic lymphocytes. Alternatively, external antigens, after processing, are presented by MHC class II molecules, resulting in the activation of CD4+ T-helper lymphocytes. Immune responses to drugs haptenized and immunogenically processed in these manners would demonstrate MHC restriction,^{6, 38, 41} a mechanism that may contribute toward the familial propensity to drug allergy. Alternatively, polymorphisms in the metabolic enzymes and transporters involved in antigen processing and presentation may contribute toward this genetic susceptibility. A third pathway by which drugs may conceivably induce immune activation is by a direct interaction with and covalently linking to MHC molecules (or to their embedded peptide). In support of such a mechanism, in at least some forms of β -lactam hypersensitivity, penicillin-specific immunogenic epitopes could be presented to T-cell clones without a requirement for antigen processing.¹⁰

The internal pathway of antigen processing has primarily evolved to allow the immune system to cope with viral infections.⁵⁰ Typically, virus-derived proteins newly synthesized in the infected cells' ribosomal-endoplasmic reticulum are noncovalently bound to newly synthesized MHC class I molecules. This process is initiated by the proteolytic cleavage of the newly synthesized viral peptide in a cell structure called the *proteosome* by a set of polymorphic enzymes termed the *large multicatalytic proteolytic particles* (LMP). These proteosomes lyse the intact peptide into the smaller 8–12 amino acid peptides, which are of the optimal size to bind to MHC molecules. In the subsequent stage of internally derived (i.e., viral) antigen processing, these peptides are actively transported across the endoplasmic reticulum by nonspecific complex transporters termed the *transporters associated with antigen presentation* (TAP-1 and TAP-2). Like the LMP enzymes, the TAP proteins are polymorphic and encoded in the MHC complex. Once in the endoplasmic reticulum the viral peptide noncovalently links to newly synthesized MHC class I molecules. These complexes then traffic to the cell surface where they are recognized by CD8+ cytotoxic T lymphocytes, which target and destroy the viral-infected cells, preventing further replication of the virus. Because all nucleated cells express MHC class I molecules, this becomes an efficient mechanism whereby virtually every cell of the organism is capable of becoming an immunologically active cell that can activate antiviral immunity and prevent further spread of virus.

Superficially, there is no obvious reason to predict that this pathway designed for mediating responses to virus-derived antigens and mediated by MHC class I-restricted CD8+ cytotoxic lymphocytes should be active in immune responses to drugs. A large body evidence, however, supports a role for these mechanisms in drug hypersensitivity reactions. Although large extracellular proteins are unlikely to be processed into the proteosome and subsequently transported by the TAP proteins into the endoplasmic reticulum (ER), this may not be true for drugs.²⁷ Drugs, many of which are weak bases, typically have a neutral charge at physiologic pH, and therefore can readily diffuse across the cell membrane and gain access to these cytoplasmic structures. The TAP molecules are closely related to the multidrug resistance (MDR) transporters, and share their ability to transport numerous unrelated complex compounds across membranes. The TAP transporters may be able to pump drugs into the ER, and allow them to be presented by MHC class I molecules to CD8+ lymphocytes. It is interesting to speculate that just as the MDR transporters can encode resistance

to numerous typically chemotherapeutic drugs, a similar process involving the TAP transporters may lead to a tendency to develop drug hypersensitivity to numerous unrelated drugs, which is observed in the multiple drug sensitivity syndrome.^{22, 30, 43} Polymorphisms in either these TAP transporters or in the LMP enzymes that make up the proteasome may influence an individual's susceptibility to drug hypersensitivity and produce the familial predisposition. MHC class I-dependent CD8⁺-mediated cytotoxicity is initiated, although in an antigen-processing-independent fashion, if the drug (or metabolite) directly binds to the surface-expressed MHC molecule (or its embedded antigen).

Although activated CD8⁺ cytotoxic lymphocytes do not produce IgE-mediated allergic drug reactions, cytotoxic immunity may be relevant to some of the most commonly observed forms of drug hypersensitivity. There are several reports of the generation of CD8⁺ MHC class I-restricted T-cell clones from individuals with drug hypersensitivity to β -lactams,^{10, 19, 20} sulfamethoxazole, phenytoin, and carbamazepine.²⁸ That cytotoxic T cells may contribute to the development of cutaneous hypersensitivity reactions is supported by the demonstration that CD8⁺ T lymphocytes are the predominant T-cell subset in individuals with β -lactam antibiotic-induced vesiculobullous exanthems,¹⁹ toxic epidermal necrolysis,^{18, 29} and maculopapular exanthems.²⁰ These works demonstrate MHC class I-restricted penicillin-specific T-lymphocyte clones, in support of the concept that drugs induce immune hypersensitivity through standard immune mechanisms. Histamine-releasing factors, such as chemokines, produced by these cells may produce the pruritus and urticaria often associated with these drug exanthems, and may not require the development of drug-specific IgE.

Cellular immune responses against drugs and the development of IgE-mediated allergic reactions are initiated by the pathway involving external antigens. Drugs (or their haptenized metabolites) are initially endocytosed into phagolysosomes by professional antigen-presenting cells (APCs), which include mononuclear phagocytic cells, B lymphocytes, dendritic cells, and cutaneous Langerhans' cells. This process is inefficient, dependent on the random mass action-dependent internalization of the drug. This internalization requires that fairly high concentrations of the antigen be exposed to the immune system over long periods of time. External antigen processing may occur at a much accelerated rate in the presence of pre-existing antibodies bound to the surface of professional APCs. Obviously, this processing can only occur as part of an amnestic response after repeat exposure to a drug and the appearance of drug-specific antibodies. While IgG may mediate this process through the Fc γ receptors, which are widely expressed on APCs, this process may also be efficiently mediated by IgE. Low affinity (Fc ϵ RII or CD23, expressed on mononuclear phagocytes, dendritic cells, and B lymphocytes) and high affinity (Fc ϵ RI, expressed on dendritic cells) may subserve this function of capturing the drug and efficiently internalizing it for antigen processing and presentation. These antigen-specific surface Igs, once expressed on the APCs, may remain present for extended periods and contribute to amnestic responses to drugs decades after the initial exposure. One possible explanation for the fixed drug eruption phenomenon involves the patchy expression of drug-specific antibodies on cutaneous Langerhans' cells, leading to the subsequent development of a localized immune response on the skin.

Once internalized into the phagolysosome of the APC, the antigen is metabolized by proteolytic and other catabolic enzymes. Subsequently, the phagolysosome fuses with vacuoles derived from the endoplasmic reticulum containing newly synthesized MHC class II molecules noncovalently linked to the invariant chain. In the phagolysosome, the invariant chain dissociates from the MHC

molecule, the antigen assumes its place within the antigen-binding cleft, and the MHC class II antigen complex subsequently traffics to and fuses with the surface membrane. It is this combination of an MHC class II molecule and antigen that is capable of interacting with the T-cell receptor and mediating the next phase of the immune response to drugs. The generation of MHC class II-restricted, penicillin-specific CD4⁺ T-lymphocyte clones in an antigen-processing-dependent fashion¹⁰ demonstrates the functioning of this mechanism in at least certain instances of drug hypersensitivity.¹⁰

T-HELPER RESPONSES

The engagement of the T lymphocyte's antigen receptor by the drug or carrier in the antigen-binding cleft of the MHC class II molecule provides antigen specificity and what is termed the *first signal for T-cell activation*. Only in the additional presence of the second signal does the T lymphocyte become activated and respond with proliferation and cytokine production. The most important second signal for T-cell activation is provided by the interaction of the B7 molecules on the antigen-presenting cells (B7.1 [CD80] or B7.2 [CD88]) with CD28 on the surface of the T lymphocyte. Additional second signals may be provided by the interaction of LFA-3 on the APC with LFA-2 (CD2) on the lymphocyte or even by secreted signals (i.e., cytokines), such as interleukin-1 (IL-1) or IL-6. Engagement of the T-cell receptor in the absence of this second signal, such as in conditions of antigen excess or inappropriately processed or presented antigen, not only precludes T-cell activation, but it may become irreversibly nonresponsive (i.e., tolerant). Such a tolerant T lymphocyte remains nonresponsive to the antigen even if it is subsequently presented appropriately. Such a process may underlie the induction of allergen nonresponsiveness, which occurs with drug desensitization. Although this process of tolerance induction is too slow to be the mechanism that permits rush desensitization to drugs, it likely is the mechanism responsible for slow desensitizations, such as to sulfamethoxazole or phenytoin. Once the drug dosing (and therefore antigen presentation) ceases, a reservoir of newly born drug-specific clones accumulates over days to weeks, which, perhaps stimulated by stores of antigen, resumes orchestration of an immune response.

Activation of T-helper lymphocytes is associated with their proliferation and secretion of cytokines. Lymphocytic proliferation has been reported with variable frequency in association with drug exposure and hypersensitivity reactions, especially with β -lactams and sulfa agents.^{5, 15, 17, 24, 31, 45, 47, 49} The value of this reaction as a diagnostic tool is mitigated by the absence of the relevant complete (i.e., haptenized) antigen with which to perform the test; however, when positive, it presumably recapitulates what occurs in vivo. The repertoire of cytokines produced by these CD4⁺ MHC class II-restricted T-helper lymphocytes determines the form the subsequent immune response will take. Production of the T-helper Type 1 (Th1) cytokines, including tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), leads to the activation of monocytes into their activated counterpart, the macrophage, which becomes capable of killing pathogens, tumor cells, and other targets in the cellular immune response. Cellular immune responses are responsible for cutaneous contact reactions; however, this mechanism also may contribute to pulmonary hypersensitivity reactions, such as to nitrofurantoin and to drug-induced interstitial nephritis. Drug-induced exanthems also may reflect cellular immune responses because they may be associated with the development of positive patch tests to the causative agent.^{33, 39, 48} Although the predominance of mononuclear cells in these reactions

suggests a cellular immune reaction, in the absence of specific immunofluorescent studies, patch tests cannot be used to distinguish CD4+ Th1-like lymphocytic responses from those mediated by CD8+ cytotoxic lymphocytes.

In contrast to cellular responses, the production of humoral immunity-inducing cytokines, such as IL-7, IL-10, and IL-14, may lead to antibody-mediated immune responses. These include the induction of IgG directed toward the drug, which may produce either immune complex disease (e.g., serum sickness) or innocent bystander damage (e.g., thrombocytopenias or hemolytic anemias). Nonpathogenic immune reactivity toward a therapeutic agent may occur fairly frequently and may be recognized in subjects demonstrating lymphocytic transformation to an agent in the absence of a hypersensitivity reaction. In addition, approximately 40% of patients who received more than 2 g of penicillin for more than 10 days demonstrated IgG antibodies against the major antigenic determinant of penicillin in the absence of clinical hypersensitivity.⁴

IgE-MEDIATED DRUG ALLERGIES

The most important and life-threatening hypersensitivity responses to therapeutics are represented by the allergic, IgE-mediated reactions. The allergic immune responses are caused by the tendency of the allergen to differentiate naive allergen-specific T-helper lymphocytes into the Th2-like phenotype. These Th2 lymphocytes are characterized by their production of cytokines associated with the allergic state, including those responsible for the immunoglobulin isotype switch to IgE (IL-4 and IL-13); eosinophil hematopoiesis, recruitment, survival, and activation (IL-5, GM-CSF, and IL-3); expression of the eosinophilic-specific adhesion molecule VCAM-1 (IL-4 and IL-13); and mast cell proliferation and differentiation (stem cell factor, IL-3, IL-9, and IL-10). The production of allergen-specific IgE after administration of a drug must have involved the generation of drug-specific Th2-like lymphocytes. Although typical drug-specific Th2-like clones have not been generated from individuals with drug hypersensitivity reactions, this may reflect the unique pathways and mechanisms by which these cells must be derived. Martin et al, however, were able to demonstrate high amounts of IL-5 from activated lymphocytes specific for sulfamethoxazole, phenytoin, and carbamazepine.²⁷

IMMUNE TISSUE SPECIFICITY AND GENETIC PREDISPOSITION TOWARD THE DEVELOPMENT OF TYPE II T-HELPER LYMPHOCYTE RESPONSES IN DRUG ALLERGY

Although the atopic state is defined by a genetic predisposition toward the differentiation of Th2 lymphocytes, this genetic predisposition does not underlie the development of drug allergies, because these reactions develop at no increased frequency in atopic subjects.^{2, 46} Any theory that attempts to explain the causes for the development of drug allergies must explain the equal likelihood that they will develop in otherwise allergic or nonallergic individuals. This likelihood is analogous to the situation of helminthic infections that produce an IgE-dependent response without regard to the atopic tendency of the infected subject. Part of the genetic predisposition to allergy may reflect an enhanced tendency to generate immune responses to pollens, dander, insect parts, and other benign bioaerosols, which are delivered to the immune system via the respiratory tract. In contrast to the immune response to inhalants, drugs are generally delivered to the immune system in the gut-associated lymphatic tissue

or through the systemic circulation in which the splenic lymphatics may be the primary site where immune responses develop. Each day, the immune organs of the gut are presented with kilograms of foreign antigens that are derived from food and bacterial antigens. The gut-associated lymphatic tissue is characterized by an overriding tendency to avoid generating immune response to these otherwise benign antigens, and typically tolerance develops. This tendency is one of the arguments for oral desensitization, including oral desensitization to drugs, because the gut lymphatics have the indigenous tendency to induce immune nonresponsiveness to orally administered antigens. Systemically presented antigens, such as those which would be associated with the parenteral administration of a therapeutic, result in the development of immune responses in the spleen and an enhanced tendency toward the production of humoral immune responses. There may be unique features of the nasal- and bronchial-associated lymphatic tissues that have a predisposition towards the development of Th2-like responses. In combination with an enhanced tendency among genetically at-risk individuals toward making immune responses in the respiratory tract, this predisposition may be responsible for the atopic individual's tendency to develop allergic responses to inhalants. Obviously, these cannot be the only mechanisms for the development of allergies, because many allergens—in addition to drugs—are not inhalants, including those derived from food antigens or hymenoptera venom. An interesting observation, however, is that similar to drug allergy, neither food nor hymenoptera allergy are atopic diseases because they develop without an allergic familial predisposition. It is important, therefore, to speculate on the basis by which Th2-mediated responses develop to therapeutics in a fashion independent of the effects of the respiratory lymphatics or a genetic predisposition toward atopy.

MECHANISM OF DIFFERENTIATION OF Th2 LYMPHOCYTES

One of the most important discoveries has been recognition of the role of IL-4 in the generation of IL-4- and IL-5-producing Th2 lymphocytes. IL-4 is absolutely essential to the development of allergic inflammation because of its unique ability to drive the differentiation of naive Th0 lymphocytes into the Th2 phenotype.^{1, 21, 44} In the presence of IL-4, Th0 lymphocytes tend to secrete IL-4, IL-5, and other cytokines associated with Th2 lymphocytes, and lose their tendency to produce IFN- γ . The role of IL-4 in the differentiation of naive Th0 lymphocytes into the Th2 phenotype has been established in studies using transgenic mice with single antigen-specific T-cell receptors. The tendency of these T cells to produce IL-4 is enhanced in a dose-dependent fashion in the additional presence of IL-4, whereas neutralizing anti-IL-4 antibodies abrogate their ability to produce Th2 cytokines. Similarly, in human studies, the presence of IL-4 is associated with the generation of Th2-like T-lymphocyte clones, whereas anti-IL-4 is inhibitory. This is a unique function of IL-4, and is not mediated by other cytokines, including IL-13.

These observations imply that for drug allergy to develop, the therapeutic must be presented to the drug-specific, naive T-helper lymphocyte (Th0) in a milieu characterized by the presence of IL-4. This milieu is not the allergic respiratory tract where IL-4-mediated immune responses may be present, because drugs are generally not administered as inhalants, and the presence of an allergic respiratory disease is neither required nor contributory to the development of drug allergies. The most important question is: What is the source for this IL-4 that must be present for an allergic reaction to drugs to develop? Although Th2 lymphocytes are characterized by their production of IL-4, they

cannot be this source because their differentiation requires the pre-existence of IL-4. Mast cells and eosinophils are also sources for IL-4, but their presence and activation assumes the establishment of an allergic inflammatory response that could not have developed in the absence of the original IL-4 that induced the Th2-mediated allergic inflammatory reaction. Recent work suggests that the original source for this IL-4 may be natural T cells.^{8, 11}

NATURAL T CELLS

Natural T cells (NT) are a specialized population of T cells that differ from conventional α/β T cells in several respects. Principally, they share many features with and coexpress receptors typical of mononuclear cells of the natural killer cell (NK) lineage. In contrast to CD4+ or CD8+ T lymphocytes, NT cells recognize antigen in association with a unique MHC class I-like structure termed the *CD1 genes* (*CD1a-e* in humans and CD1.1 and CD1.2 in the mouse). These CD1 molecules are structurally similar to the MHC class I gene, including sharing their noncovalent linkage to β_2 -microglobulin. In contrast to the MHC class I genes, however, these CD1 structures are not polymorphic and are not expressed in the chromosomal MHC locus. NT cells are characterized by their expression of a restricted T-cell receptor repertoire ($V\alpha 14$ -Ja281 associated with polyclonal $V\beta 8$, $V\beta 7$, or $V\beta 2$). NT cells comprise approximately 0.5% of thymocytes and 1% of mature mononuclear cells.⁹

The most striking characteristic of these cells is their tendency to produce promptly large amounts of cytokines and, in particular, IL-4 on stimulation through their T-cell receptor complex. For example, stimulation of NT cells with anti-CD3 monoclonal antibody results in prodigious amounts of IL-4 within 2 hours in vivo.¹¹ Compared with normal mice, transgenic mice expressing only $V\alpha 14$ -Ja281 NT cells produce over tenfold more IL-4 but four times less IFN- γ following anti-CD3 treatment in vivo.⁸ NT cells enhance IgE antibody production. Injection of goat anti-IgD antibodies induces polyclonal IgG1-IgE responses that are IL-4- and CD4-dependent. β_2 -microglobulin deficient mice (which lack CD1 and therefore do not express NT cells) are severely impaired in their capacity to induce IL-4 or IgE following anti-IgD stimulation, whereas CD8 or class II knockout mice respond normally. In vivo immune reconstitution experiments in these β_2 -microglobulin knockout mice provide direct evidence that NT cells are responsible for this response.⁵¹

Because NT cells are an important early source of IL-4, they are an excellent candidate for the induction of allergen-specific IgE responses to drugs (and other allergens). We can therefore speculate that induction of allergic responses to drugs involves the activation of NT cells, thereby creating a milieu characterized by high concentrations of IL-4. One aspect of NT activation supports this possibility. As noted previously, NT cells are characterized by their restriction by and recognition of antigen in association with CD1. These MHC class I-like molecules are characterized by an ability to bind unusual antigens, including hydrophobic substances (e.g., polyaromatic compounds). Drugs may also be recognized in this way, and because of the IL-4-producing characteristics of NT cells, any drug capable of binding and being presented by CD1 molecules is likely to produce an allergic hypersensitivity response in that individual, regardless of atopic tendency. One study generated penicillin-specific CD4+ T-helper clones from penicillin-allergic individuals using autologous antigen-presenting cells and T lymphocytes.¹⁰ The subsequent clones produced high amounts of IL-2, IFN- γ , and TNF- α , but variable levels of IL-4 and IL-5. The investigators' failure

to reproduce the *in vivo* generation of Th2-like lymphocytes supports the concept that the necessary cellular source for IL-4 (e.g., NT cells) was lacking in their experimental approach.

CONCLUSION/FUTURE DIRECTIONS

Little is known regarding the unique features that produce hypersensitivity reactions to drugs. With few exceptions, the antigenic form of these therapeutics, their specific antigen-processing and presentation pathways, or the immune mechanisms of most nonallergic immune-mediated drug reactions are not understood. The technology does exist, however, to produce this understanding. Our ability to grow and maintain antigen-specific T-cell lines and clones should lead to a knowledge of the nature and phenotype of these responding cells. It should be possible to purify and characterize structurally the complete antigenic form of these drug hapten or carrier complexes. This structural information includes sequential data regarding the chemical form of the complete antigen and, equally importantly, the physical structure of the haptenized complex as it is bound in the antigen-binding cleft of MHC molecules and becomes capable of interacting with and activating the T-cell receptor. Useful information regarding drug hypersensitivity will arrive, including the ability to produce drugs that will be less capable of being metabolized into antigenic forms. Additionally, knowledge of the antigenic form of the hapten or carrier complex will have therapeutic usefulness. The availability of structural data regarding the IgE-binding form of the haptenized drug will be used to generate accurate reagents to perform diagnostic testing for the presence of drug allergy. More importantly, it should be possible to generate haptenized peptides capable of binding the T-cell receptor but not surface IgE present on mast cells or basophils. Such an agent could be used similarly to the current use of peptide-based immunotherapy to perform safe and rapid antigenic-specific hyposensitization. In an era increasingly characterized by multidrug-resistant bacteria, clinicians are often forced to choose higher cost agents or, worse yet, they may be faced with the dilemma that alternative therapies are not available. These pressures should drive the development of hypoallergenic therapeutics or safer agents with which to perform desensitizations. The authors propose that assigning a higher priority to drug allergy research and encouraging collaboration between immunopharmacologists and allergist and immunologists, will reduce iatrogenic morbidity and prove to be cost effective.

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