# Immunopharmacology of Hypersensitivity Reactions to Drugs

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**Current Allergy and Asthma Reports** 2003, **3:**22–29
Current Science Inc. ISSN 1529-7322


Drug hypersensitivity reactions are characterized by their unpredictability, lack of simple dose-dependency, host sensitivity, and potentially serious clinical outcome. They occur in a small proportion of patients, and usually the predisposing factors are unknown, although there is increasing evidence for genetic predisposition and disease being significant risk factors. The current understanding of the chemical basis of immune-mediated reactions is based on the hapten hypothesis, which requires drug bioactivation, covalent binding to proteins, followed by uptake, antigen processing, and a polyclonal immune response. The recently proposed "danger hypothesis" can be considered to be an essential addition to the hapten hypothesis. According to the danger hypothesis, the immune response to a drug-derived antigen requires the presence of co-stimulatory signals and cytokines, which propagate and determine the type of immune response. The "danger signal" might result from chemical, physical, or viral stress.

## Introduction

Adverse drug reactions are common and occur in up to 5% of patients. Most adverse effects suffered by individuals are relatively mild, self-limiting, and rapidly reversible on drug discontinuation. In some cases, however, adverse effects can be more severe, result in hospitalization, or in the worst cases, cause death [1].

From a clinical perspective, adverse drug reactions can be divided into two basic types [1]:

- Type A reactions can be predicted from the pharmacology of the drug, and represent an augmentation of its known effects. They are typically dose-dependent, and may be amenable to dose reduction.
- Type B reactions cannot be predicted from the known pharmacology of the drug. They are also called bizarre or idiosyncratic adverse reactions. There is no simple dose-response relationship, and the drug often has to be withdrawn on development of the adverse reaction.

The type A reactions are more common than type B reactions, accounting for 80% of all reactions. In general, type A reactions are less severe than type B reactions, but it is important to remember that type A reactions, like type B reactions, can cause fatalities. Bleeding with warfarin and fatal overdose with antidepressants exemplify such reactions.

Type B reactions are still poorly understood and, therefore, unpredictable, in terms of both the chemistry of the drug and the biology of the individual patient. There are several potential mechanisms [2]. In general, they can be divided into immune-mediated hypersensitivity reactions and non–immune-mediated, which are sometimes referred to as metabolic idiosyncrasy.

The purpose of this review is to highlight recent advances in our understanding of immune-mediated type B or hypersensitivity adverse drug reactions, and in particular to consider how such information can be used to prevent such reactions through improved drug design or by individualization of drug therapy.

## Clinical Features of Drug Hypersensitivity

The definition of a drug reaction as a hypersensitivity reaction is usually based on clinical criteria [1,3]. The following characteristics are indicative of an immunologic etiology.

- Variable clinical presentation, both in terms of severity and type of toxicity, with the same drug
- General features—rash, fever, eosinophilia, lymphadenopathy, arthralgia
- Time-course—reactions usually take at least two weeks to occur
- Reactions occur more rapidly on rechallenge
- Reactions resolve on drug withdrawal
- Reactions can be avoided by slow dose escalation (*eg*, lamotrigine [4]), indicating induction of tolerance

In some instances, laboratory tests such as the eosinophil count, the presence of autoantibodies, drug-specific T cells, or cytokine synthesis may provide useful additional information.

The clinical presentation of drug hypersensitivity is highly variable and dependent on both the drug and the patient. Indeed, the same drug can produce completely

different clinical manifestations in different patients. Many patients, however, have nonspecific manifestations suggestive of hypersensitivity, such as fever, rash, arthralgia, lymphadenopathy, and eosinophilia, as well as the symptoms resulting from the organs affected by toxicity [3,5].

The situation is complicated further by the fact that the same drug under different conditions can cause either direct metabolite-mediated toxicity or immune-mediated toxicity. For example, the inhalational anesthetic halothane can cause two forms of hepatic injury. Reductive metabolism of halothane can lead to the development of hepatitis (type I) in up to 20% of individuals, which is usually mild and self-limiting. In contrast, oxidative metabolism can lead to the formation of acyl halide metabolites that may cause immune-mediated hepatotoxicity (type II hepatitis) [6]. Although this is less common than type I hepatitis, it is much more severe and carries a high mortality. In keeping with the immune basis of toxicity, patients with type II hepatitis have circulating lymphocytes and antibodies in their blood directed against halothane-derived liver neoantigens that are expressed predominantly in the microsomal fraction of the liver [7,8].

Drug hypersensitivity reactions can affect almost any organ system, and they may be of a generalized nature or organ (cell) specific. The skin is the organ most commonly affected, and skin rashes occur in 3% of hospitalized patients.

## Chemical Aspects of Drug Hypersensitivity and the Role of Drug Metabolism

Therapeutic drugs associated with drug hypersensitivity have a number of common chemical features that include:

- High mass dose. Idiosyncratic toxicity in general is rarely seen with drugs given at a dose of less than 100 mg per day.
- Inherent protein reactivity. Drugs and chemicals, which can react directly with proteins, are nearly always associated with some form of hypersensitivity reaction in exposed individuals. The clinical phenotype is similar, irrespective of chemical structure, and is more commonly associated with a Th2 profile than a Th1 profile.
- Formation of chemically reactive metabolites. Most drugs investigated that cause hypersensitivity in humans have been shown to undergo metabolic activation by mammalian enzymes to a protein-reactive intermediate. The clinical phenotype for this group of drugs again shows no obvious relationship with chemical structure and is more commonly associated with a Th1 rather than a Th2 profile.

Drug metabolism is a detoxification process, which facilitates the physiologic clearance of lipophilic chemicals. However, metabolism by both phase I and phase II processes can lead to the formation of chemically reactive metabolites [9]. In most instances, chemically reactive metabolites undergo bioinactivation leading to detoxification and excretion of the metabolites. Glutathione is the most important chemical defense for the immediate chemical neutralization of soft electrophiles such as chemically reactive metabolites. Therefore, an imbalance between bioactivation and bioinactivation pathways may allow the reactive metabolite to bind to cellular macromolecules and induce various forms of toxicity [9•], including liver necrosis after paracetamol overdose.

The role of drug metabolism in drug hypersensitivity remains a controversial topic. It is widely theorized that drugs, in line with other low–molecular weight compounds are not immunogenic per se, and, therefore, must form stable adducts with endogenous proteins to initiate an immune response [10]. This is the basis of the hapten hypothesis of drug hypersensitivity (Fig. 1), in which the critical step is the formation of adducts (drug-protein conjugates) between the drug (metabolite) and an endogenous protein [9•,11]. The immunochemical literature shows that compounds with a molecular weight of less than 1000 Daltons must be covalently bound to high–molecular weight proteins to act as effective immunogens. Classical studies by Landsteiner and Jacobs [12] showed that chemicals that can bind covalently to protein are potent sensitizing agents; for example, the model hapten dinitrofluorobenzene reacts spontaneously with lysine groups in autologous proteins, and is a potent contact sensitizer [13]. More recently, we have demonstrated that chemically reactive metabolites derived from drugs (*eg*, nitrososulphamethoxazole) are extremely immunogenic in animal models [14•]. Furthermore, the ex vivo T-cell response to drug metabolite could be blocked by glutathione and was shown to be antigen-processing dependent [15••].

Protein adducts may be formed by two mechanisms: either by direct chemical reaction or by generation of electrophilic metabolites that react with nucleophilic groups on proteins [13]. Some drugs, including penicillins, cephalosporins, and anti-cancer agents, can react directly under physiologic conditions with the nucleophilic groups that are present in proteins. These drugs generate chemically reactive intermediates, such as penicillinic acid, which are hard electrophiles, and consequently not detoxified by glutathione. One consequence of such spontaneous formation of protein adducts is that extracellular antigen is formed, which is more likely to lead to a Th2 response [16].

Most drugs associated with drug hypersensitivity are chemically inert. It has, therefore, been proposed [9•,11] that such drugs must form chemically reactive metabolites, as outlined earlier, to initiate an immune response. According to current concepts in immunology, the disposition of the antigen will influence both the type of immune response and the site of tissue damage [9•]. Drug-derived antigen must serve at least two important functions [17]:

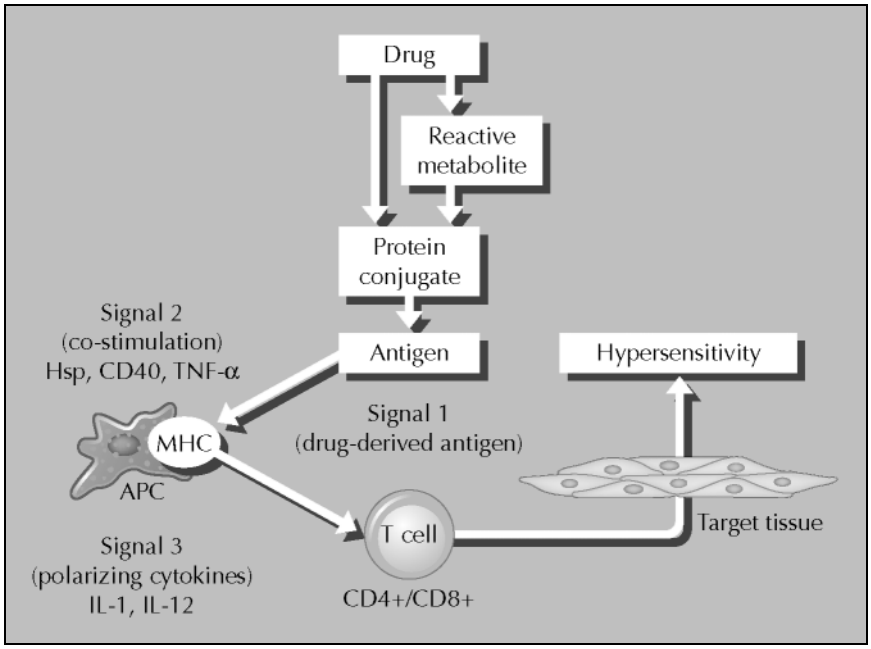


**Figure 1.** Schematic representation depicting our current understanding of the role of drug metabolites in hypersensitivity reactions. APC—antigen-presenting cell; Hsp—heat shock protein; IL—interleukin; MHC— major histocompatibility complex; TNF—tumor necrosis factor.

first, to act as an immunogenic signal to stimulate T-cell proliferation. Second, to act as an antigenic signal to direct the effector arm of the immune response to the target cells (tissue). The first contact of the protein adduct with the immune system is recognition of the haptenated protein as being foreign by professional antigen-presenting cells. Immunologic recognition of haptenated autologous proteins is a function of the number of hapten molecules covalently attached to each individual protein molecule [13]. Therefore, in skin, Langerhans cells are efficient antigen-presenting cells and represent efficient antigen-presenting cells for activation of drug-specific T cells in local lymph nodes, which can target keratinocytes, which present drug-specific antigen on major histocompatibility complex (MHC) class 1 molecules.

There is strong circumstantial evidence to support the role of chemically reactive metabolites in the pathogenesis of drug hypersensitivity reactions. For example, metabolism is an obligatory step in the pathogenesis of halothane hepatitis through the formation of acyl halides, which can directly modify hepatic proteins [18]. In humans, halothane undergoes approximately 20% hepatic metabolism to chemically reactive intermediates. By contrast, enflurane and isoflurane, which undergo 3% and less than 1% metabolism, respectively, form smaller quantities of reactive metabolites and are associated with a greatly reduced incidence of hepatotoxicity [19].

Although the liver is quantitatively the major site of drug metabolism, almost all extrahepatic organs have a complement of P450 isoforms and phase II enzymes. However, it is not the absolute level of enzymes that is important, but the cellular relationship between the enzymes that can affect drug bioactivation and the signalling process responsible for immune-response processes. The immune system requires only a small amount of chemical signal to initiate a response; minor perturbations in the balance between drug bioactivation and bioinactivation may be all that may be needed to initiate an immune-mediated reaction. In this respect, it is interesting to note that skin, which is commonly affected by hypersensitivity, expresses numerous drug metabolizing enzymes [20]. Furthermore, keratinocytes can bioactivate drugs such as sulphamethoxazole to protein reactive intermediates [21•]. Certain cells may contain different enzymes that are also capable of causing drug bioactivation. This is clearly the case for neutrophils, which contain high levels of myeloperoxidase, and have been shown to promote drug bioactivation [22], which can readily result in glutathione depletion and cellular necrosis and apoptosis [23]. One intriguing possibility is that drug metabolism within antigen-presenting cells may provide the chemical signal (signal one) to initiate the immune response. To explore this possibility, we are currently developing novel mass spectrometric techniques, which will allow us to explore metabolism at the intracellular level and thus test this hypothesis.

The fundamental concept that protein-conjugation is an obligatory step in the process of immune recognition of drugs has however recently been challenged by the observation that T-cell clones from patients who are hypersensitive to a number of drugs undergo proliferation in an antigen-processing independent (but MHC-restricted) manner [24,25••]. This involves labile, reversible binding of drug to the MHC complexes on antigen-presenting cells. The relevance of these in vitro findings to T-cell activation in vivo still needs to be defined. Nevertheless, these studies show unequivocally a T-cell response to drug-derived antigen and alert us to the possibility of novel mechanisms of antigen presentation in cells from hypersensitive patients, which do not operate in animal models of chemical immunogenicity [15••].

Some groups have found that lymphocyte proliferation assays lack sensitivity but can overcome this by the inclusion of a metabolizing system [26].

## Immunologic Aspects of Drug Hypersensitivity and Danger Signals

Co-stimulatory signals are essential to drive an immune response to a chemical antigen. The danger hypothesis proposed by Matzinger [27] states that the immune system distinguishes between self and non-self, but its primary driving force is to protect against danger. Presentation of an antigen in the absence of danger results in tolerance, whereas the presence of a danger signal will result in an immune response. It has been proposed that molecules such as heat shock proteins and cytokines released or produced by cells undergoing either stress or necrotic cell death can activate resting antigen-presenting cells, which, by offering co-stimulatory signals, initiate an immune response [28]. Although proposed as a model to explain how the body responds to pathogenic microbes, the danger hypothesis is relevant to drug hypersensitivity [9•,11].

It is theorized that three signals are required to produce an immune response to an antigen [29•]. For drug hypersensitivity, signal 1 represents the interaction between the MHC-restricted antigen and the T-cell receptor. In the absence of any other signals, tolerance will result. Signal 2 is represented by co-stimulatory molecule–receptor interactions and a series of pro-inflammatory cytokines such as interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ that act indirectly on antigen-presenting cells to upregulate the expression of co-stimulatory molecules. Signal 3 represents polarizing cytokines that act directly on T cells. It is known that Th1 cells produce IL-12 and IFN-γ, which promote the activation of macrophages and cell-mediated immunity. By contrast, Th2 cells produce IL-4 and IL-13; these provide help for the humoral immune response by promoting immunoglobulin G (IgG) to IgE class switching [17]. Therefore, in terms of drug hypersensitivity, a drug (metabolite) could serve several functions. First, a source of drug-derived antigen in line with the conventional hapten hypothesis; and second, such metabolites may also be toxic toward the target cell and, thus, indirectly provide a source of co-stimulatory signals.

The danger hypothesis may provide an explanation of why drug hypersensitivity reactions are more common in patients with certain concomitant viral infections. It is well established that acute infection with the Epstein-Barr virus (EBV) results in a rash in 95% of patients given amoxicillin, which does not recur when the drug is given after recovery from EBV [3]. More recently, it has also been shown that infection with human herpesvirus 6 (HHV-6) increases the risk of allergic drug reactions [30]. Perhaps the best example of a virus increasing the risk of allergic drug reactions is seen in HIV-positive patients, who have a much higher frequency of reactions to drugs [31]. It is possible that the higher frequency of hypersensitivity drug reactions in these viral infections is a result of increased levels of cytokines, which amplify the potential of a drug to cause an immune reaction. In HIV, various cytokines, including IFN-γ, are elevated in the sera of patients. IFN-γ can increase the expression of various pro-inflammatory cytokines, which contributes to the oxidative stress seen in HIV disease [32]. Another effect of IFN-γ overexpression is the upregulation of MHC class II and co-stimulatory molecules on antigen-presenting cells and other cells, including keratinocytes, which will lead to enhancement of antigen presentation [33].

## Hypersensitivity and the Skin

Cutaneous adverse drug reactions, which show marked inter-individual variation in clinical presentation and severity, represent the most common form of hypersensitivity. Reactions are observed in 2% to 3% of hospitalized patients [34]. Clinical manifestations indicate that most skin reactions have an immunologic basis; these include urticaria, exanthemas (maculopapular), vasculitis, purpura, bullous eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalized hypersensitivity syndrome.

Animal models provide a useful framework with which to understand the immune response to chemicals in the skin. Contact hypersensitivity to reactive chemicals such as dinitrofluorobenzene is a T-cell-mediated cutaneous reaction that can be studied in murine models. The irreversible interaction between the chemical and skin generates a potent antigen that is taken up by Langerhans cells, which, following antigen recognition, migrate to local lymph organs where they present and, therefore, prime naïve CD4+ and CD8+ T cells [35]. This sensitization phase is followed by clonal expansion of antigen-specific T cells that target skin on subsequent antigen exposure. These reactions have been studied extensively: CD8+ T cells secrete IFN-γ and, in most incidences, incite tissue damage; CD4+ T cells secrete IL-4 or IL-10 and can have regulatory functions [36]. With the advent of gene knockout mice, we are beginning to understand the molecular mechanisms of how simple chemicals cause hypersensitivity reactions. Using mice that are deficient in perforin, FAS, or both, Kehren *et al.* [37••] have shown that antigen-specific MHC-class I restricted CD8+ T cells cause tissue damage via either pathway. Double-deficient mice generate antigen-specific CD8+ T cells, but they do not develop contact hypersensitivity. More recent investigations by the same group have shown that skin-infiltrating CD8+ T cells can induce keratinocyte apoptosis, the extent of which peaks with the contact hypersensitivity reaction [38].

At present, we have no methodology to study which drug will cause immune reactions, and, indeed, which patient will develop a reaction to that drug. Animal models have not been developed because we do not yet understand the risk factors that predispose individuals to drug

**Table 1. Drug-specific T cells isolated from hypersensitive patients**

| Drug | Clinical characteristics |
|---|---|
| Abacavir | Hypersensitivity and pneumonitis |
| Amoxicillin | Rash and nephritis |
| Carbamazepine | Hypersensitivity syndrome |
| Lamotrigine | Hypersensitivity syndrome |
| Phenobarbital | Hypersensitivity syndrome |
| Phenindione | Hypersensitivity syndrome |
| Sulfamethoxazole | Maculopapular rash |
| Isoniazid | Hepatotoxicity |
| Acetaminophen | Rash |

hypersensitivity. Therefore, the utilization of T cells isolated retrospectively from hypersensitive human donors is the only system currently available to generate meaningful functional data. We have recently used the lymphocyte transformation assay to show the presence of drug-specific T cells in the peripheral circulation of patients who had previously developed hypersensitivity reactions to a number of drugs (Table 1). The response to each drug was dose dependent and seen at therapeutic drug concentrations. To characterize the chemical and cellular nature of drug hypersensitivity and, therefore, begin to understand the mechanism by which T cells cause serious tissue injury in humans, we recently cloned T cells from carbamazepine- and lamotrigine-hypersensitive patients.

Carbamazepine and lamotrigine are commonly used anti-epileptic drugs that can only be used restrictively in certain patients owing to the occurrence of hypersensitivity reactions that can be severe and cause deaths. Cutaneous manifestations (either maculopapular or bullous eruptions) are often accompanied by fever, systemic symptoms such as hepatic failure, and eosinophila. Laboratory investigations have shown the presence of activated CD4+ and CD8+ T cells in inflamed dermis and epidermis, respectively [39]. Carbamazepine and lamotrigine are compounds with known oxidative metabolism [40,41]; however, the role of covalent binding in hypersensitivity is not clear. Our recent studies of cloned T cells from hypersensitive patients suggest that IFN-γ production by CD4+, skin-homing cytotoxic T cells is a common characteristic of anticonvulsant hypersensitivity. IFN- γ producing cells produced the chemokines MIP-1α, MIP-1β, and RANTES, which have recently been classified as a group of "type 1 cytokines" that act together as a functional unit by cells of the innate and adaptive immune system to drive antigen-specific responses in vivo [42•]. Although the identification of drug-specific cytotoxic CD4+ T cells contradicts animal models of contact hypersensitivity, it is becoming increasingly apparent that activation of CD4+ T cells may be sufficient to cause the cutaneous symptoms of many drug hypersensitivity reactions [33]. Immunohistochemical studies of skin in the acute phase of drug hypersensitivity, which shows a dominant dermal and epidermal infiltration of cytotoxic CD4+ T cells, confirm our in vitro observations [43]. Identification of large numbers of T-cell receptor Vβ5.1+ cells from patients who are hypersensitive to carbamazepine and lamotrigine in our studies, and phenobarbital elsewhere [44•], suggests that the T-cell receptor may be a susceptibility factor for the development of hypersensitivity. Carbamazepine and lamotrigine presentation was HLA-DR and -DQ restricted, and occurred in the apparent absence of drug metabolism, covalent binding, and antigen processing. It is also possible that drug metabolite–specific T cells exist; however, the absence of synthetic, protein-reactive metabolites preclude these structural investigations. Figure 2 provides an overview of our current understanding of the chemical and cellular mechanisms of drug hypersensitivity in humans.

## Pharmacogenetics of Drug Hypersensitivity

Drug hypersensitivity reactions usually affect only a few individuals exposed to the drug. They represent, therefore, a prime example of a reaction that is host dependent. Although environmental factors such as HIV infection contribute to individual susceptibility, it is likely that there is also a genetic contribution.

Pharmacogenetics is the study of variability in drug response due to heredity. Much of the early work in this area focused on drug metabolizing enzyme gene polymorphisms, particularly in relation to type A reactions, but also in relation to immune-mediated adverse drug reactions. For example, patients deficient in *N*-acetyl transferase type 2 (NAT2), so-called slow acetylators, are susceptible to developing systemic lupus erythematosus (SLE) with drugs such as hydralazine and procainamide [2]. Further work on hydralazine-induced SLE showed that predisposition to SLE was also dependent on the presence of HLA-DR4 [45]. This was one of the first examples to show that predisposition to immune-mediated adverse drug reactions is unlikely to be dependent on one gene, and is more likely to depend on the interaction between different genes (see later).

Given the pivotal role of the MHC in the immune response, many of the early studies on drug hypersensitivity reactions focused on HLA phenotyping. Several positive associations were identified [2]; however, there were also contradictory data between different groups, and, in most cases, the numbers of patients studied were small.

With the completion of the first draft of the human genome project, there has been renewed interest in pharmacogenetics. It is now clear that predisposition to drug hypersensitivity is likely to be polygenic, dependent on the interaction of a number of genes with the environment—each gene contributing to the risk of developing the hypersensitivity reaction, but each individual gene not sufficient by itself to cause the reaction [46]. Although many novel genes are likely to be identified as predisposing factors to drug hypersensitivity over the

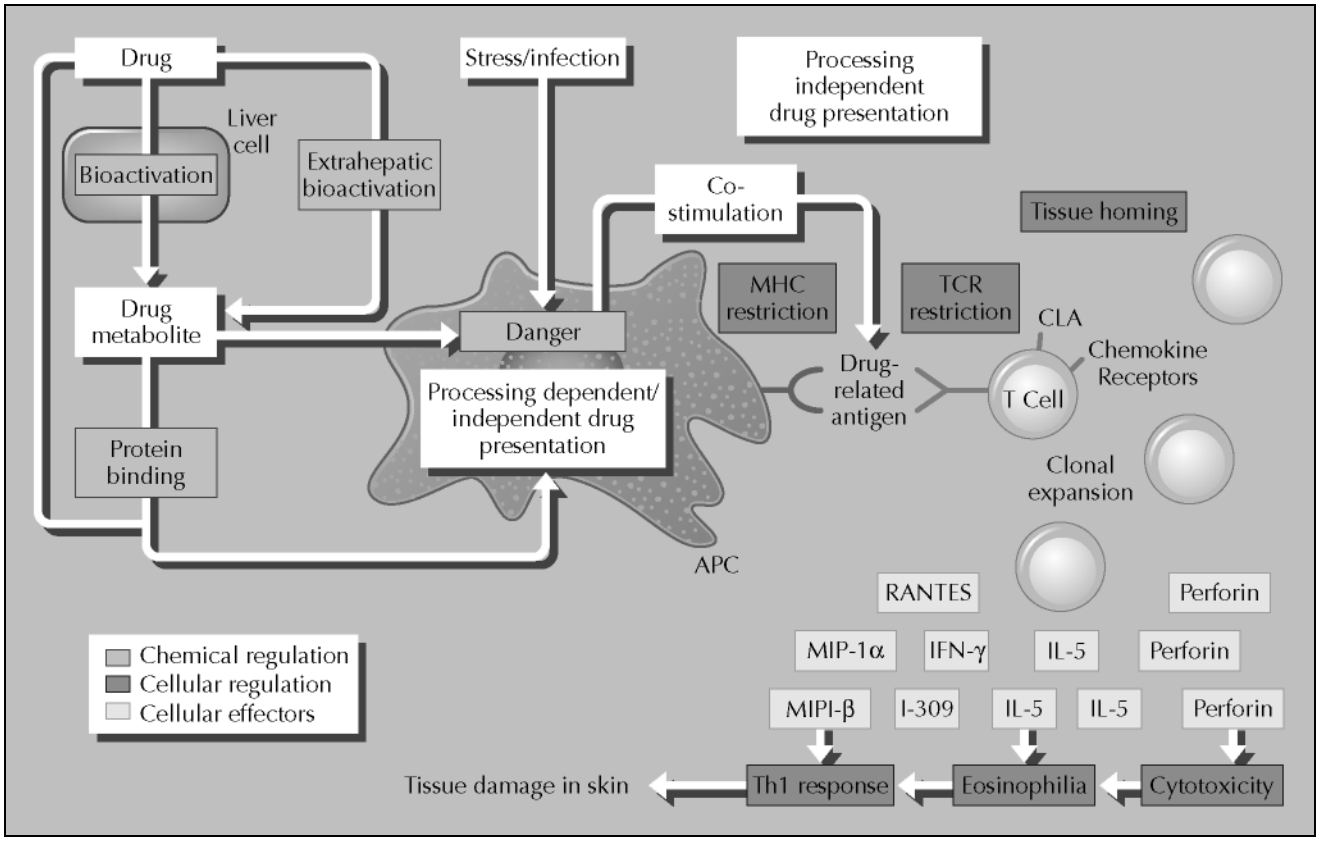


**Figure 2.** Schematic representation of our current understanding of the chemical and cellular mechanisms of anticonvulsant hypersensitivity reactions. APC—antigen presenting cell; IFN—interferon; IL—interleukin.

next few years, with the current state of knowledge it is possible to divide the predisposing genes into several categories [1]:

- Drug bioactivation: genes involved in the metabolism of drugs into chemically reactive metabolites. The most important enzymes in this group are the P450 superfamily of enzymes, many of which are polymorphically expressed (http://www.imm.ki.se/CYPalleles/).
- Drug bioinactivation: genes involved in the bioinactivation of toxic metabolites, which include not only the P450 enzymes, but also phase II enzymes such as glutathione transferases.
- Immune responsiveness: genes involved in mounting an immune response including those coding for MHC, T-cell receptors, and co-stimulatory molecules.
- Tissue injury: genes involved in causing and repairing tissue damage; clearly the balance between such processes will be crucial in limiting any tissue damage. Typical candidates include cytokines, chemokines, and prostaglandins.

Although all four categories may be important, recent findings suggest that the latter two (*ie*, immune responsiveness and tissue injury) are far more important in the predisposition to drug hypersensitivity than the former two. This can be illustrated with reference to two drugs:

1. Carbamazepine is a widely used anticonvulsant, well known to cause hypersensitivity reactions, as discussed earlier. No association of carbamazepine hypersensitivity has been demonstrated with drug-metabolizing enzyme gene polymorphisms [47]. We have recently demonstrated an association between the –308 TNF-α gene polymorphism and the MHC haplotype TNF2-DR3-DQ2, and serious, but interestingly not nonserious, hypersensitivity reactions to carbamazepine [48].
2. Abacavir is a non-nucleoside reverse transcriptase inhibitor that causes hypersensitivity reactions in 4% of patients. The reaction has typical clinical features of an immune-mediated reaction. Recent studies have shown that there is a strong association of abacavir hypersensitivity with an ancestral haplotype that includes HLA-B57 [49••,50••]. We have been able to replicate this in our own population in the UK (unpublished data). It has, therefore, been suggested that patients due to start abacavir should have pre-prescription genotyping. However, the utility of this has not been evaluated, and, in particular, HLA B57 is unlikely to be the

predisposing gene in all populations, and its positive predictive value has varied considerably in the two studies published to date [49••,50••], and in our own data (unpublished).

It is likely that as we learn more about the human genome, further predisposing genes will be identified for the new and well-recognized drug hypersensitivity reactions. However, for the progress to continue, it is crucial that such patients are identified and accurately phenotyped, and their DNA is archived. Given the rarity of some of these reactions, this is going to require an international effort to ensure that genetic studies of the future are appropriately powered.

## Conclusions

Immune-mediated or hypersensitivity drug reactions are a form of idiosyncratic toxicity. They are usually categorized as being immune-mediated on the basis of clinical manifestations, although laboratory investigations of T cells ex vivo are providing direct chemical and functional evidence that these are drug-related events. The pathogenesis of drug hypersensitivity reactions is complex. The chemical basis of such reactions is based on the hapten hypothesis, although alternative novel mechanisms of antigen presentation are a subject of active investigation. Co-stimulatory signals for both the extent and type of immune response are becoming well known. Such information will provide a framework for understanding the idiosyncratic nature of drug hypersensitivity. We are beginning to realize how disease may perturb the immune response and thus enhance individual hypersensitivity to a given drug. Furthermore, there are now emerging data that HLA restriction and polymorphisms that influence cytokine expression are risk factors for hypersensitivity to certain drugs.

## Acknowledgments

We thank the MRC (UK) and The Wellcome Trust for their support. DJN is a Wellcome Trust Research Career Development Fellow.

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